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Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

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ABSTRACT

BACKGROUND

Nintedanib (formerly known as BIBF 1120) is an intracellular inhibitor that targets multiple tyrosine kinases. A phase 2 trial suggested that treatment with 150 mg of nintedanib twice daily reduced lung-function decline and acute exacerbations in patients with idiopathic pulmonary fibrosis.

METHODS

We conducted two replicate 52-week, randomized, double-blind, phase 3 trials (INPULSIS-1 and INPULSIS-2) to evaluate the efficacy and safety of 150 mg of nintedanib twice daily as compared with placebo in patients with idiopathic pulmonary fibrosis. The primary end point was the annual rate of decline in forced vital capacity (FVC). Key secondary end points were the time to the first acute exacerbation and the change from baseline in the total score on the St. George's Respiratory Questionnaire, both assessed over a 52-week period.

RESULTS

A total of 1066 patients were randomly assigned in a 3:2 ratio to receive nintedanib or placebo. The adjusted annual rate of change in FVC was –114.7 ml with nintedanib versus –239.9 ml with placebo (difference, 125.3 ml; 95% confidence interval [CI], 77.7 to 172.8; P<0.001) in INPULSIS-1 and –113.6 ml with nintedanib versus –207.3 ml with placebo (difference, 93.7 ml; 95% CI, 44.8 to 142.7; P<0.001) in INPULSIS-2. In INPULSIS-1, there was no significant difference between the nintedanib and placebo groups in the time to the first acute exacerbation (hazard ratio with nintedanib, 1.15; 95% CI, 0.54 to 2.42; P=0.67); in INPULSIS-2, there was a significant benefit with nintedanib versus placebo (hazard ratio, 0.38; 95% CI, 0.19 to 0.77; P=0.005). The most frequent adverse event in the nintedanib groups was diarrhea, with rates of 61.5% and 18.6% in the nintedanib and placebo groups, respectively, in INPULSIS-1 and 63.2% and 18.3% in the two groups, respectively, in INPULSIS-2.

CONCLUSIONS

In patients with idiopathic pulmonary fibrosis, nintedanib reduced the decline in FVC, which is consistent with a slowing of disease progression; nintedanib was frequently associated with diarrhea, which led to discontinuation of the study medication in less than 5% of patients. (Funded by Boehringer Ingelheim; INPULSIS-1 and INPULSIS-2 ClinicalTrials.gov numbers, NCT01335464 and NCT01335477.)

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

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Idiopathic pulmonary fibrosis is a fatal lung disease characterized by worsening dyspnea and progressive loss of lung function.[1] A decline in forced vital capacity (FVC) is consistent with disease progression and is predictive of reduced survival time.[1-6]

Idiopathic pulmonary fibrosis is believed to arise from an aberrant proliferation of fibrous tissue and tissue remodeling due to the abnormal function and signaling of alveolar epithelial cells and interstitial fibroblasts.[7] The activation of cell-signaling pathways through tyrosine kinases such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) has been implicated in the pathogenesis of the disease.[8-10]

Nintedanib (formerly known as BIBF 1120) is an intracellular inhibitor that targets multiple tyrosine kinases, including the VEGF, FGF, and PDGF receptors.[11] The results of an earlier trial (To Improve Pulmonary Fibrosis with BIBF 1120 [TOMORROW]), a randomized, double-blind, placebo-controlled, phase 2 dose-finding study involving 432 patients with idiopathic pulmonary fibrosis, suggested that 12 months of treatment with 150 mg of nintedanib twice daily was associated with a reduced decline in FVC, fewer acute exacerbations, and the preservation of health-related quality of life.[12] We conducted two replicate phase 3 trials (INPULSIS-1 and INPULSIS-2) to evaluate the efficacy and safety of treatment with 150 mg of nintedanib twice daily in patients with idiopathic pulmonary fibrosis.

Methods

Study Design and Oversight

The INPULSIS studies were randomized, double-blind, placebo-controlled, parallel-group trials performed at 205 sites in 24 countries in the Americas, Europe, Asia, and Australia. An independent data monitoring committee regularly reviewed the data, particularly serious adverse events, adverse events leading to discontinuation of the study drug, and the results of laboratory analyses, and made recommendations concerning the continuation of the trials. An adjudication committee that was independent of the investigators and whose members were unaware of the group assignments reviewed medical documentation to adjudicate the primary cause of all deaths. The committee also adjudicated all adverse events reported by site investigators as acute exacerbations, in order to determine whether the events met the criteria for an acute exacerbation of idiopathic pulmonary fibrosis as defined in the protocol, available with the full text of this article at NEJM.org. The members of these committees are listed in Section B in the Supplementary Appendix, also available at NEJM.org.

Both trials were conducted in accordance with the principles of the Declaration of Helsinki and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization and were approved by local authorities. The clinical protocol was approved by an independent ethics committee or institutional review board at each participating center. All patients provided written informed consent before study entry.

All the authors were involved in the design of the study and had access to the data, which were analyzed by the study sponsor, Boehringer Ingelheim. All the authors vouch for the accuracy and completeness of the data analyses and the fidelity of each study to the protocol. The protocol and statistical analysis plans are available at NEJM.org. The manuscript was drafted by the first, second, and last authors and revised by all the authors. Medical writing assistance, paid for by Boehringer Ingelheim, was provided by the Fleishman-Hillard Group.

