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Nintedanib in progressive interstitial lung diseases: data from the whole INBUILD trial

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Abstract

The primary analysis of the INBUILD trial showed that in subjects with progressive fibrosing interstitial lung diseases (ILDs), nintedanib slowed the decline in forced vital capacity (FVC) over 52 weeks. We report the effects of nintedanib on ILD progression over the whole trial.

Subjects with fibrosing ILDs other than idiopathic pulmonary fibrosis, who had ILD progression within the 24 months before screening despite management deemed appropriate in clinical practice, were randomised to receive nintedanib or placebo. Subjects continued on blinded randomised treatment until all subjects had completed the trial. Over the whole trial, mean (SD) exposure to trial medication was 15.6 (7.2) and 16.8 (5.8) months in the nintedanib and placebo groups, respectively.

In the nintedanib (n=332) and placebo (n=331) groups, respectively, the proportions of subjects who had ILD progression (absolute decline in FVC ≥10% predicted) or died were 40.4% and 54.7% in the overall population (HR 0.66 [95% CI: 0.53, 0.83]; p=0.0003), and 43.7% and 55.8% among subjects with a usual interstitial pneumonia (UIP)-like fibrotic pattern on high-resolution computed tomography (HRCT) (HR 0.69 [0.53, 0.91]; p=0.009). In the nintedanib and placebo groups, respectively, the proportions who had an acute exacerbation of ILD or died were 13.9% and 19.6% in the overall population (HR 0.67 [95% CI: 0.46, 0.98]; p=0.04), and 15.0% and 22.8% among subjects with a UIP-like fibrotic pattern on HRCT (HR 0.62 [0.39, 0.97]; p=0.03).

Based on data from the whole INBUILD trial, nintedanib reduced the risk of events indicating ILD progression.

Introduction

Nintedanib, an intracellular inhibitor of tyrosine kinases, inhibits processes fundamental to the progression of lung fibrosis [1]. Randomised placebo-controlled trials demonstrated that nintedanib reduces the rate of progression of interstitial lung disease (ILD) over 52 weeks in patients with idiopathic pulmonary fibrosis (IPF) [2], systemic sclerosis-associated ILD (SSc-ILD) [3], and chronic fibrosing interstitial lung disease (ILDs) with a progressive phenotype [4], resulting in the regulatory approval of nintedanib for the treatment of these conditions.

The INBUILD trial enrolled subjects with chronic fibrosing ILDs other than IPF who met criteria for progression of ILD within the previous two years despite management deemed appropriate in clinical practice [4]. Over 52 weeks, nintedanib reduced the rate of decline in forced vital capacity (FVC) (mL/year) versus placebo by 57% in the overall population and by 61% in subjects with a usual interstitial pneumonia (UIP])-like fibrotic pattern on high-resolution computed tomography (HRCT) (the co-primary analysis populations) [4]. In subgroup analyses, no heterogeneity was detected in the effect of nintedanib versus placebo on the rate of FVC decline across diagnostic subgroups [5]. As subjects continued to receive blinded randomised treatment until the last subject had completed the trial, most subjects received trial medication for longer than 52 weeks. Here, we report the effects of nintedanib versus placebo on time-to-event endpoints assessing progression of ILD over the whole INBUILD trial.

Methods

Subjects

The design of the INBUILD trial (NCT02999178) has been described and the protocol is publicly available [4]. Briefly, eligible subjects had a fibrosing ILD other than IPF, diagnosed by the investigator according to their usual practice, 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 (DLco) ≥30%–<80% predicted. Subjects met ≥1 of the following criteria for ILD 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; worsened respiratory symptoms and increased extent of fibrosis on HRCT. These criteria were determined by the investigator with no central adjudication. Subjects taking azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, rituximab, cyclophosphamide, or oral glucocorticoids >20 mg/day were not enrolled. Initiation of these medications was allowed after 6 months of the trial in cases of deterioration of ILD or autoimmune disease.

