ORIGINAL ARTICLE

Nintedanib in Progressive Fibrosing Interstitial Lung Diseases

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ABSTRACT

BACKGROUND

Preclinical data have suggested that nintedanib, an intracellular inhibitor of tyrosine kinases, inhibits processes involved in the progression of lung fibrosis. Although the efficacy of nintedanib has been shown in idiopathic pulmonary fibrosis, its efficacy across a broad range of fibrosing lung diseases is unknown.

METHODS

In this double-blind, placebo-controlled, phase 3 trial conducted in 15 countries, we randomly assigned patients with fibrosing lung disease affecting more than 10% of lung volume on high-resolution computed tomography (CT) to receive nintedanib at a dose of 150 mg twice daily or placebo. All the patients met criteria for progression of interstitial lung disease in the past 24 months despite treatment and had a forced vital capacity (FVC) of at least 45% of the predicted value and a diffusing capacity of the lung for carbon monoxide ranging from 30 to less than 80% of the predicted value. Randomization was stratified according to the fibrotic pattern (a pattern of usual interstitial pneumonia [UIP] or other fibrotic patterns) on high-resolution CT. The primary end point was the annual rate of decline in the FVC, as assessed over a 52-week period. The two primary populations for analysis were the overall population and patients with a UIP-like fibrotic pattern.

RESULTS

A total of 663 patients were treated. In the overall population, the adjusted rate of decline in the FVC was −80.8 ml per year with nintedanib and −187.8 ml per year with placebo, for a between-group difference of 107.0 ml per year (95% confidence interval [CI], 65.4 to 148.5; P<0.001). In patients with a UIP-like fibrotic pattern, the adjusted rate of decline in the FVC was −82.9 ml per year with nintedanib and −211.1 ml per year with placebo, for a difference of 128.2 ml (95% CI, 70.8 to 185.6; P<0.001). Diarrhea was the most common adverse event, as reported in 66.9% and 23.9% of patients treated with nintedanib and placebo, respectively. Abnormalities on liver-function testing were more common in the nintedanib group than in the placebo group.

CONCLUSIONS

In patients with progressive fibrosing interstitial lung diseases, the annual rate of decline in the FVC was significantly lower among patients who received nintedanib than among those who received placebo. Diarrhea was a common adverse event. (Funded by Boehringer Ingelheim; INBUILD ClinicalTrials.gov number, NCT02999178.)

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*A complete list of investigators in the INBUILD trial is provided in the Supplementary Appendix, available at NEJM.org.

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Patients with a spectrum of lung disorders, including idiopathic pulmonary fibrosis (IPF),[1,2] have a progressive fibrosing clinical phenotype that is characterized by an increasing extent of fibrosis on high-resolution computed tomography (CT), decline in lung function, worsening of symptoms and quality of life, and early death despite current therapy.[3-6] On the basis of the clinical and pathophysiological similarities among these diseases, it has been postulated that such disorders with a progressive phenotype have a common pathobiologic mechanism regardless of the cause and thus could all have a response to similar treatment.[4]

Nintedanib is an intracellular inhibitor of tyrosine kinases.[7] Preclinical data have suggested that nintedanib inhibits processes involved in the progression of lung fibrosis.[7-11] In patients with IPF and systemic sclerosis-associated interstitial lung disease, treatment with 150 mg of nintedanib twice daily reduced the rate of decline in the forced vital capacity (FVC).[12-14] We conducted the INBUILD trial to investigate the efficacy and safety of nintedanib in patients with fibrosing interstitial lung diseases with a progressive phenotype.

Methods

Trial Design and Oversight

The INBUILD trial was a randomized, double-blind, placebo-controlled, parallel-group trial conducted at 153 sites in 15 countries.[3] The trial was carried out in compliance with the protocol (available with the full text of this article at NEJM.org) and with the principles of the Declaration of Helsinki and the Harmonised Tripartite Guideline for Good Clinical Practice of the International Conference on Harmonisation; the trial was approved by the local authorities. All the patients provided written informed consent before trial entry.

All the authors had access to the data, which were analyzed by the sponsor, Boehringer Ingelheim. The authors assume responsibility for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Medical writing assistance, funded by the sponsor, was provided by FleishmanHillard Fishburn.