Patients

Patients were eligible to participate in the two trials if they were 40 years of age or older and had received a diagnosis of idiopathic pulmonary fibrosis within the previous 5 years. Additional eligibility criteria were an FVC that was 50% or more of the predicted value, a diffusion capacity of the lung for carbon monoxide (DLCO) that was 30 to 79% of the predicted value, and high-resolution computed tomography (HRCT) of the chest performed within the previous 12 months. HRCT images (for all patients) and lung-biopsy specimens (if available) were reviewed centrally by a single radiologist and a single pathologist to verify eligibility according to the protocol. Eligibility criteria with regard to findings on HRCT and surgical lung biopsy are shown in Table S1 and Table S2, respectively, in the Supplementary Appendix.

Concomitant therapy with up to 15 mg of prednisone per day, or the equivalent, was permitted if the dose had been stable for 8 or more

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weeks before screening; patients receiving other therapies for idiopathic pulmonary fibrosis, including high-dose prednisone, azathioprine, *N*-acetylcysteine, and any investigational treatments for idiopathic pulmonary fibrosis, were excluded. After 6 months of study treatment, patients whose condition had deteriorated could receive azathioprine, cyclophosphamide, cyclosporine, *N*-acetylcysteine, or more than 15 mg of prednisone per day, or the equivalent, at the discretion of the investigator. In cases of acute exacerbation reported by an investigator at any time during the trial, any treatments could be initiated or doses increased as deemed appropriate by the investigator. Other key exclusion criteria are listed in Section C in the Supplementary Appendix.

STUDY PROTOCOL

After a screening period, eligible patients were randomly assigned in a 3:2 ratio to receive 150 mg of nintedanib twice daily or placebo for 52 weeks. An interactive telephone and Web-based response system was used to perform randomization. Patients, investigators, and the study sponsor were unaware of the study-group assignments throughout the study. Completion of the 52-week treatment period was followed by a follow-up visit 4 weeks later. Spirometric tests were conducted at baseline; at 2, 4, 6, 12, 24, 36, and 52 weeks; and at the follow-up visit. Spirometric testing was conducted in accordance with criteria published by the American Thoracic Society and the European Respiratory Society.[13] All spirometric measurements were performed on machines provided by the sponsor, and the results were centrally reviewed, with training and ongoing feedback provided for the site investigators.

Dose interruption or reduction of the dose from 150 mg twice daily to 100 mg twice daily was allowed for the management of adverse events. After an adverse event had resolved, the dose could be reinstituted at 150 mg twice daily. The site investigators were provided with recommendations for the management of diarrhea and elevated levels of liver enzymes. To minimize the amount of missing data, patients who discontinued the study drug prematurely were asked to attend all scheduled visits and to undergo all examinations as originally planned. For patients who discontinued the drug prematurely but did not agree to attend all visits, data on vital status were collected at week 52.

END POINTS

The primary end point for both INPULSIS trials was the annual rate of decline in FVC (measured in milliliters per year). Key secondary end points were the time to the first acute exacerbation (as reported by a site investigator) and the change from baseline in the total score on the St. George's Respiratory Questionnaire (SGRQ), both assessed over the 52-week treatment period. The SGRQ is a self-administered questionnaire that is used to assess health-related quality of life. It comprises three domains (symptoms, activity, and impact). The total score and the score for each domain range from 0 to 100, with higher scores indicating worse health-related quality of life.[14,15] A minimally important difference in the score has not been established for patients with idiopathic pulmonary fibrosis; in patients with chronic obstructive pulmonary disease, this difference is 4 points.[16] Patients completed the SGRQ at baseline and at 6, 12, 24, and 52 weeks. Acute exacerbations were defined as events meeting all of the following criteria: unexplained worsening or development of dyspnea within the previous 30 days; new diffuse pulmonary infiltrates visualized on chest radiography, HRCT, or both, or the development of parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities) since the preceding visit; and exclusion of any known causes of acute worsening, including infection, left heart failure, pulmonary embolism, and any identifiable cause of acute lung injury, in accordance with routine clinical practice and microbiologic studies. All acute exacerbations reported by the site investigators were categorized by the adjudication committee, whose members were unaware of the study-group assignments, as confirmed or suspected or were not considered to be an acute exacerbation according to prespecified criteria.[17]

Other prespecified secondary end points included the absolute change from baseline in FVC (in milliliters and as a percentage of the predicted value) over the 52-week treatment period, the proportion of patients with an FVC response (defined as the proportion of patients in whom the percentage of predicted FVC did not decline by more than 5 percentage points or by more than 10 percentage points at week 52), the risk of an acute exacerbation, the change from baseline in SGRQ domain scores over the 52-week treatment period, death from any cause, death

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from a respiratory cause, and death that occurred between randomization and 28 days after the last dose of the study drug. All mortality end points were measured as the time to death. Safety was assessed by means of clinical and laboratory evaluation at study visits and the recording of adverse events.

STATISTICAL ANALYSIS

Efficacy and safety analyses were conducted for patients who were randomly assigned to a study group and received at least one dose of the study medication. The primary end point was analyzed with the use of a random coefficient regression model (with random slopes and intercepts) that included sex, age, and height as covariates. The treatment effect was determined by using estimated slopes for each study group (on the basis of the time-by-treatment interaction term from the mixed model). All available FVC values from baseline to week 52 were used in the primary model, including FVC measurements at the follow-up visit for patients who discontinued the study medication prematurely and did not complete the study visits through week 52. The statistical model used for the primary analysis allowed for missing data, assuming that they were missing at random; missing data were not imputed for the primary analysis, but data collected after discontinuation of the study drug were used in the primary analysis. Significance tests were two-sided, with an alpha value of 0.05.