Trial design

Subjects were randomised to receive nintedanib 150 mg twice daily (bid) or placebo, stratified by fibrotic pattern on HRCT (UIP-like fibrotic pattern or other fibrotic patterns) based on central review [4]. 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 randomised treatment until all the subjects had completed the trial. Subjects who discontinued treatment were asked to attend all visits as planned, including an end-of-treatment visit and a follow-up visit 4 weeks later. Subjects who were still on treatment at the end of Part B were eligible to enter an open-label extension study, INBUILD-ON (NCT03820726). The final database lock took place after all subjects had completed the follow-up visit or had entered INBUILD-ON (Figure 1).

Analyses

In the overall population and in subjects with a UIP-like fibrotic pattern on HRCT, we assessed the effects of nintedanib on time to the following: absolute and relative declines in FVC ≥5% predicted, absolute and relative declines in FVC ≥10% predicted, death, ILD progression (absolute decline in FVC ≥10% predicted) or death, acute exacerbation of ILD

(defined in [4]) or death. Acute exacerbations of ILD were not adjudicated. Analyses were based on time to first event. Analyses were based on a log-rank test (stratified by UIP-like fibrotic pattern or other fibrotic patterns on HRCT in analyses in the overall population) and a Cox proportional hazards model, stratified by the same factor, was used to derive the hazard ratio (HR) and 95% confidence interval (CI). Adverse events, reported irrespective of causality, in the overall population were coded using preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA) and are presented descriptively. Analyses were based on subjects who received ≥1 dose of trial medication. Analyses were pre-specified except for the analyses of time to absolute and relative declines in FVC % predicted.

Results

Subjects

In the overall population, 663 subjects received nintedanib (n=332) or placebo (n=331); 412 subjects (62.1%) had a UIP-like fibrotic pattern on HRCT (n=206 in each treatment group). The baseline characteristics of the patient population have been described [4,5]. In the overall population, the mean (SD) age was 65.8 (9.8) years, FVC was 69.0 (15.6) % predicted, DLco was 46.1 (13.6) % predicted and the most frequent ILD diagnoses were chronic hypersensitivity pneumonitis (26.1%) and autoimmune ILDs (25.6%) (Supplementary Table S1). Over the whole trial, mean (SD) exposure to trial medication was 15.6 (7.2) and 16.8 (5.8) months in the nintedanib and placebo groups, respectively; 34.3% and 30.2% of subjects in these groups, respectively, prematurely discontinued trial medication. The median follow-up time for the time to event endpoints was approximately 19 months.

Time to event endpoints

The proportions of subjects with an absolute decline in FVC ≥5% predicted were 65.4% and 79.5% in the nintedanib and placebo groups, respectively, in the overall population (HR 0.67

[95% CI 0.56, 0.81]; nominal p<0.0001) and 66.5% and 81.6%, respectively, in subjects with a UIP-like fibrotic pattern on HRCT (0.64 [95% CI 0.51, 0.80]; nominal p<0.0001) (Table 1). The proportions with a relative decline in FVC ≥5% predicted were 73.8% and 86.1% in the nintedanib and placebo groups, respectively, in the overall population (HR 0.71 [95% CI 0.60, 0.84]; nominal p<0.0001) and 73.8% and 86.4%, respectively, in subjects with a UIP-like fibrotic pattern on HRCT (0.69 [95% CI 0.55, 0.86]; nominal p=0.0006) (Table 1).

The proportions of subjects with an absolute decline in FVC ≥10% predicted were 34.3% and 48.3% in the nintedanib and placebo groups, respectively, in the overall population (HR 0.64 [95% CI 0.50, 0.81]; nominal p=0.0002) and 37.4% and 48.1%, respectively, in subjects with a UIP-like fibrotic pattern on HRCT (HR 0.69 [95% CI 0.51, 0.93]; nominal p=0.0138) (Table 1). The proportions with a relative decline in FVC ≥10% predicted were 48.5% and 66.8% in the nintedanib and placebo groups, respectively, in the overall population (HR 0.63 [95% CI 0.51, 0.77]; nominal p<0.0001) and 49.0% and 68.0%, respectively in subjects with a UIP-like fibrotic pattern on HRCT (0.61 [95% CI 0.47, 0.79]; nominal p=0.0001) (Table 1).