Patients

Recruitment began in February 2017 and ended in April 2018. Eligible patients were adults (≥18 years of age) with a physician-diagnosed fibrosing interstitial lung disease. Because patients with IPF had already been studied, specific efforts were made to enroll patients with a progressive fibrotic phenotype other than IPF. Enrolled patients had features of fibrosing lung disease affecting more than 10% of lung volume on high-resolution CT, as confirmed by central review (Section B in the Supplementary Appendix, available at NEJM.org).

The patients were required to meet at least one of the following criteria for progression of interstitial lung disease within the 24 months before screening, despite standard treatment with an agent other than nintedanib or pirfenidone: a relative decline in the FVC of at least 10% of the predicted value, a relative decline in the FVC of 5% to less than 10% of the predicted value and worsening of respiratory symptoms or an increased extent of fibrosis on high-resolution CT, or worsening of respiratory symptoms and an increased extent of fibrosis. At the time of enrollment, patients were required to have an FVC of at least 45% of the predicted value and a diffusing capacity of the lung for carbon monoxide (corrected for hemoglobin) of 30 to less than 80% of the predicted value.

Patients who were treated with azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, rituximab, cyclophosphamide, or oral glucocorticoids (at a dose of more than 20 mg per day for glucocorticoids) were excluded. At the discretion of the investigator, initiation of these medications was allowed after 6 months of trial treatment in patients with clinically significant deterioration of interstitial lung disease or connective tissue disease. Key exclusion criteria are provided in Section C in the Supplementary Appendix.

Trial Treatment

Patients were randomly assigned in a 1:1 ratio to receive oral nintedanib (at a dose of 150 mg twice daily) or placebo with the use of interactive-response technology. Since some studies have suggested that the progression of fibrosing interstitial lung disease is more rapid in patients with an imaging pattern of usual interstitial pneumonia (UIP) on high-resolution CT than in those with other fibrotic patterns,[15-18] randomization was stratified according to the imaging pattern (UIP-like fibrotic pattern or other fibrotic patterns) on the basis of central review. An enrichment

design[19] was planned, with stratification of the trial population so that two thirds of the patients had a UIP-like fibrotic pattern (as identified according to the criteria of the INPULSIS trials[13]) (Section B in the Supplementary Appendix) and one third had other fibrotic patterns (i.e., a 2:1 ratio). However, stratification caps were not implemented, since recruitment led to a ratio close to 2:1 without the need for active management.

For each patient, the trial consisted of two parts: Part A, which was conducted during the first 52 weeks, and Part B, which was a variable treatment period beyond week 52 during which patients continued to receive either nintedanib or placebo until all the patients had completed Part A. (Details are provided in Section D in the Supplementary Appendix.) At the end of the trial, all the patients had the option of receiving nintedanib in an open-label extension trial. Patients who had adverse events were permitted to interrupt treatment or to reduce the dose of nintedanib to 100 mg twice daily. Patients who discontinued either nintedanib or placebo were asked to attend all visits as originally planned. The first database lock took place after the last patient had completed the week 52 visit.

END POINTS

The primary end point was the annual rate of decline in the FVC, as assessed over the 52-week period. Spirometry was performed at baseline and at weeks 2, 4, 6, 12, 24, 36, and 52, in accordance with international guidelines[20] with the use of sponsor-provided spirometers (Flowscreen CT).

The main secondary end points were the absolute change from baseline in the total score on the King's Brief Interstitial Lung Disease (K-BILD) questionnaire at week 52, the time until the first acute exacerbation of interstitial lung disease or death over the 52-week period, and the time until death over the 52-week period. (The K-BILD questionnaire is a self-administered health-status questionnaire that has been developed in patients with interstitial lung diseases.[21] It consists of 15 items in three domains: breathlessness and activities, psychological factors, and chest symptoms. Domain and total scores range from 0 to 100, with higher scores representing better health status. The minimal clinically important difference has not been established, but a change of between 4 and 8 points has been suggested to represent a meaningful change.[22-24]) Further end points included a composite of an acute exacerbation of interstitial lung disease or death or death alone as assessed during the period until the first database lock.