The superiority of nintedanib over placebo with respect to the primary and key secondary end points was tested with the use of a hierarchical procedure to account for multiple comparisons (see Section D in the Supplementary Appendix). Sensitivity analyses were performed to assess the robustness of the results for the primary and key secondary end points. Multiple imputation sensitivity analyses were performed to assess the effect of missing data and provide estimates of the treatment effect under different assumptions about missing data (Fig. S2 in the Supplementary Appendix). For the time to the first acute exacerbation, a sensitivity analysis based on the occurrence of confirmed or suspected acute exacerbations (as determined by the adjudication committee) in pooled data from the two trials was prespecified.

The frequency and severity of adverse events were documented according to the *Medical Dictionary for Regulatory Activities*, version 16.1. Safety analyses were descriptive. For information on the statistical analysis of other end points, see Section D in the Supplementary Appendix.

For each trial, the sample size was calculated to provide 90% power to detect a between-group difference of 100 ml in the annual rate of FVC decline. On the basis of data from the phase 2 trial, the standard deviation for the change in FVC from baseline was assumed to be 300 ml in both groups. Assuming that it would not be possible to evaluate data for 2% of patients, the sample size was calculated as 194 patients in the placebo group and 291 patients in the nintedanib group for a two-group t-test at a one-sided significance level of 2.5%. Since the primary analysis was based on a random coefficient regression model that included adjustment for several variables and took into account information across time, we expected that the power would be greater than the 90% calculated for the t-test.

RESULTS

PATIENTS

Between May 2011 and September 2012, a total of 1066 patients underwent randomization: 515 patients in INPULSIS-1 and 551 patients in INPULSIS-2 (Fig. S1 in the Supplementary Appendix). In INPULSIS-1, a total of 513 patients received at least one dose of the study medication (309 received nintedanib and 204 received placebo). A total of 78 patients (25.2%) in the nintedanib group and 36 patients (17.6%) in the placebo group discontinued the study medication prematurely. Of these patients, 31 (39.7%) in the nintedanib group and 11 (30.6%) in the placebo group completed visits up to week 52. The most frequent reason for premature discontinuation of the study medication was at least one adverse event (65 patients [21.0%] in the nintedanib group and 24 [11.8%] in the placebo group). In INPULSIS-2, a total of 548 patients received at least one dose of the study medication (329 received nintedanib and 219 received placebo). A total of 78 patients (23.7%) in the nintedanib group and 44 patients (20.1%) in the placebo group discontinued the study medication prematurely. Of these patients, 26 (33.3%) in the nintedanib group and 10 (22.7%) in the placebo group completed visits up to week 52. The most frequent reason for premature discontinu-

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ation of the study medication was at least one adverse event (62 patients [18.8%] in the nintedanib group and 35 [16.0%] in the placebo group). The proportion of patients with missing FVC data at week 52 was approximately 15%; the proportion of patients with missing data did not differ significantly between the nintedanib and placebo groups (Fig. S2 in the Supplementary Appendix).

In each trial, the baseline characteristics of patients in the nintedanib and placebo groups were similar (Table 1, and Table S3 in the Supplementary Appendix). The mean duration of exposure to the study drug in the nintedanib and placebo groups was similar (approximately 45 weeks in each trial), but a higher proportion of patients in the nintedanib group than in the placebo group had dose reductions or interrup-

Table 1. Baseline Characteristics of Patients in INPULSIS-1 and INPULSIS-2.*

Characteristic	INPULSIS-1		INPULSIS-2	
	Nintedanib (N=309)	Placebo (N=204)	Nintedanib (N=329)	Placebo (N=219)
Male sex — no. (%)	251 (81.2)	163 (79.9)	256 (77.8)	171 (78.1)
Age — yr	66.9±8.4	66.9±8.2	66.4±7.9	67.1±7.5
Weight — kg	82.0±16.8	81.2±16.3	76.6±15.9	76.3±16.5
Body-mass index†	28.6±4.5	28.1±4.6	27.6±4.6	27.2±4.5
Smoking status — no. (%)				
Never smoked	71 (23.0)	51 (25.0)	103 (31.3)	71 (32.4)
Former smoker	217 (70.2)	144 (70.6)	218 (66.3)	139 (63.5)
Current smoker	21 (6.8)	9 (4.4)	8 (2.4)	9 (4.1)
Time since diagnosis of idiopathic pulmonary fibrosis — yr	1.7±1.4	1.6±1.4	1.6±1.3	1.6±1.3
Specimen from surgical lung biopsy available — no. (%)	60 (19.4)	33 (16.2)	84 (25.5)	52 (23.7)
Systemic corticosteroid therapy — no. (%)‡	68 (22.0)	43 (21.1)	68 (20.7)	46 (21.0)
FVC				
Mean — ml	2757±735	2845±820	2673±776	2619±787
Median — ml	2700	2721	2615	2591
Percentage of predicted value	79.5±17.0	80.5±17.3	80.0±18.1	78.1±19.0
FEV_1:FVC (%)	81.5±5.4	80.8±6.1	81.8±6.3	82.4±5.7
DLCO				
mmol/min/kPa	4.0±1.2	4.0±1.1	3.8±1.2	3.7±1.3
Percentage of predicted value§	47.8±12.3	47.5±11.7	47.0±14.5	46.4±14.8
SpO_2 — %	95.9±2.0	95.9±1.9	95.8±2.6	95.7±2.1
Total SGRQ score¶	39.6±17.6	39.8±18.5	39.5±20.5	39.4±18.7

* Plus–minus values are means ±SD. FEV_1 denotes forced expiratory volume in 1 second, FVC forced vital capacity, and SpO_2 oxygen saturation of peripheral blood.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Prednisone at a dose of no more than 15 mg per day or the equivalent was permitted if the dose had been stable for at least 8 weeks before screening.
§ The percentage of the predicted value for the diffusion capacity of the lung for carbon monoxide (DLCO) was calculated with the use of the equation described by the European Community for Steel and Coal in Cotes et al.[18] In INPULSIS-2, data were available for 218 patients in the placebo group.
¶ In INPULSIS-1, the total score on the St. George's Respiratory Questionnaire (SGRQ) was available for 298 patients in the nintedanib group and 202 patients in the placebo group; in INPULSIS-2, the total SGRQ score was available for 326 patients in the nintedanib group and 217 patients in the placebo group. The total score ranges from 0 to 100, with higher scores indicating worse health-related quality of life.

