ORIGINAL ARTICLE

Nintedanib with Add-on Pirfenidone in Idiopathic Pulmonary Fibrosis
Results of the INJOURNEY Trial

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Abstract

Rationale: Nintedanib and pirfenidone slow the progression of idiopathic pulmonary fibrosis (IPF), but the disease continues to progress. More data are needed on the safety and efficacy of combination therapy with nintedanib and add-on pirfenidone.

Objectives: To investigate safety, tolerability, and pharmacokinetic and exploratory efficacy endpoints in patients treated with nintedanib and add-on pirfenidone versus nintedanib alone.

Methods: Patients with IPF and FVC greater than or equal to 50% predicted at screening who completed a 4- to 5-week run-in with nintedanib 150 mg twice daily without dose reduction or treatment interruption were randomized to receive nintedanib 150 mg twice daily with add-on pirfenidone (titrated to 801 mg three times daily) or nintedanib 150 mg twice daily alone in an open-label manner for 12 weeks. The primary endpoint was the percentage of patients with on-treatment gastrointestinal adverse events from baseline to Week 12. Analyses were descriptive and exploratory.

Measurements and Main Results: On-treatment gastrointestinal adverse events were reported in 37 of 53 patients (69.8%) treated with nintedanib with add-on pirfenidone and 27 of 51 patients (52.9%) treated with nintedanib alone. Predose plasma trough concentrations of nintedanib were similar when it was administered alone or with add-on pirfenidone. Mean (SE) changes from baseline in FVC at Week 12 were −13.3 (17.4) ml and −40.9 (31.4) ml in patients treated with nintedanib with add-on pirfenidone ($n = 48$) and nintedanib alone ($n = 44$), respectively.

Conclusions: Nintedanib with add-on pirfenidone had a manageable safety and tolerability profile in patients with IPF, in line with the adverse event profiles of each drug. These data support further research into combination regimens in the treatment of IPF.

Clinical trial registered with www.clinicaltrials.gov (NCT02579603).

Keywords: interstitial lung diseases; clinical trial; drug therapy; adverse drug event

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrosing interstitial pneumonia characterized by progressive decline in lung function (1). The pathogenesis of IPF is believed to be driven by dysfunction of the alveolar epithelium after recurrent episodes of injury. Activated alveolar epithelial cells release fibrogenic growth factors that promote the migration, activation, and differentiation of fibroblasts and myofibroblasts, resulting in excessive deposition of extracellular matrix and the destruction of the lung architecture (2).

Nintedanib, a potent intracellular inhibitor of tyrosine kinases, has been

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At a Glance Commentary

Scientific Knowledge on the Subject: The antifibrotic drugs nintedanib and pirfenidone reduce the progression of idiopathic pulmonary fibrosis (IPF), as shown by a slower decline in FVC versus placebo, but ultimately the disease continues to progress. Nintedanib and pirfenidone are thought to target different aspects of the fibrotic cascade, so combined therapy with both drugs may provide better outcomes than monotherapy.

What This Study Adds to the Field: In the open-label randomized INJOURNEY trial, treatment with nintedanib with add-on pirfenidone had a manageable safety and tolerability profile in patients with IPF, in line with the adverse profiles of the individual drugs. Plasma trough concentrations of nintedanib were similar when it was administered alone or with add-on pirfenidone. Decline in FVC over 12 weeks appeared to be less in patients treated with nintedanib with add-on pirfenidone than with nintedanib alone, but these results should be interpreted with caution, given the exploratory nature of this analysis. These data support further research into combination regimens in the treatment of IPF.

approved for the treatment of IPF in several countries, including the United States (3). In the two placebo-controlled, 52-week phase III INPULSIS (Safety and Efficacy of BIBF 1120 at High Dose in Idiopathic Pulmonary Fibrosis Patients) trials, nintedanib 150 mg twice daily significantly reduced the decline in FVC in patients with IPF. Gastrointestinal adverse events, particularly diarrhea, were the most frequent adverse events (4). Pirfenidone, a pyridone derivative, has also been widely approved for the treatment of IPF, including in the United States (5). In the phase III ASCEND (Efficacy and Safety of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis [IPF]) trial, pirfenidone 2,403 mg/d (801 mg three times daily) significantly reduced the decline in FVC in patients with IPF, with nausea and rash being the most frequent adverse events (6). Nintedanib and pirfenidone both received conditional recommendations for use in the most recent clinical practice guideline for the treatment of IPF, indicating that they would be an appropriate treatment choice for a majority of patients (7). The guideline provided no recommendations for or against the use of combination regimens or sequential therapies.