In line with the categorization of acute exacerbations of IPF in the latest international working group report,[25] we defined acute exacerbations of interstitial lung disease as acute, clinically significant respiratory deteriorations characterized by evidence of new, widespread alveolar abnormality meeting all the following criteria: acute worsening or development of dyspnea (typically of <1 month duration), CT with new bilateral ground-glass opacity or consolidation superimposed on a background pattern consistent with fibrosing interstitial lung disease, and deterioration not fully explained by cardiac failure or fluid overload. Infection was not an exclusion criterion for an acute exacerbation. Safety was assessed by clinical and laboratory evaluation and the recording of adverse events, as coded with the use of the *Medical Dictionary for Regulatory Activities*, version 22.0.

STATISTICAL ANALYSIS

All analyses were conducted in patients who had received at least one dose of nintedanib or placebo. The two primary populations were the overall population and patients with a UIP-like fibrotic pattern on high-resolution CT. The primary end point and safety were assessed in the overall population, in patients with a UIP-like fibrotic pattern, and in patients with other fibrotic patterns. Analyses of the secondary and further efficacy end points were limited to the overall population and to patients with a UIP-like fibrotic pattern. The primary end point was analyzed with the use of a random coefficient regression model (with random slopes and intercepts), including baseline FVC (reported in milliliters) and imaging pattern as covariates. The slope of the FVC decline was calculated for every patient and the average compared between the two assigned groups. The analysis was based on all measurements obtained over the 52-week period, including those from patients who had discontinued nintedanib or placebo. The model allowed for missing data on the assumption that data were missing at random.

To maintain a type I error rate of 5%, a Hochberg procedure was used.[26] For the primary end point, statistical significance was indicated if

the analyses in the two primary populations were significant at a two-sided 5% level or the analysis in either primary population was significant at a two-sided 2.5% level. Sensitivity analyses for the primary end point were performed to analyze the potential effects of missing data and assumptions made in the primary analysis model. (Details are provided in Sections E and F in the Supplementary Appendix.) All other end points were exploratory (Section G in the Supplementary Appendix). Because the statistical analysis plan did not include a provision for correcting for multiple comparisons for secondary or other outcomes, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiple comparisons, so the intervals should not be used to infer definitive treatment effects.

In the determination of sample size, between-group differences in the adjusted rate of decline in the FVC were assumed to be 75 to 100 ml per year in patients with a UIP-like fibrotic pattern and 60 to 75 ml per year among those with other fibrotic patterns. This calculation was based on assumptions that the rate of decline in the FVC in the trial population would be similar to that in patients with IPF but slightly lower in patients with a fibrotic pattern other than a UIP-like pattern, along with the assumption that as in patients with IPF,[13] the rate of decline in the FVC would be 50% lower in the nintedanib group than in the placebo group. We determined that a sample of 600 patients, including two thirds (400 patients) with a UIP-like fibrotic pattern, would provide a power of approximately 90% to detect a between-group difference of 100 ml per year in patients with a UIP-like fibrotic pattern (assumed standard deviation, 300 ml) and to detect a between-group difference of 92 ml per year in the overall population (assumed standard deviation, 337 ml).

RESULTS

PATIENTS

A total of 663 patients underwent randomization and received at least one dose of nintedanib or placebo (332 in the nintedanib group and 331 in the placebo group); of the 663 patients, 412 (62.1%) had a UIP-like fibrotic pattern (Fig. 1). The baseline characteristics of the patients were similar in the two primary populations and in the two treatment groups (Table 1, and Sections H and I in the Supplementary Appendix).

In the overall population, the mean (±SD) age was 65.8±9.8 years, the FVC was 69.0±15.6% of the predicted value, and the diffusing capacity of the lung for carbon monoxide was 46.1±13.6% of the predicted value. The most frequent diagnoses of interstitial lung disease were chronic hypersensitivity pneumonitis (in 26.1% of the patients) and autoimmune interstitial lung diseases (in 25.6%). Section J in the Supplementary Appendix provides details regarding the use of restricted background therapies at baseline (a use that was balanced in the two trial groups) and regarding restricted therapies that were added over the 52 weeks of treatment.

In the overall population, 252 patients (75.9%) in the nintedanib group and 282 (85.2%) in the placebo group completed 52 weeks of treatment (Fig. 1). The mean duration of exposure during 52 weeks was 10.3±3.8 months in the nintedanib group and 11.2±2.6 months in the placebo group. The mean duration of exposure before the first database lock was 15.0±6.8 months in the nintedanib group and 16.2±5.5 months in the placebo group.