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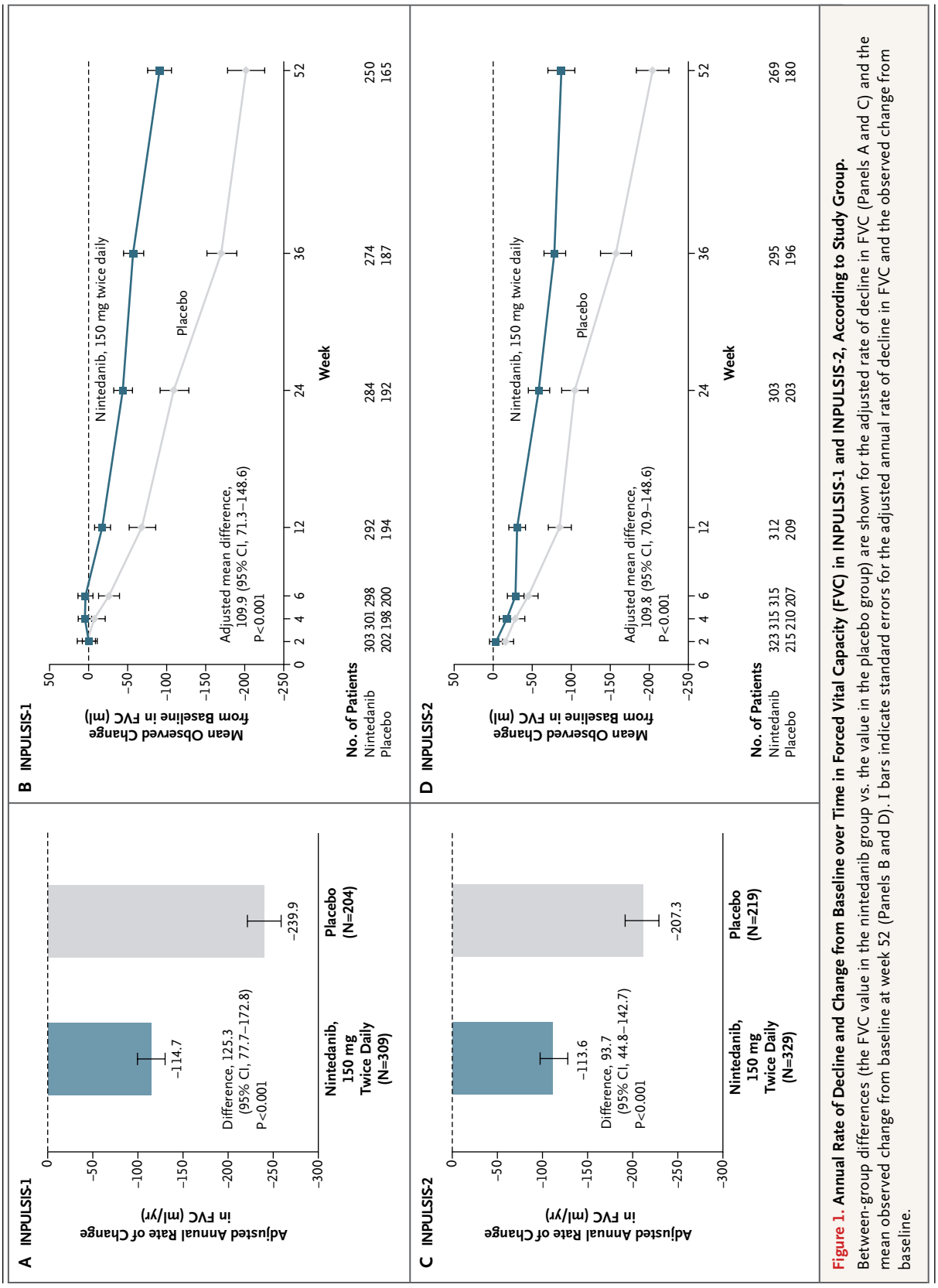

Figure 1. Annual Rate of Decline and Change from Baseline over Time in Forced Vital Capacity (FVC) in INPULSIS-1 and INPULSIS-2, According to Study Group.

Between-group differences (the FVC value in the nintedanib group vs. the value in the placebo group) are shown for the adjusted rate of decline in FVC (Panels A and C) and the mean observed change from baseline at week 52 (Panels B and D). I bars indicate standard errors for the adjusted annual rate of decline in FVC and the observed change from baseline.

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tions (Table S4 in the Supplementary Appendix). The dose intensity — the amount of drug administered divided by the amount that would have been administered had the regimen of 150 mg twice daily been followed throughout the study or until permanent discontinuation of the study medication — was more than 90% in 75.9% of patients in the nintedanib groups.