Although both nintedanib and pirfenidone reduce the rate of disease progression in patients with IPF, the disease continues to progress and is ultimately fatal. With the availability of two antifibrotic drugs, it is expected that combination therapy is likely to be the future of treatment of IPF (8), similar to the management of other chronic progressive diseases, such as pulmonary arterial hypertension and several types of cancer. Nintedanib and pirfenidone have pleiotropic effects and are thought to target different aspects of the fibrotic cascade (9, 10), suggesting that therapy with both drugs may provide additive or even synergistic effects, resulting in a greater improvement in outcomes than either monotherapy. However, given the overlapping adverse event profiles of nintedanib and pirfenidone, data on potential additive adverse events and the overall benefit/risk ratio of combined therapy are needed.

Data from a phase II randomized, placebo-controlled (within each dose group) dose escalation study of nintedanib in 50 Japanese patients with IPF, with a maximum treatment duration of 28 days, suggested a trend toward lower exposure of nintedanib, with moderate to high interpatient variability, when nintedanib was added to chronic pirfenidone treatment than when it was given alone (11). Coadministration of nintedanib had no effect on the pharmacokinetics (PK) of pirfenidone (11). Patients who completed this trial and were still receiving pirfenidone could receive combination therapy with nintedanib and pirfenidone in an open-label extension study. After a mean exposure of 27 months in this extension study, no new safety signals were identified, but definite conclusions could not be drawn on the basis of the small number of patients ($n = 20$) (12).

No data on the safety, tolerability, and efficacy of nintedanib with add-on pirfenidone have been presented. We present results from the INJOURNEY (Safety, Tolerability, and PK [Pharmacokinetics] of Nintedanib in Combination with Pirfenidone in IPF) trial, in which safety, tolerability, PK, and exploratory efficacy endpoints were evaluated in patients treated with nintedanib with add-on pirfenidone versus nintedanib alone. Some of these results were presented at the 2017 European Respiratory Society (ERS) International Congress in abstract form.

Methods

Trial Design

We conducted an open-label, randomized trial of nintedanib with add-on pirfenidone compared with nintedanib alone in patients with IPF (NCT02579603). After a 4- to 5-week run-in with nintedanib 150 mg twice daily, patients were randomized (1:1) to receive add-on pirfenidone or continue nintedanib 150 mg twice daily alone for 12 weeks with a follow-up visit 4 weeks later (Figure 1). Patients who had a nintedanib dose reduction or treatment interruption during the run-in were not randomized.

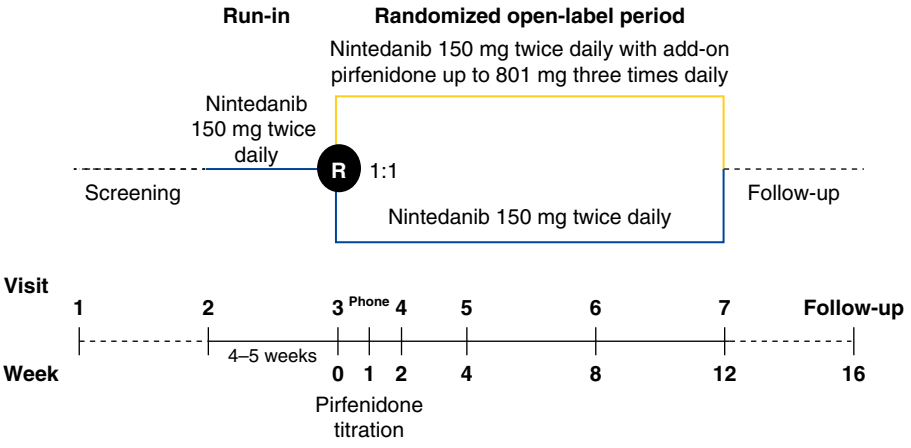


Figure 1. INJOURNEY trial design. R = randomization.

The pirfenidone dose was titrated as recommended in the prescribing information: 267 mg three times daily from randomization to Week 1, 534 mg three times daily from Week 1 to Week 2, and 801 mg three times daily from Week 2.