PRIMARY AND OTHER FVC END POINTS

In the overall population, the adjusted rate of decline in the FVC over the 52-week period (the primary end point) was −80.8 ml per year in the nintedanib group and −187.8 ml per year in the placebo group (between-group difference, 107.0 ml; 95% confidence interval [CI], 65.4 to 148.5; P<0.001). In patients with a UIP-like fibrotic pattern, the adjusted rate of decline in the FVC over the 52-week period was −82.9 ml per year in the nintedanib group and −211.1 ml per year in the placebo group (between-group difference, 128.2 ml; 95% CI, 70.8 to 185.6; P<0.001) (Table 2, and Section K in the Supplementary Appendix). Box-and-whisker plots of the adjusted annual rate of decline in the FVC are provided in Section L in the Supplementary Appendix.

In patients with other fibrotic patterns, the adjusted rate of decline in FVC was −79.0 ml per year in the nintedanib group and −154.2 ml per year in the placebo group (between-group difference, 75.3 ml; 95% CI, 15.5 to 135.0). The treatment effect between subgroups according to the

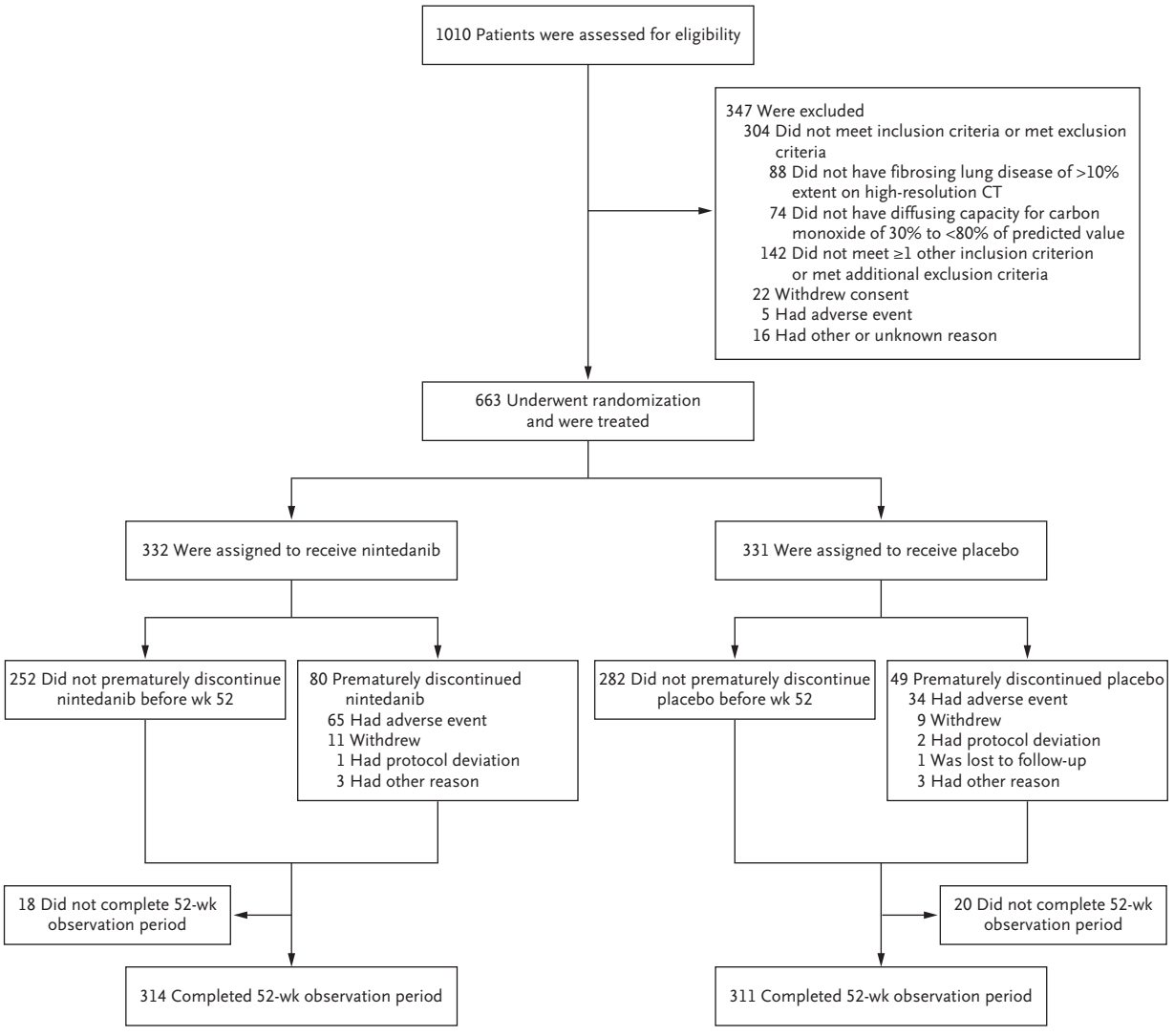


Figure 1. Enrollment and Randomization in the Overall Population.

A list of other key exclusion criteria is provided in Section C in the Supplementary Appendix.

imaging pattern was consistent (Section M in the Supplementary Appendix). All sensitivity analyses related to the handling of missing data were supportive of the findings in the primary analysis (Sections E and F in the Supplementary Appendix). In addition, the curves of observed change from baseline in the FVC in the two groups separated early and continued to diverge (Fig. 2).

MAIN SECONDARY END POINTS

At week 52, the adjusted mean absolute change from baseline in the total score on the K-BILD questionnaire (measuring activity level, psychological factors, and chest symptoms) was 0.55 points in the nintedanib group and −0.79 points in the placebo group (between-group difference, 1.34 points; 95% CI, −0.31 to 2.98) in the overall population and 0.75 points and −0.78 points, respectively (between-group difference, 1.53; 95% CI, −0.68 to 3.74) in patients with a UIP-like fibrotic pattern. The percentage of patients who either died or had an acute exacerbation of interstitial lung disease over the 52-week period was 7.8% in the nintedanib group and 9.7% in the