LUNG FUNCTION

In both trials, the adjusted annual rate of change in FVC was significantly lower in the nintedanib group than in the placebo group. In INPULSIS-1, the rate was –114.7 ml per year in the nintedanib group as compared with –239.9 ml per year in the placebo group, representing a difference of 125.3 ml per year (95% confidence interval [CI], 77.7 to 172.8; P<0.001) (Fig. 1A). In INPULSIS-2, the rate was –113.6 ml per year in the nintedanib group as compared with –207.3 ml per year in the placebo group, representing a difference of 93.7 ml per year (95% CI, 44.8 to 142.7; P<0.001) (Fig. 1C). In both trials, the results of prespecified sensitivity analyses were consistent with the results of the primary analysis (Fig. S2 in the Supplementary Appendix). In particular, in the multiple imputation analyses, which were based on the conservative assumption that missing data were informative rather than random, the estimates of treatment effect and the corresponding confidence intervals were consistent with the results of the primary analysis in each study. This finding shows that the primary results are robust and were not influenced by alternative assumptions about missing data. In addition, the mean observed changes in FVC over time (unadjusted, nonimputed results) were consistent with the results of the primary analysis in both trials (Fig. 1B and 1D).

In each trial, a significantly greater proportion of patients in the nintedanib group than in the placebo group had a response in FVC when patients with a response were defined as those who did not have an absolute decline in the percentage of predicted FVC that was more than 5 percentage points at week 52 (Table 2). When patients with a response in FVC were defined as those who did not have an absolute decline in the percentage of predicted FVC that was more than 10 percentage points at week 52, a significantly greater proportion of patients in the nintedanib group than in the placebo group had a response

Table 2. Secondary Lung-Function End Points at Week 52.

End Point	INPULSIS-1				INPULSIS-2			
	Nintedanib (N=307)	Placebo (N=204)	Difference, Nintedanib vs. Placebo (95% CI)	P Value	Nintedanib (N=327)	Placebo (N=217)	Difference, Nintedanib vs. Placebo (95% CI)	P Value
Adjusted absolute mean change from baseline in FVC — ml	–95.1	–205.0	109.9 (71.3 to 148.6)	<0.001	–95.3	–205.0	109.8 (70.9 to 148.6)	<0.001
Adjusted absolute mean change from baseline in FVC — % of predicted value	–2.8	–6.0	3.2 (2.1 to 4.3)	<0.001	–3.1	–6.2	3.1 (1.9 to 4.3)	<0.001
FVC response at wk 52 — no. (%)*								
FVC decline ≤5 percentage points	163 (52.8)	78 (38.2)	1.85 (1.28 to 2.66)	0.001	175 (53.2)	86 (39.3)	1.79 (1.26 to 2.55)	0.001
FVC decline ≤10 percentage points	218 (70.6)	116 (56.9)	1.91 (1.32 to 2.79)	<0.001	229 (69.6)	140 (63.9)	1.29 (0.89 to 1.86)	0.18

* Between-group differences are expressed as odds ratios for FVC response. FVC decline denotes an absolute decline in the percentage of the predicted value. For the FVC response at week 52, there was a total of 309 participants in the nintedanib group in INPULSIS-1 and a total of 329 participants in the nintedanib group and 219 participants in the placebo group in INPULSIS-2.

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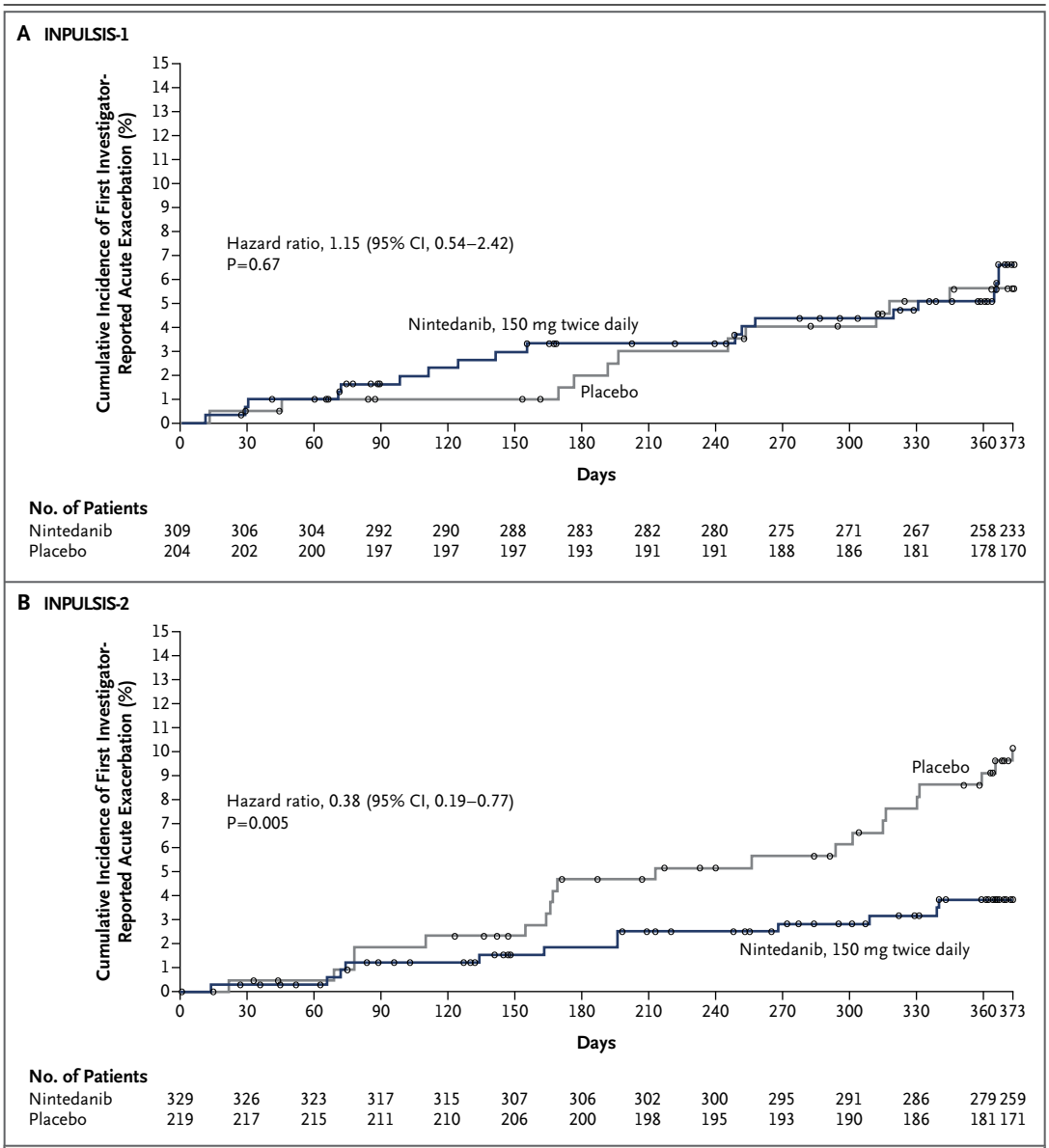