In the overall population, 36 subjects (10.8%) in the nintedanib group and 45 subjects (13.6%) in the placebo group died (HR 0.78 [95% CI: 0.50, 1.21]; nominal p=0.26) (Figure 2a). Among subjects with a UIP-like fibrotic pattern on HRCT, 25 subjects (12.1%) in the nintedanib group and 36 subjects (17.5%) in the placebo group died (HR 0.66 [95% CI: 0.40, 1.10]; nominal p=0.11) (Figure 2b).

In the overall population, 134 subjects (40.4%) in the nintedanib group and 181 subjects (54.7%) in the placebo group had ILD progression (absolute decline in FVC ≥10% predicted) or died (HR 0.66 [95% CI: 0.53, 0.83]; p=0.0003) (Figure 3a). Among subjects with a UIP-like fibrotic pattern on HRCT, 90 subjects (43.7%) in the nintedanib group and 115 subjects (55.8%) in the placebo group had ILD progression or died (HR 0.69 [95% CI: 0.53, 0.91]; nominal p=0.009) (Figure 3b).

In the overall population, 46 subjects (13.9%) in the nintedanib group and 65 subjects (19.6%) in the placebo group had an acute exacerbation of ILD or died (HR 0.67 [95% CI: 0.46, 0.98]; nominal p=0.04) (Figure 4a). Among subjects with a UIP-like fibrotic pattern on HRCT, 31 subjects (15.0%) in the nintedanib group and 47 subjects (22.8%) in the placebo group had an acute exacerbation of ILD or died (HR 0.62 [95% CI: 0.39, 0.97]; nominal p=0.03) (Figure 4b).

Adverse events

In the overall population, diarrhoea was the most frequent adverse event (136.4 events per 100 patient-years in the nintedanib group and 23.0 events per 100 patient-years in the placebo group) (Table 2). Nausea, vomiting, decreased appetite, and weight decrease were also more frequently reported in the nintedanib group than in the placebo group (Table 2). Adverse events led to permanent discontinuation of trial medication in 73 subjects (22.0%) and 48 subjects (14.5%) in the nintedanib and placebo groups, respectively. In the nintedanib and placebo groups, respectively, 131 subjects (39.5%) and 20 subjects (6.0%) had ≥1 dose reduction and 128 subjects (38.6%) and 41 subjects (12.4%) had ≥1 treatment interruption to manage adverse events. Serious adverse events occurred in 147 subjects (44.3%) and 164 subjects (49.5%) in the nintedanib and placebo groups, respectively (Table 3).

Adverse events of increase in alanine aminotransferase (ALT) and increase in aspartate aminotransferase (AST) were more common in subjects treated with nintedanib than placebo (Table 2). Based on laboratory tests, elevations in ALT and/or AST to ≥3 times the upper limit of the normal range were observed in 47 subjects (14.2%) in the nintedanib group and 6 subjects (1.8%) in the placebo group. For most of these cases (43 of 47 subjects in the nintedanib group and 6 of 6 subjects in the placebo group), these elevations returned to within the normal range spontaneously with continued treatment or after dose reduction or treatment interruption. One subject in each treatment group had concurrent elevations in liver enzymes and bilirubin that met criteria for Hy's law.

Discussion

These analyses, based on the longest duration of follow-up in the INBUILD trial (median of approximately 19 months), show that in patients with fibrosing ILDs that have progressed within the two years prior to enrolment, events indicating further progression of ILD occurred frequently. In the placebo group, 55% of subjects in the overall population and 56% of subjects with a UIP-like fibrotic pattern on HRCT had progression of ILD (absolute decline in FVC ≥10% predicted) or died. These findings support previous analyses showing that over 52 weeks, subjects who received placebo in the INBUILD trial had a clinical course similar to patients with untreated IPF, irrespective of the underlying ILD diagnosis or the fibrotic pattern on HRCT [6]. Our observations lend further support to the concept that there are patients with progressive fibrosing ILDs who can be managed based on their similarity in longitudinal clinical behaviour despite treatment considered appropriate in clinical practice [1, 7, 8].