Table 1. Characteristics of the Overall Population at Baseline.*

Characteristic	Nintedanib (N=332)	Placebo (N=331)
Male sex — no. (%)	179 (53.9)	177 (53.5)
Age — yr	65.2±9.7	66.3±9.8
Former or current smoker — no. (%)	169 (50.9)	169 (51.1)
UIP-like fibrotic pattern on high-resolution CT — no. (%)	206 (62.0)	206 (62.2)
Criteria for disease progression in previous 24 mo — no. (%)		
Relative decline in FVC of ≥10% of predicted value	160 (48.2)	172 (52.0)
Relative decline in FVC of 5% to <10% of predicted value plus worsening of respiratory symptoms or increased extent of fibrosis on high-resolution CT	110 (33.1)	97 (29.3)
Worsening of respiratory symptoms and increased extent of fibrosis on high-resolution CT	62 (18.7)	61 (18.4)
FVC		
Mean value — ml	2340±740	2321±728
Percent of predicted value	68.7±16.0	69.3±15.2
Diffusing capacity for carbon monoxide†		
Mean value — mmol/min/kPa	3.5±1.2	3.7±1.3
Percent of predicted value	44.4±11.9	47.9±15.0
Total score on K-BILD questionnaire‡	52.5±11.0	52.3±9.8

* Plus–minus values are means ±SD. FVC denotes forced vital capacity, and UIP usual interstitial pneumonia.
† The values for diffusing capacity for carbon monoxide were corrected for the hemoglobin level.
‡ Scores on the King's Brief Interstitial Lung Disease (K-BILD) questionnaire range from 0 to 100, with higher scores representing better health status.

placebo group (hazard ratio, 0.80; 95% CI, 0.48 to 1.34) in the overall population and 8.3% and 12.1%, respectively (hazard ratio, 0.67; 95% CI, 0.36 to 1.24) in patients with a UIP-like fibrotic pattern. The percentage of patients who died over the 52-week period was 4.8% in the nintedanib group and 5.1% in the placebo group (hazard ratio, 0.94; 95% CI, 0.47 to 1.86) in the overall population and 5.3% and 7.8% (hazard ratio, 0.68; 95% CI, 0.32 to 1.47) in patients with a UIP-like fibrotic pattern.