Figure 2. Time to First Investigator-Reported Acute Exacerbation in INPULSIS-1 and INPULSIS-2.

in INPULSIS-1; in INPULSIS-2, the difference between the groups was not significant.

A prespecified pooled analysis of the primary end point showed a significant treatment effect, (between-group difference in the annual rate of FVC change, –109.9 ml [95% CI, 75.9 to –144.0]) (Fig. S3A in the Supplementary Appendix). Pooled data on the absolute change from baseline in FVC are shown in Table S5 and Figure S3B in the Supplementary Appendix. A prespecified pooled analysis of data from the two trials showed that a significantly greater proportion of patients in the nintedanib group than in the placebo group had an FVC response with both definitions of a response (a decline in the percentage of predicted FVC that was not more than 5 percentage points and a decline that was not more than 10 percentage points at week 52) (Table S5 in the Supplementary Appendix).

ACUTE EXACERBATIONS

In INPULSIS-1, there was no significant difference between the nintedanib and placebo groups in the time to the first acute exacerbation (haz-

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ard ratio in the nintedanib group, 1.15; 95% CI, 0.54 to 2.42; P=0.67) (Fig. 2A), and the proportion of patients with at least one investigator-reported acute exacerbation was similar in the nintedanib and placebo groups (6.1% and 5.4%, respectively). In INPULSIS-2, there was a significant increase in the time to the first acute exacerbation in the nintedanib group as compared with the placebo group (hazard ratio, 0.38; 95% CI, 0.19 to 0.77; P=0.005) (Fig. 2B), and the proportion of patients with at least one investigator-reported acute exacerbation was lower in the nintedanib group than in the placebo group (3.6% vs. 9.6%). In the prespecified pooled analysis, there was no significant difference between the nintedanib and placebo groups in time to first investigator-reported acute exacerbation (hazard ratio, 0.64; 95% CI, 0.39 to 1.05; P=0.08); the proportion of patients with at least one investigator-reported acute exacerbation was 4.9% in the nintedanib group and 7.6% in the placebo group (Fig. S4 and S5 in the Supplementary Appendix). A prespecified sensitivity analysis of pooled data on the time to the first adjudicated acute exacerbation (confirmed or suspected) showed that nintedanib had a significant benefit as compared with placebo (Table S6 and Fig. S6 in the Supplementary Appendix).

SGRQ Score

In INPULSIS-1, there was no significant between-group difference in the adjusted mean change in the total SGRQ score from baseline to week 52 (4.34 points in the nintedanib group and 4.39 points in the placebo group; difference, −0.05; 95% CI, −2.50 to 2.40; P=0.97); in INPULSIS-2, there was a significantly smaller increase in the total SGRQ score at week 52 (consistent with less deterioration in health-related quality of life) in the nintedanib group than in the placebo group (2.80 points vs. 5.48 points; difference, −2.69; 95% CI, −4.95 to −0.43; P=0.02) (Fig. S7A and S7B in the Supplementary Appendix).

In the prespecified pooled analysis of the total SGRQ score, there was no significant difference in the adjusted mean change from baseline to week 52 between the nintedanib and placebo groups (difference, −1.43 points; 95% CI, −3.09 to 0.23; P=0.09) (Fig. S7C in the Supplementary Appendix). Changes from baseline in SGRQ domain scores were consistent with the changes in the total SGRQ score in each trial (Tables S7A and S7B in the Supplementary Appendix) and in the pooled analysis (Table S7C in the Supplementary Appendix).

Deaths

In the prespecified pooled analysis, there was no significant between-group difference in death from any cause, death from a respiratory cause, or death that occurred between randomization and 28 days after the last dose of the study drug (Table S8 in the Supplementary Appendix). The proportion of patients who died from any cause over the 52-week treatment period was 5.5% in the nintedanib group and 7.8% in the placebo group (hazard ratio in the nintedanib group, 0.70; 95% CI, 0.43 to 1.12; P=0.14) (Fig. S8 in the Supplementary Appendix).