Investigators were provided with recommendations for the management of diarrhea, phototoxicity/rash, liver enzyme elevations, and adverse events that the investigator regarded as drug related (*see* Table E1 and Figure E1 in the online supplement). In the randomized period, the nintedanib dose could be reduced from 150 mg twice daily to 100 mg twice daily or interrupted to manage adverse events. After resolution of the adverse event, the dose of nintedanib could be reescalated to 150 mg twice daily or resumed after treatment interruption at a dose of 150 mg twice daily or 100 mg twice daily (with the option to increase to 150 mg twice daily). Pirfenidone dose could be reduced from 801 mg three times daily to 534 mg three times daily or 267 mg three times daily, or could be interrupted, to manage adverse events. After resolution of the adverse event, the dose could be reescalated to the maximum dose. Pirfenidone could be resumed at the dose received prior to an interruption if the interruption was less than 14 days but was reinitiated using the initial 2-week titration scheme if the interruption was 14 days or more.

The trial was approved by local ethics committees and was performed in compliance with the protocol, the principles of the Declaration of Helsinki, International Conference on Harmonization good clinical practice guidelines, and applicable regulatory requirements. The principal investigators are listed in the online supplement.

Trial Population

To be eligible to participate in this trial, patients had to be aged 40 years or older and have an FVC greater than or equal to 50% predicted at screening. The diagnosis of IPF, according to American Thoracic Society/ERS/Japanese Respiratory Society/Latin American Thoracic Association guidelines (1), was confirmed by the investigator on the basis of a chest high-resolution computed tomographic scan obtained within 12 months of screening. Patients who were taking nintedanib prior to entering the trial and patients who were nintedanib-naive were eligible to participate. Exclusion criteria included alanine transaminase (ALT) or aspartate aminotransferase (AST) or total bilirubin more than 1.5 times the upper limit of normal (ULN), history of myocardial infarction within 6 months or unstable angina within 1 month of screening, bleeding risk (e.g., requiring full-dose anticoagulation or high-dose antiplatelet therapy), and history of a thrombotic event within 12 months of screening. Patients who had previously received pirfenidone, had previously discontinued nintedanib because of adverse events, or who required dose reduction or treatment interruption during the run-in period with nintedanib 150 mg twice daily were excluded.

Trial Endpoints

The primary endpoint was the percentage of patients with on-treatment gastrointestinal adverse events from baseline to Week 12. On-treatment adverse events were defined as adverse events with onset from the day of the first dose to the day of the last dose of randomized treatment (inclusive). Gastrointestinal adverse events were defined as adverse events in the system organ class "gastrointestinal disorders" in the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.

Secondary endpoints were predose plasma concentrations at steady state of nintedanib (at baseline, Week 2, and Week 4) and of pirfenidone (at Weeks 2 and 4). Further safety endpoints included time to first gastrointestinal adverse event, percentage of patients with ALT and/or AST greater than or equal to three times the ULN during the randomized treatment period, and time to first ALT and/or AST greater than or equal to three times the ULN. In addition, safety was assessed via physical examination, vital signs, laboratory parameters, 12-lead ECG, and the recording of adverse events. Adverse events were coded using MedDRA version 19.1.

Exploratory efficacy endpoints were absolute and relative changes from baseline in FVC (in milliliters and percent predicted values) at Week 12, rate of decline in FVC (ml/12 wk), and change from baseline in EuroQoL-5D (EQ-5D) total score at Week 12. FVC was measured at baseline and Weeks 2, 4, 8, and 12. Spirometry was conducted in accordance with criteria published by the American Thoracic Society and the ERS (13). Spirometric measurements were performed on devices provided by the sponsor and were centrally reviewed. The EQ-5D was completed as per the visit schedule for FVC and prior to any other trial-related procedures.