While there is no established definition for progressive fibrosing ILD, a number of sets of criteria have been proposed based on a multi-faceted approach including measurement of decline in FVC [8-10]. Our observations demonstrate that the inclusion criteria used in the INBUILD trial identified patients with progressive ILD who were at high risk of further progression and mortality. This does not mean that patients do not need to receive an accurate diagnosis of ILD – this remains essential to ensure that systemic and environmental causes of ILD can be addressed – but highlights the importance of prompt identification of patients whose ILD is progressing so that they can be managed appropriately.

A decline in FVC of >10% predicted has consistently been associated with mortality in studies across fibrosing ILDs [11-14]. Previous analyses of data from the INBUILD trial have shown that over 52 weeks, a relative decline in FVC of >10% predicted was associated with a more than three-fold increase in the risk of death, both in the overall population and in

subjects with a UIP-like fibrotic pattern on HRCT [6]. Over the whole trial, nintedanib reduced the risk of a relative decline in FVC of ≥10% predicted by 37% compared with placebo in the overall population and by 39% in subjects with a UIP-like fibrotic pattern on HRCT.

Acute exacerbations are a recognised feature of the natural history of IPF [15]. While there is no established definition for an acute exacerbation of ILDs other than IPF, there is increasing evidence that acute exacerbations of ILD occur in a proportion of patients with such ILDs and are associated with high mortality [16,17]. Over the whole INBUILD trial, 20% of subjects in the placebo group had an acute exacerbation of ILD or died. Nintedanib reduced the risk of an acute exacerbation or death by 33% versus placebo in the overall population and by 38% in those with a UIP-like fibrotic pattern on HRCT, similar to the reduction in the risk of acute exacerbations observed with nintedanib in patients with IPF [18].

The adverse event profile of nintedanib over the whole INBUILD trial was consistent with that observed over the first 52 weeks [4], with no new safety signals observed. The adverse event profile of nintedanib in the INBUILD trial was consistent with that observed in subjects with IPF [2,19] and SSc-ILD [3,20]. Gastrointestinal adverse events, particularly diarrhoea, were the most common adverse events. Elevations in liver enzymes were more common in subjects treated with nintedanib than placebo, but most normalised spontaneously or after dose reduction or treatment interruption.

In conclusion, analyses based on the data from the whole INBUILD trial show that in patients with chronic fibrosing ILDs that had shown progression within the two years prior to enrolment, events indicating further progression of ILD occurred frequently. Nintedanib slowed the progression of ILD, with an adverse event profile that was consistent with that observed over 52 weeks.

A plain language summary of this article is available at:

https://globalmedcomms.com/respiratory/flaherty/PLSforINBUILD

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TABLE 1. Time to absolute and relative declines in forced vital capacity (FVC) >5% predicted or >10% predicted using data up to the final database lock in the INBUILD trial.

	Overall population		**Subjects with UIP-like fibrotic pattern on HRCT**	
	Nintedanib (n=332)	**Placebo (n=331)**	**Nintedanib (n=206)**	**Placebo (n=206)**
Absolute decline in FVC ≥5% predicted, n (%)	217 (65.4)	263 (79.5)	137 (66.5)	168 (81.6)
Hazard ratio (95% CI)	0.67 (0.56, 0.81)		0.64 (0.51, 0.80)	
Nominal p-value	<0.0001		<0.0001	
Relative decline in FVC ≥5% predicted, n (%)	245 (73.8)	285 (86.1)	152 (73.8)	178 (86.4)
Hazard ratio (95% CI)	0.71 (0.60, 0.84)		0.69 (0.55, 0.86)	
Nominal p-value	<0.0001		0.0006	
Absolute decline in FVC ≥10% predicted, n (%)	114 (34.3)	160 (48.3)	77 (37.4)	99 (48.1)
Hazard ratio (95% CI)	0.64 (0.50, 0.81)		0.69 (0.51, 0.93)	
Nominal p-value	0.0002		0.0138	

Relative decline in FVC ≥10% predicted, n (%)	161 (48.5)	221 (66.8)	101 (49.0)	140 (68.0)
Hazard ratio (95% CI)	0.63 (0.51, 0.77)		0.61 (0.47, 0.79)	
Nominal p-value	<0.0001		0.0001	

HRCT: high-resolution computed tomography; UIP: usual interstitial pneumonia.