Adverse Events

The most frequent adverse event in the nintedanib groups in both trials was diarrhea (Table 3). Among the patients in the nintedanib groups who had diarrhea, most reported events that were of mild or moderate intensity (93.7% in INPULSIS-1 and 95.2% in INPULSIS-2). Diarrhea led to premature discontinuation of the study drug in 14 patients receiving nintedanib (4.5%) and none of the patients receiving placebo in INPULSIS-1 and in 14 patients receiving nintedanib (4.3%) and 1 receiving placebo (0.5%) in INPULSIS-2.

In both trials, the proportion of patients with serious adverse events was similar in the nintedanib and placebo groups (Table 3). In INPULSIS-1, serious adverse events were reported in 31.1% of patients in the nintedanib group and in 27.0% of patients in the placebo group; in INPULSIS-2, the percentages were 29.8% and 32.9%, respectively.

In both trials, a higher proportion of patients in the nintedanib groups than in the placebo groups had elevated levels of liver enzymes (Table S9 in the Supplementary Appendix). In INPULSIS-1, a total of 15 patients in the nintedanib group (4.9%) and 1 patient in the placebo group (0.5%) had levels of aspartate aminotransferase, alanine aminotransferase, or both that were three or more times the upper limit of the normal range. In INPULSIS-2, a total of 17 patients in the nintedanib group (5.2%) and 2 patients in the placebo group (0.9%) had such elevations.

Among the infrequent events (those occurring

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Table 3. Adverse Events.

Event	INPULSIS-1		INPULSIS-2	
	Nintedanib (N=309)	Placebo (N=204)	Nintedanib (N=329)	Placebo (N=219)
	number of patients (percent)			
Any adverse event	298 (96.4)	181 (88.7)	311 (94.5)	198 (90.4)
Any adverse event, excluding progression of idiopathic pulmonary fibrosis*	296 (95.8)	179 (87.7)	311 (94.5)	197 (90.0)
Most frequent adverse events†				
Diarrhea	190 (61.5)	38 (18.6)	208 (63.2)	40 (18.3)
Nausea	70 (22.7)	12 (5.9)	86 (26.1)	16 (7.3)
Nasopharyngitis	39 (12.6)	34 (16.7)	48 (14.6)	34 (15.5)
Cough	47 (15.2)	26 (12.7)	38 (11.6)	31 (14.2)
Progression of idiopathic pulmonary fibrosis*	31 (10.0)	21 (10.3)	33 (10.0)	40 (18.3)
Bronchitis	36 (11.7)	28 (13.7)	31 (9.4)	17 (7.8)
Upper respiratory tract infection	28 (9.1)	18 (8.8)	30 (9.1)	24 (11.0)
Dyspnea	22 (7.1)	23 (11.3)	27 (8.2)	25 (11.4)
Decreased appetite	26 (8.4)	14 (6.9)	42 (12.8)	10 (4.6)
Vomiting	40 (12.9)	4 (2.0)	34 (10.3)	7 (3.2)
Weight loss	25 (8.1)	13 (6.4)	37 (11.2)	2 (0.9)
Severe adverse events‡	81 (26.2)	37 (18.1)	93 (28.3)	62 (28.3)
Serious adverse events‡	96 (31.1)	55 (27.0)	98 (29.8)	72 (32.9)
Fatal adverse events	12 (3.9)	10 (4.9)	25 (7.6)	21 (9.6)
Adverse events leading to treatment discontinuation§	65 (21.0)	22 (10.8)	58 (17.6)	33 (15.1)
Gastrointestinal disorders	26 (8.4)	3 (1.5)	21 (6.4)	2 (0.9)
Respiratory, thoracic, and mediastinal disorders	12 (3.9)	10 (4.9)	8 (2.4)	18 (8.2)
Investigation results¶	10 (3.2)	1 (0.5)	8 (2.4)	1 (0.5)
Cardiac disorders	5 (1.6)	4 (2.0)	2 (0.6)	3 (1.4)
General disorders and conditions involving site of study-drug administration‖	8 (2.6)	3 (1.5)	2 (0.6)	1 (0.5)

* Progression of idiopathic pulmonary fibrosis was defined in accordance with the definition of idiopathic pulmonary fibrosis in the *Medical Dictionary for Regulatory Activities*, version 16.1, which includes disease worsening and exacerbations of idiopathic pulmonary fibrosis.

† The most frequent adverse events were defined as those with an incidence of more than 10% in any study group.

‡ A severe adverse event was related to intensity and 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 any adverse event that resulted in death, was immediately life-threatening, resulted in persistent or clinically significant disability or incapacity, required or prolonged hospitalization, was related to a congenital anomaly or birth defect, or was deemed serious for any other reason.

§ Adverse events leading to study-drug discontinuation were reported when they occurred in 2% or more of patients in any study group and are listed according to system organ class. The analysis included adverse events with an onset after administration of the first dose of study medication and up to 28 days after administration of the last dose.

¶ Investigation results refer to the results of clinical laboratory tests, radiologic tests, physical examination, and physiologic tests.

‖ These events include disorders or conditions that involve several body systems or sites, including chest pain, fatigue, asthenia, and general deterioration of physical health.

in less than 2% of a study group) that were of potential clinical importance, myocardial infarction was reported in 5 patients in the nintedanib group (1.6%) and 1 patient in the placebo group (0.5%) in INPULSIS-1, and in 5 patients in the nintedanib group (1.5%) and 1 patient in the placebo group (0.5%) in INPULSIS-2. In total, two events in the nintedanib groups and one event in

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the placebo groups were fatal. Occurrences of adverse events related to cardiac disorders, including ischemic heart disease, are summarized in Table S10 in the Supplementary Appendix.