ADDITIONAL PRESPECIFIED END POINTS

During the period until the first database lock, the percentage of patients in the overall population who either died or had an acute exacerbation of interstitial lung disease was 12.3% in the nintedanib group and 17.8% in the placebo group (hazard ratio, 0.68; 95% CI, 0.46 to 1.01); the percentage of patients who died was 8.1% and 11.5%, respectively (hazard ratio, 0.70; 95% CI, 0.43 to 1.15). Similar results were observed in patients with a UIP-like fibrotic pattern (Table 2, and Section N in the Supplementary Appendix).

ADVERSE EVENTS

In the overall population over the 52-week period, the percentages of patients with any adverse events and serious adverse events were similar in the nintedanib group and the placebo group (Table 3). A greater percentage of patients in the nintedanib group than in the placebo group had adverse events leading to a permanent dose reduction (33.1% vs. 4.2%) and to discontinuation of either nintedanib or placebo (19.6% vs. 10.3%). Fatal adverse events were less frequent in the nintedanib group than in the placebo group (3.3% vs. 5.1%). The most frequent adverse event was diarrhea, which was reported in 222 patients (66.9%) in the nintedanib group and in 79 patients (23.9%) in the placebo group. The worst episode of diarrhea (according to the Common Terminology Criteria for Adverse Events, version 4.03) was grade 3 in 23 patients in the nintedanib

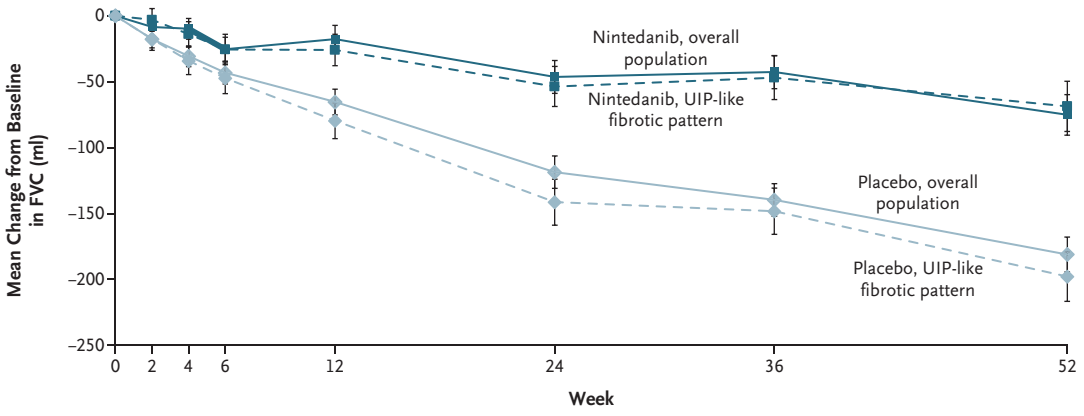
Table 2. Efficacy End Points.*

End Point	Nintedanib (N=332)	Placebo (N=331)	Difference (95% CI)
Primary end point			
Rate of decline in the FVC at 52 wk — ml/yr†			
Overall population	−80.8±15.1	−187.8±14.8	107.0 (65.4 to 148.5)‡
Patients with a UIP-like fibrotic pattern	−82.9±20.8	−211.1±20.5	128.2 (70.8 to 185.6)‡
Patients with other fibrotic patterns	−79.0±21.6	−154.2±21.2	75.3 (15.5 to 135.0)§
Main secondary end points			
Absolute change from baseline in total score on K-BILD questionnaire at 52 wk¶			
Overall population	0.55±0.60	−0.79±0.59	1.34 (−0.31 to 2.98)§
Patients with a UIP-like fibrotic pattern	0.75±0.80	−0.78±0.79	1.53 (−0.68 to 3.74)§
Acute exacerbation of interstitial lung disease or death at 52 wk — no. with event/total no. (%)			
Overall population	26/332 (7.8)	32/331 (9.7)	0.80 (0.48 to 1.34)§‖
Patients with a UIP-like fibrotic pattern	17/206 (8.3)	25/206 (12.1)	0.67 (0.36 to 1.24)§‖
Death at 52 wk — no. with event/total no. (%)			
Overall population	16/332 (4.8)	17/331 (5.1)	0.94 (0.47 to 1.86)§‖
Patients with a UIP-like fibrotic pattern	11/206 (5.3)	16/206 (7.8)	0.68 (0.32 to 1.47)§‖
Additional end points assessed during period until first database lock			
Acute exacerbation of interstitial lung disease or death — no. with event/total no. (%)			
Overall population	41/332 (12.3)	59/331 (17.8)	0.68 (0.46 to 1.01)§‖
Patients with a UIP-like fibrotic pattern	28/206 (13.6)	44/206 (21.4)	0.61 (0.38 to 0.98)§‖
Death — no. with event/total no. (%)			
Overall population	27/332 (8.1)	38/331 (11.5)	0.70 (0.43 to 1.15)§‖
Patients with a UIP-like fibrotic pattern	20/206 (9.7)	31/206 (15.0)	0.63 (0.36 to 1.10)§‖