TABLE 2. Rates per 100 patient–years of the most frequent adverse events in the overall population of the INBUILD trial.

	Nintedanib (n=332)	**Placebo (n=331)**
Diarrhoea	136.4	23.0
Nausea	30.8	7.6
Vomiting	17.3	3.5
Decreased appetite	14.0	5.1
Nasopharyngitis	13.9	11.4
Dyspnoea	12.9	13.3
Bronchitis	12.1	15.4
Weight decrease	12.4	3.9
Alanine aminotransferase increased	12.4	2.8
Cough	9.8	12.1
Progression of interstitial lung disease*	6.5	12.7
Aspartate aminotransferase increased	10.8	2.8

Based on adverse events reported (irrespective of causality) between the first trial drug intake and 28 days after the last trial drug intake. Adverse events were coded using preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events with an incidence rate of >10 events per 100 patient-years in either treatment group are shown. *Corresponded to the MedDRA preferred term “interstitial lung disease”.

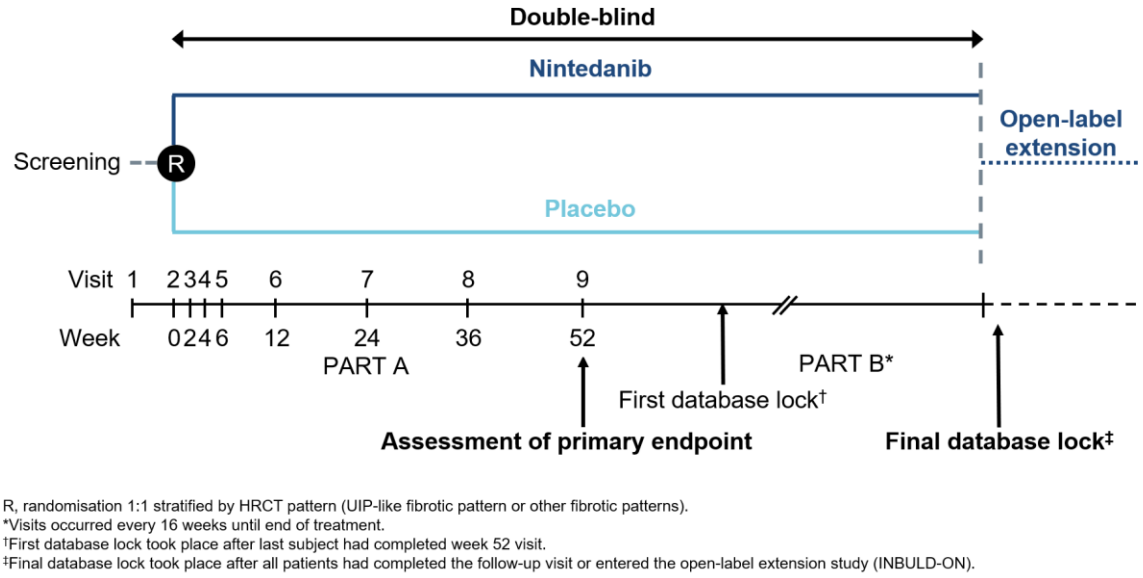
TABLE 3. Rates per 100 patient–years of the most frequent serious adverse events in the overall population of the INBUILD trial.

	Nintedanib (n=332)	**Placebo (n=331)**
Progression of interstitial lung disease*	4.4	10.1
Pneumonia	5.6	3.5
Acute respiratory failure	3.7	1.5
Dyspnoea	1.4	2.8
Respiratory failure	2.5	2.1

Based on serious adverse events reported (irrespective of causality) between the first trial drug intake and 28 days after the last trial drug intake. Adverse events were coded using preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA). Serious adverse events were defined as 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. Serious adverse events with an incidence rate of >2 events per 100 patient-years in either treatment group are shown.