Statistical Methods

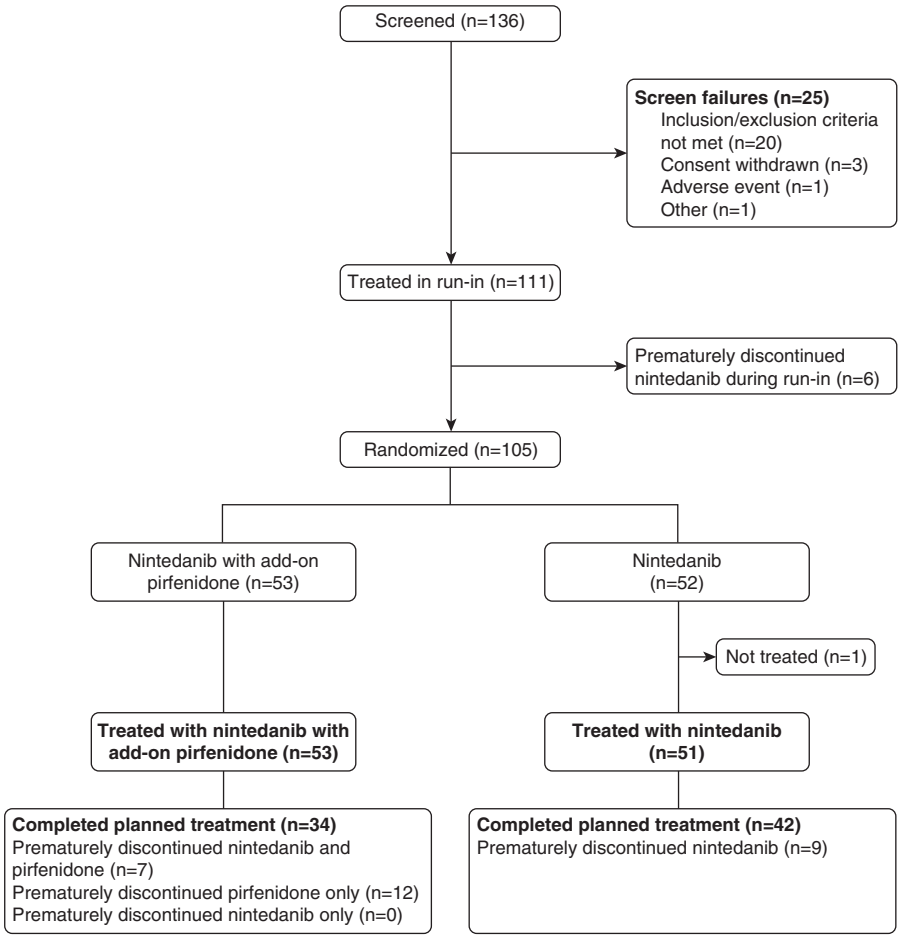
Safety and efficacy endpoints were assessed in randomized patients who received at least one dose of trial medication. PK endpoints were assessed in patients who had received at least one dose of trial medication and who provided evaluable data for at least one PK endpoint without important protocol violations relevant to the evaluation of PK (e.g., missed dose, blood taken postdose rather than predose). Analyses were descriptive and exploratory. Adjusted rate of decline in FVC (ml/12 wk) was based on a random coefficient regression with fixed effects for treatment, baseline FVC, and random effect of patient-specific intercept and time. For the analyses of FVC, values measured after Week 12 but within 27 days after the last dose of randomized treatment were assigned to the Week 12 time point. Time to first event endpoints were analyzed using Kaplan-Meier estimates calculated from the time of first intake of randomized trial drug.

Results

Patients

Of 136 screened patients, 111 were treated with nintedanib 150 mg twice daily in the run-in period. Six patients prematurely discontinued nintedanib during the run-in period, and 105 were randomized to receive nintedanib 150 mg twice daily alone ($n = 52$) or nintedanib 150 mg twice daily with add-on pirfenidone titrated to 801 mg three times daily ($n = 53$). One patient randomized to nintedanib alone was not treated (Figure 2).

Baseline characteristics were generally similar between treatment groups (Table 1). Most patients were male (82.7%) and white (96.2%). The mean age of the patients was 68.9 years, mean FVC was 84.0% predicted, and mean diffusing capacity of the lung for carbon monoxide was 47.0% predicted. Medical conditions and baseline therapies of interest are presented in Tables E2 and E3. In total, 30 patients (56.6%) treated with nintedanib with add-on pirfenidone and 30 patients (58.8%) treated with



Fifty-one and 48 patients completed the planned observation period (defined as having completed the follow-up visit after the last drug intake) in the nintedanib plus pirfenidone and nintedanib groups, respectively.

Figure 2. Patient disposition.

nintedanib alone were nintedanib naive before entering the trial.

Exposure

Mean (SD) exposure to nintedanib during the randomized period was 11.3 (2.7) weeks in patients treated with nintedanib with add-on pirfenidone and 10.9 (2.9) weeks in patients treated with nintedanib alone. Mean (SD) exposure to pirfenidone during the randomized period was 9.8 (3.7) weeks in patients treated with nintedanib with add-on pirfenidone.