* Changes from baseline are adjusted means ±SE based on the statistical models. The two primary populations for analysis were the overall population and patients with a UIP-like fibrotic pattern.
† For the primary end point, the patients with a UIP-like fibrotic pattern included 206 in each treatment group. The patients with other fibrotic patterns included 126 in the nintedanib group and 125 in the placebo group.
‡ P<0.001.
§ The widths of the confidence intervals have not been adjusted for multiple comparisons, so the intervals should not be used to infer definitive treatment effects.
¶ For the analysis of the scores on the K-BILD questionnaire, 332 patients were included in the nintedanib group and 330 in the placebo group in the overall population; among the patients with a UIP-like fibrotic pattern, included were 206 patients and 205 patients, respectively.
‖ The difference was assessed as a hazard ratio.

group and in 5 patients in the placebo group. No patients in either group had grade 4 or 5 diarrhea. Nausea, vomiting, abdominal pain, decreased appetite, and weight decrease were more frequent in the nintedanib group than in the placebo group. Adverse events that were evaluated during the period until the first database lock were consistent with those reported over the 52-week period (Section O in the Supplementary Appendix).

Hepatic adverse events were more common in patients treated with nintedanib than in those treated with placebo (Table 3). On the basis of laboratory tests, elevations in alanine aminotransferase, aspartate aminotransferase, or both to lev-



No. of Patients								
Overall population								
Nintedanib	332	326	320	322	314	298	285	265
Placebo	331	325	326	325	320	311	296	274
Patients with UIP-like fibrotic pattern								
Nintedanib	206	203	200	199	193	180	171	160
Placebo	206	202	202	201	197	190	176	162

Figure 2. Decline from Baseline in Forced Vital Capacity (FVC).

Shown is the observed mean change from baseline in FVC over the 52-week trial period in the overall population and in patients with an imaging pattern of usual interstitial pneumonia (UIP) on high-resolution computed tomography in the nintedanib group and the placebo group. The I bars indicate the standard error.

els that were at least three times the upper limit of the normal range were observed in 43 patients (13.0%) treated with nintedanib and 6 patients (1.8%) treated with placebo over the 52-week period (Section P in the Supplementary Appendix). One patient in each treatment group had concurrent elevations in liver enzymes and bilirubin that met the criteria for Hy's law. Elevations in liver enzymes were reversible, with a normalization of values or a trend toward normalization on dose reduction and after treatment interruption or discontinuation, along with some instances of spontaneous normalization. The side-effect profile of nintedanib was similar in patients with a UIP-like fibrotic pattern and in those with other fibrotic patterns (Section Q in the Supplementary Appendix).

DISCUSSION

In the INBUILD trial, we enrolled patients who had a broad range of fibrosing interstitial lung diseases, which were identified on the basis of the presence of pulmonary fibrosis on chest imaging and common progressive clinical features. The patients who received nintedanib had a slower progression of interstitial lung disease than those who received placebo, as shown by a lower annual rate of decline in the FVC over the 52-week period, both in the overall trial population and in patients with a UIP-like fibrotic pattern on high-resolution CT. The absolute treatment effects in these patient populations were similar in magnitude to those observed in pooled data from the INPULSIS trials in patients with IPF (a between-group difference of 107.0 ml in the overall population and 128.2 ml in patients with a UIP-like fibrotic pattern in our trial, as compared with a between-group difference of 109.9 ml in the INPULSIS trials). The relatively lower rate of FVC decline with nintedanib than with placebo was similar in patients with a UIP-like fibrotic pattern and in those with other fibrotic patterns. Changes in health-related quality of life, as measured on the K-BILD questionnaire over the 52-week period, were small in the two treatment groups.