*Corresponded to the MedDRA preferred term “interstitial lung disease”.

FIGURE LEGENDS



R, randomisation 1:1 stratified by HRCT pattern (UIP-like fibrotic pattern or other fibrotic patterns).
*Visits occurred every 16 weeks until end of treatment.
†First database lock took place after last subject had completed week 52 visit.
‡Final database lock took place after all patients had completed the follow-up visit or entered the open-label extension study (INBULD-ON).

FIGURE 1. INBUILD trial design [4].

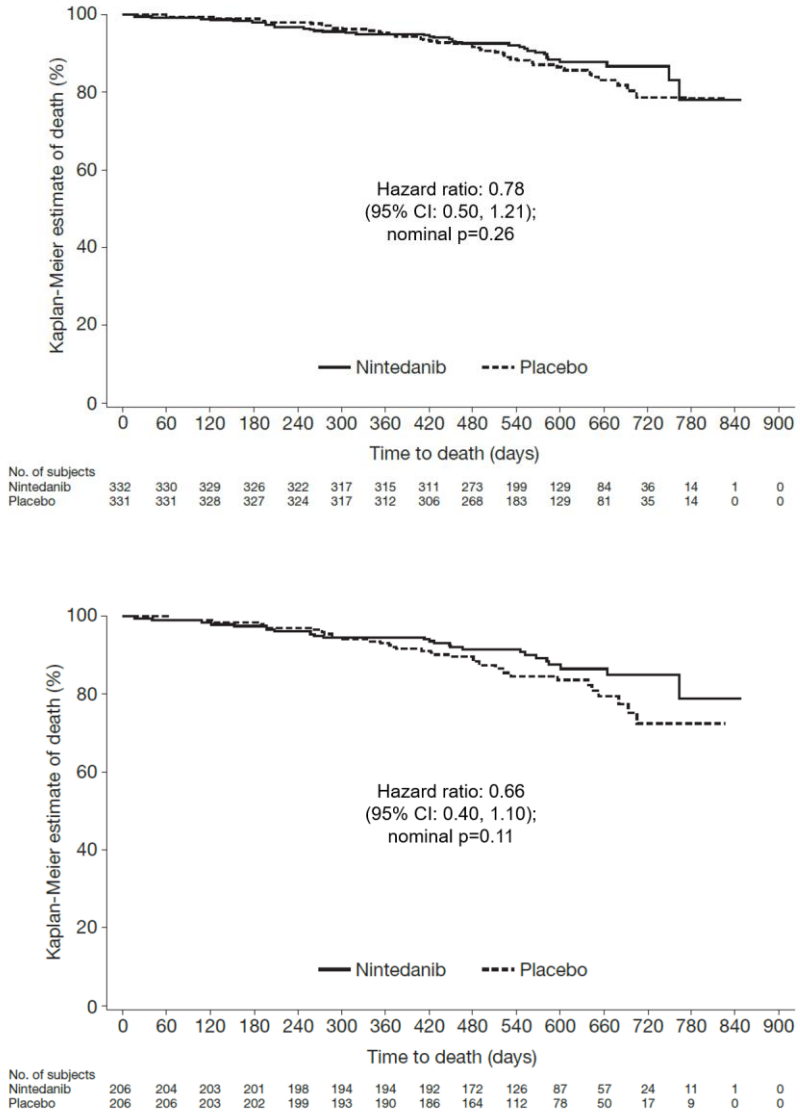
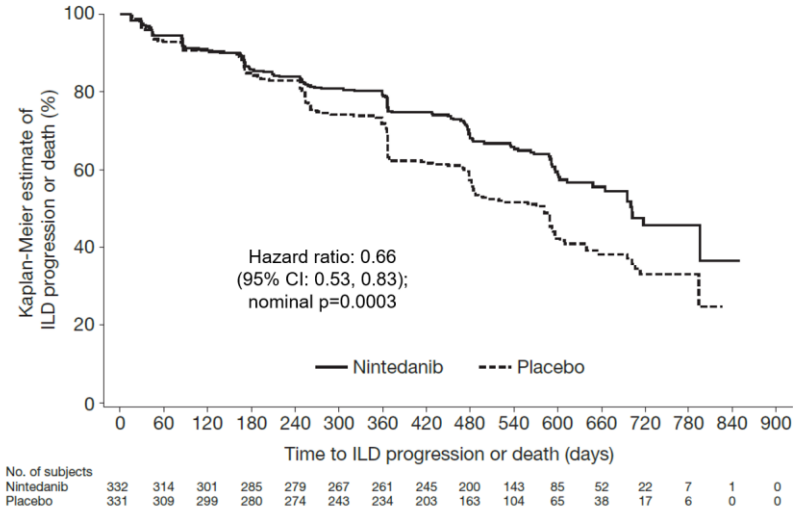