Nintedanib dose reductions occurred in four patients (7.5%) treated with nintedanib with add-on pirfenidone and in six patients (11.8%) treated with nintedanib alone. Nintedanib was prematurely discontinued in seven patients (13.2%) treated with nintedanib with add-on pirfenidone and in nine patients (17.6%) treated with nintedanib alone (Table E4). In patients treated with nintedanib with add-on pirfenidone, pirfenidone dose reductions occurred in 19 patients (35.8%), and pirfenidone was prematurely discontinued in 19 patients (35.8%) (Table E5).

Dose intensity was defined as the amount of drug administered over the study period divided by the amount that would have been received had the protocol-defined dose been administered throughout the treatment period or until permanent treatment discontinuation. Mean (SD) dose intensity of nintedanib was 99.6% (6.6) and 98.6% (8.0) in patients treated with nintedanib with add-on pirfenidone and nintedanib alone, respectively. Mean (SD) dose intensity of pirfenidone was 88.4% (20.2) in patients treated with nintedanib with add-on pirfenidone. In total, 50 patients (94.3%) treated with nintedanib with add-on pirfenidone and 45 patients (88.2%) treated with nintedanib alone received nintedanib 150 mg twice daily as their last dose. For patients treated with nintedanib with add-on pirfenidone, 12 (22.6%), 11 (20.8%), and 30 (56.6%) patients received pirfenidone 267 mg three times daily, 534 mg three times daily, and 801 mg three times daily, respectively, as their last dose.

Safety Outcomes

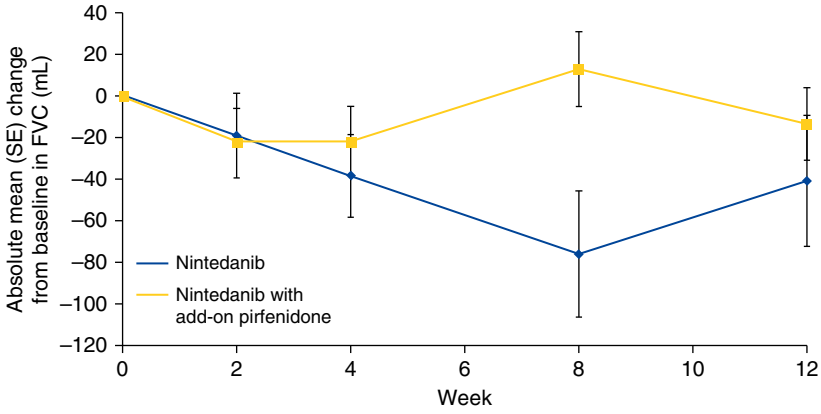
On-treatment gastrointestinal adverse events were reported in 37 patients (69.8%) treated with nintedanib with add-on pirfenidone and 27 patients (52.9%) treated with nintedanib alone. Time to first gastrointestinal adverse event is shown in Figure E2. During the randomized treatment period, ALT and/or AST at least three times the ULN was reported in three patients (5.7%) treated with nintedanib with add-on pirfenidone and no patients treated with nintedanib alone (Table 2). No cases of Hy's law were observed.

PK Outcomes

Predose plasma trough concentrations of nintedanib were similar at each time point, regardless of whether nintedanib 150 mg twice daily was administered alone or with add-on pirfenidone 534 mg or 801 mg three times daily (Table 3; Figure E3). Moderate to high variability was observed in both treatment groups. Predose geometric mean (geometric coefficient of variation in percent) concentrations of pirfenidone were 1,120 (122) and 1,220 (91) ng/ml at Week 2 and Week 4, respectively (Figure E4).

Exploratory Efficacy Outcomes

Mean (SE) absolute changes from baseline in FVC at Week 12 were −13.3 (17.4) ml in patients treated with nintedanib with add-on pirfenidone ($n = 48$) and −40.9 (31.4) ml in patients treated with nintedanib alone ($n = 44$) (Figure 3). Mean (SE) absolute changes from baseline in FVC percent predicted at Week 12 were −0.3% (0.5) and −1.3% (0.8) in these groups, respectively. The rate of change in FVC was 3.6 ml/12 wk (increase) in patients treated with nintedanib with add-on pirfenidone and −48.0 ml/12 wk (decrease) in patients treated with nintedanib alone (difference, 51.7 ml; 95% confidence interval, −13.3,



n					
Nintedanib	51	49	48	45	44
Nintedanib with add-on pirfenidone	53	52	50	50	48

FVC values from seven patients assigned to the week 12 time-point came from measurements made after week 12; the latest measurement was performed on day 96 and 1 day after the last dose of randomized treatment.

Figure 3. Absolute change from baseline in FVC over time.