The safety and side-effect profile of nintedanib

Table 3. Adverse Events in the Overall Population.*

Event	Nintedanib (N=332)	Placebo (N=331)
	no. of patients (%)	
Adverse event		
Any	317 (95.5)	296 (89.4)
Any except for progression of interstitial lung disease†	317 (95.5)	295 (89.1)
Most frequent adverse events‡		
Diarrhea	222 (66.9)	79 (23.9)
Nausea	96 (28.9)	31 (9.4)
Bronchitis	41 (12.3)	47 (14.2)
Nasopharyngitis	44 (13.3)	40 (12.1)
Dyspnea	36 (10.8)	44 (13.3)
Vomiting	61 (18.4)	17 (5.1)
Cough	33 (9.9)	44 (13.3)
Decreased appetite	48 (14.5)	17 (5.1)
Headache	35 (10.5)	23 (6.9)
Alanine aminotransferase increased	43 (13.0)	12 (3.6)
Progression of interstitial lung disease†	16 (4.8)	39 (11.8)
Weight loss	41 (12.3)	11 (3.3)
Aspartate aminotransferase increased	38 (11.4)	12 (3.6)
Abdominal pain	34 (10.2)	8 (2.4)
Severe adverse event§	60 (18.1)	73 (22.1)
Serious adverse event¶	107 (32.2)	110 (33.2)
Fatal adverse event		
Any	11 (3.3)	17 (5.1)
Any except for progression of interstitial lung disease†	10 (3.0)	14 (4.2)
Adverse event leading to treatment discontinuation	65 (19.6)	34 (10.3)
Adverse event leading to permanent dose reduction	110 (33.1)	14 (4.2)

* Listed are adverse events that were reported over the 52-week trial period or until 28 days after the last dose in patients who discontinued nintedanib or placebo before week 52.

† The phrase "progression of interstitial lung disease" was based on the preferred term "interstitial lung disease" in the *Medical Dictionary for Regulatory Activities* (MedDRA).

‡ Listed are adverse events that were reported in more than 10% of the patients in either treatment group. These events were coded with the use of preferred terms in MedDRA.

§ A severe adverse event was defined as an event that was incapacitating or that caused an inability to work or to perform usual activities.

¶ A serious adverse event was defined as an event that resulted in death, in hospitalization or prolongation of hospitalization, or in persistent or clinically significant disability or incapacity; or was life-threatening, a congenital anomaly or birth defect, or deemed to be serious for any other reason.

in patients with progressive fibrosing interstitial lung diseases was similar to that observed in patients with IPF[27] and systemic sclerosis-associated interstitial lung disease.[14] More patients stopped nintedanib than stopped placebo because of adverse effects, with diarrhea being the most common adverse event. Liver-enzyme elevations were more frequently observed in patients in the nintedanib group than in the placebo group.

Beyond exploring the effects of nintedanib, the INBUILD trial provided insights into the natural history of progressive fibrosing interstitial lung diseases. The annual rates of decline in the FVC in placebo-treated patients in the overall population and in patients with a UIP-like fibrotic pattern were similar to those seen in pooled data from the INPULSIS trials in patients who met a case definition for IPF (–187.8 ml per year, –211.1 ml per year, and –223.5 ml per year, respectively). In our trial, the rate of decline in the FVC in placebo-treated patients with other (non–UIP-like) fibrotic patterns (–154.2 ml per year) was only slightly lower than that in patients with a UIP-like fibrotic pattern and was still clinically relevant, a finding that was consistent with previous observations.[15-18] These data support the hypothesis that progressive fibrosing interstitial lung diseases, regardless of clinical diagnosis, have a similar pathobiologic mechanism.

In conclusion, we found that patients who received nintedanib had a slower rate of progression of interstitial lung disease than those who received placebo, independent of the fibrotic pattern on high-resolution CT. This change in physiological outcomes was not accompanied by meaningful changes in measures of quality of life, although nintedanib was associated with a higher frequency of diarrhea, nausea, and vomiting.

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APPENDIX

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