FIGURE 2. Kaplan-Meier estimates of time to death in (a) the overall population and (b) subjects with a UIP-like fibrotic pattern on HRCT in the INBUILD trial.



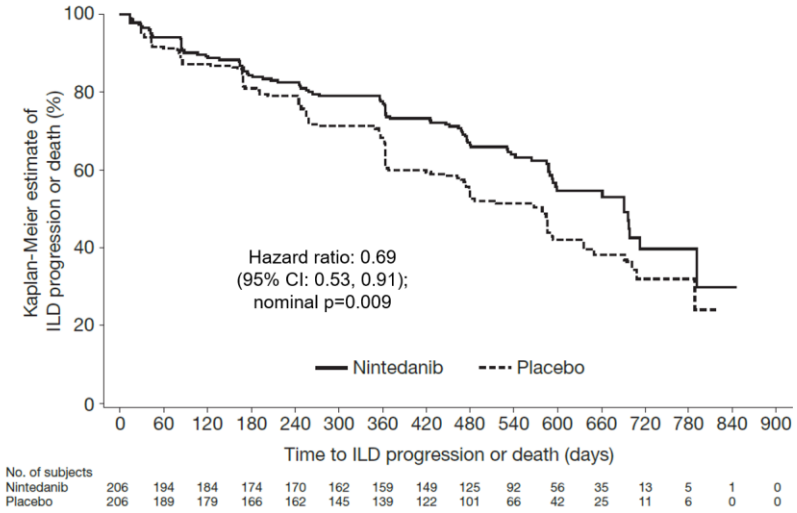
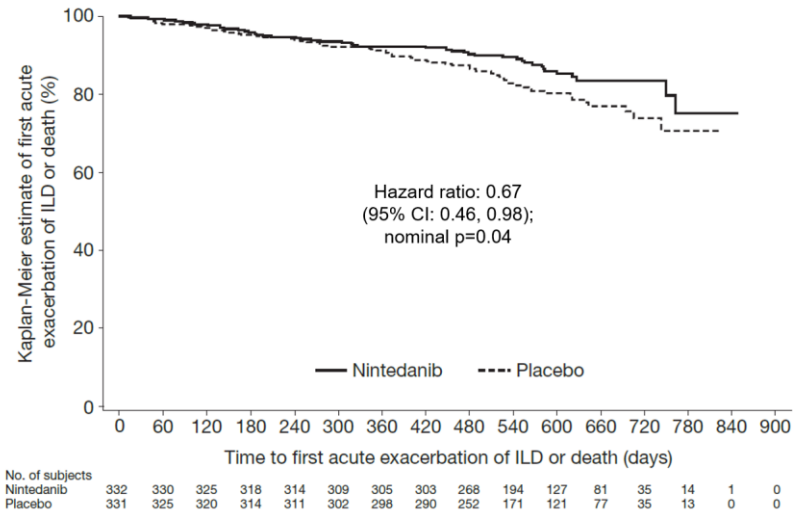


FIGURE 3. Kaplan-Meier estimates of time to progression of ILD or death in (a) the overall population and (b) subjects with a UIP-like fibrotic pattern on HRCT in the INBUILD trial.