DISCUSSION

In both the INPULSIS trials, nintedanib significantly reduced the rate of decline in FVC over the 52-week treatment period. The robustness of this finding was supported by the results of all prespecified sensitivity analyses, including those assessing alternative ways of handling missing data. The treatment effect for the annual rate of decline in FVC was consistent with the treatment effect for the absolute change from baseline in FVC. The curves for changes from baseline in FVC over time in the nintedanib and placebo groups separated early in the two studies and continued to diverge over time.

A smaller proportion of patients in the nintedanib groups than in the placebo groups had an absolute decline in the percentage of predicted FVC of more than 5 percentage points, an observation that supports the clinical relevance of the results. No consistent effect of nintedanib on the time to the first acute exacerbation or on the change in the total SGRQ score was observed in the two trials. This difference in the key secondary end point results between INPULSIS-1 and INPULSIS-2 was not explained by the differences in baseline characteristics between the trials.

Acute exacerbations of idiopathic pulmonary fibrosis are events of major clinical significance that are associated with high morbidity and mortality.[17,19] The INPULSIS trials showed that the effect of nintedanib was inconsistent with respect to the risk of investigator-reported acute exacerbations. Exacerbations are relatively rare events in patients with idiopathic pulmonary fibrosis who are in clinical trials and are difficult to assess and categorize, which may explain some of the heterogeneity in our findings.[20]

In both trials, the most frequent adverse events in the nintedanib groups were gastrointestinal in nature, with the majority of patients who received nintedanib reporting diarrhea. However, the proportion of patients in the nintedanib groups with diarrhea that led to premature discontinuation of the study medication was less than 5% (4.5% in INPULSIS-1 and 4.3% in INPULSIS-2). In both trials, the mean dose intensity in the nintedanib groups was greater than 90%. These results show that although adverse events associated with nintedanib treatment were not infrequent, the dosing regimen used in the INPULSIS trials was successful in minimizing treatment discontinuations. Although serious adverse events reflecting ischemic heart disease were balanced between the nintedanib and placebo groups, a higher percentage of patients in the nintedanib groups had myocardial infarctions. The clinical significance of this finding is unknown, and further observation in larger cohorts is needed.

In conclusion, data from the INPULSIS trials show that in patients with idiopathic pulmonary fibrosis, nintedanib reduced the decline in FVC, which is consistent with a slowing of disease progression. There were significant differences in favor of nintedanib for the time to the first acute exacerbation and the change from baseline in the total SGRQ score in INPULSIS-2 but not in INPULSIS-1. Adverse events were common in the nintedanib groups in both trials; nonetheless, most patients continued to receive nintedanib for the duration of the treatment period.

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APPENDIX

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REFERENCES

1. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement — idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011; 183:788-824.
2. du Bois RM, Weycker D, Albera C, et al. Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. Am J Respir Crit Care Med 2011;184: 1382-9.
3. Collard HR, King TE Jr, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2003;168:538-42.
4. Flaherty KR, Mumford JA, Murray S, et al. Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. Am J Respir Crit Care Med 2003;168:543-8.
5. Latsi PI, du Bois RM, Nicholson AG, et al. Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends. Am J Respir Crit Care Med 2003;168:531-7.
6. King TE Jr, Safrin S, Starko KM, et al. Analyses of efficacy end points in a controlled trial of interferon-gamma1b for idiopathic pulmonary fibrosis. Chest 2005; 127:171-7.
7. King TE Jr, Pardo A, Selman M. Idiopathic pulmonary fibrosis. Lancet 2011; 378:1949-61.
8. Chaudhary NI, Roth GJ, Hilberg F, et al. Inhibition of PDGF, VEGF and FGF signalling attenuates fibrosis. Eur Respir J 2007;29:976-85.
9. Coward WR, Saini G, Jenkins G. The pathogenesis of idiopathic pulmonary fibrosis. Ther Adv Respir Dis 2010;4:367-88.
10. Wollin L, Maillet I, Quesniaux V, Holweg A, Ryffel B. Anti-fibrotic and anti-inflammatory activity of the tyrosine kinase inhibitor nintedanib in experimental models of lung fibrosis. J Pharmacol Exp Ther 2014;349:209-20.
11. Hilberg F, Roth GJ, Krssak M, et al. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res 2008;68: 4774-82.
12. Richeldi L, Costabel U, Selman M, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med 2011;365:1079-87.
13. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005;26:319-38.
14. Jones PW, Quirk FH, Baveystock CM. The St. George's Respiratory Questionnaire. Respir Med 1991;85:Suppl B:25-31.
15. Barr JT, Schumacher GE, Freeman S, LeMoine M, Bakst AW, Jones PW. American translation, modification, and validation of the St. George's Respiratory Questionnaire. Clin Ther 2000;22:1121-45.
16. Jones PW. St. George's Respiratory Questionnaire: MCID. COPD 2005;2:75-9.
17. Collard HR, Moore BB, Flaherty KR, et al. Acute exacerbations of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2007;176:636-43.
18. Cotes JE, Chinn DJ, Quanjer PH, Roca J, Yernault JC. Standardization of the measurement of transfer factor (diffusing capacity). Report of the Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official statement of the European Respiratory Society. Eur Respir J Suppl 1993;16:41-52.
19. Song JW, Hong SB, Lim CM, Koh Y, Kim DS. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. Eur Respir J 2011;37:356-63.
20. Collard HR, Yow E, Richeldi L, Anstrom KJ, Glazer C. Suspected acute exacerbation of idiopathic pulmonary fibrosis as an outcome measure in clinical trials. Respir Res 2013;14:73.

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