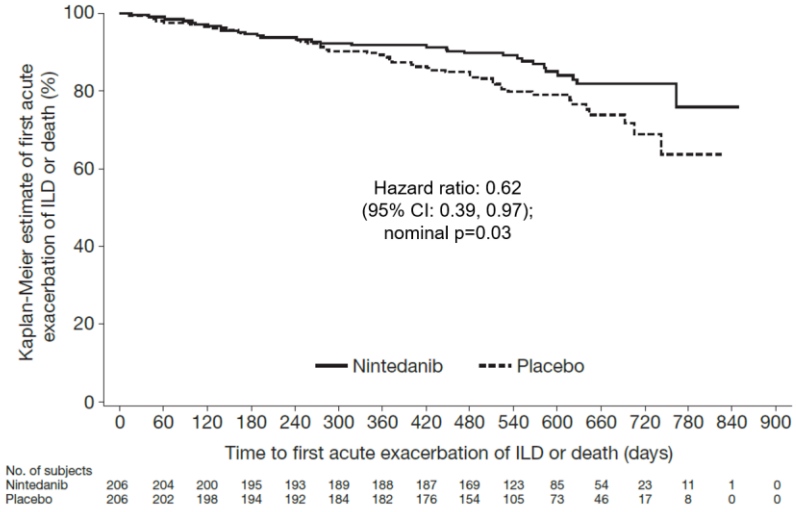


FIGURE 4. Kaplan-Meier estimates of time to first acute exacerbation of ILD or death in (a) the overall population and (b) subjects with a UIP-like fibrotic pattern on HRCT in the INBUILD trial.

Supplementary material

Supplementary Table S1. Clinical ILD diagnoses documented on the case report form in the overall population of the INBUILD trial (n=663).

Hypersensitivity pneumonitis	173 (26.1)
Idiopathic non-specific interstitial pneumonia	125 (18.9)
Unclassifiable idiopathic interstitial pneumonia	114 (17.2)
Rheumatoid arthritis-associated ILD	89 (13.4)
Systemic sclerosis-associated ILD	39 (5.9)
Exposure-related ILD	39 (5.9)
Mixed connective tissue disease-associated ILD	19 (2.9)
Sarcoidosis	12 (1.8)
Other ILDs*	53 (8.0)
Pleuroparenchymal fibroelastosis	10 (1.5)
Sjögren's syndrome	7 (1.1)
Desquamative interstitial pneumonia	5 (0.8)
Interstitial pneumonia with autoimmune features	5 (0.8)
Cryptogenic organizing pneumonia	4 (0.6)
Combined pulmonary fibrosis and emphysema	3 (0.5)
Systemic lupus erythematosus-ILD	2 (0.3)
After chemotherapy	1 (0.2)
ANCA-associated ILD	1 (0.2)
Chronic eosinophilic pneumonia	1 (0.2)
CTD-ILD	1 (0.2)
CTD-organizing pneumonia	1 (0.2)
IgG4-related lung disease	1 (0.2)
Lipoidic fibrosis	1 (0.2)
Antisynthetase syndrome	1 (0.2)
MPA-associated ILD	1 (0.2)
Outcome of acute interstitial pneumonia	1 (0.2)

Overlap NSIP/OP without underlying CTD	1 (0.2)
Polymyositis CTD-ILD	1 (0.2)
Pulmonary alveolar proteinosis	1 (0.2)
Respiratory bronchiolitis-ILD with fibrosis	1 (0.2)
UCTD-ILD with positive anti-PL7 auto-antibodies	1 (0.2)
Unclassified connective tissue disease	1 (0.2)
Undifferentiated connective tissue disease-ILD	1 (0.2)

*Verbatim from case report form.
Data are no (%) of patients.
ANCA, anti-neutrophil cytoplasm antibodies; CTD, connective tissue disease; IgG4, immunoglobulin G4; ILD, interstitial lung disease; MPA, microscopic polyangiitis; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; UCTD, undifferentiated connective tissue disease