116.6). Relative changes from baseline in FVC at Week 12 (in milliliters and percent predicted) are presented in Figures E5 and E6.

Mean (SE) absolute changes from baseline in EQ-5D total score at Week 12 were −1.1 (2.7) in patients treated with nintedanib with add-on pirfenidone and −1.0 (1.7) in patients treated with nintedanib alone.

Table 1. Baseline Characteristics

	Nintedanib 150 mg Twice Daily with Add-on Pirfenidone (*n* = 53)	Nintedanib 150 mg Twice Daily (*n* = 51)	Total (*n* = 104)
Male, *n* (%)	42 (79.2)	44 (86.3)	86 (82.7)
Age, yr, mean (SD)	68.9 (6.6)	68.9 (6.8)	68.9 (6.6)
Weight, kg, mean (SD)	86.1 (14.5)	83.4 (17.4)	84.8 (16.0)
Body mass index, kg/m^2, mean (SD)	28.9 (3.8)	28.2 (5.1)	28.6 (4.5)
Race, *n* (%)			
White	51 (96.2)	49 (96.1)	100 (96.2)
Asian	2 (3.8)	2 (3.9)	4 (3.8)
Time since diagnosis of IPF, yr, mean (SD)	1.1 (1.3)	1.4 (1.8)	1.2 (1.6)
Smoking status, *n* (%)			
Never	16 (30.2)	11 (21.6)	27 (26.0)
Former	34 (64.2)	38 (74.5)	72 (69.2)
Current	3 (5.7)	2 (3.9)	5 (4.8)
Nintedanib status before study, *n* (%)			
Naive	30 (56.6)	30 (58.8)	60 (57.7)
Pretreated	23 (43.4)	21 (41.2)	44 (42.3)
FVC, ml, mean (SD)	2,992 (787)	3,119 (931)	3,054 (859)
FVC, % predicted, mean (SD)	83.1 (18.9)	85.0 (20.0)	84.0 (19.4)
D_{LCO}, % predicted, mean (SD)	45.6 (14.1)	48.6 (15.5)	47.0 (14.8)
EQ-5D total score, mean (SD)	74.6 (14.9)	74.9 (14.7)	74.7 (14.7)

Definition of abbreviations: EQ-5D = EuroQoL-5D scale; IPF = idiopathic pulmonary fibrosis.
D_{LCO} was corrected for hemoglobin.

Adverse Events

Adverse events were reported in 47 patients (88.7%) treated with nintedanib with add-on pirfenidone and 45 patients (88.2%) treated with nintedanib alone. Serious adverse events were reported in two patients (3.8%) and five patients (9.8%) in these treatment groups, respectively (Table E6). No fatal adverse events occurred.

Diarrhea, nausea, and vomiting were the most frequent adverse events (Table 4). Diarrhea was reported in 20 patients (37.7%) treated with nintedanib with add-on pirfenidone and 16 patients (31.4%) treated with nintedanib alone. Nausea was reported in 22 (41.5%) and 6 (11.8%) patients, and vomiting in 15 (28.3%) and 6 (11.8%) patients, treated with nintedanib with add-on pirfenidone and with nintedanib alone, respectively.

Discussion

In this 12-week, open-label, randomized trial, the adverse event profile of nintedanib with add-on pirfenidone was in line with the safety and tolerability profiles of the individual drugs (3, 5) and was manageable in the majority of patients. Serious adverse events were uncommon in both treatment groups. Gastrointestinal adverse events were reported in approximately half and two-thirds of patients treated with nintedanib and nintedanib with add-on pirfenidone, respectively. Diarrhea was reported in 31% of patients treated with nintedanib and 38% treated with nintedanib with add-on pirfenidone (based on 12 weeks of treatment) in the INJOURNEY trial compared with 62% of patients treated with nintedanib and 22% of patients treated with pirfenidone in the INPULSIS and ASCEND trials, respectively (based on 52 weeks of treatment) (4, 6). Nausea was reported in 12% and 42% of patients treated with nintedanib and nintedanib with add-on pirfenidone, respectively, in the INJOURNEY trial (12 weeks of treatment) compared with 25% of patients treated with nintedanib and 36% of patients treated with pirfenidone in the INPULSIS and ASCEND trials (52 weeks of treatment), respectively (4, 6). In the INPULSIS and ASCEND trials, the majority of gastrointestinal adverse events

Table 2. Hepatic Enzyme Elevations

	Nintedanib 150 mg Twice Daily with Add-on Pirfenidone (*n* = 53)	Nintedanib 150 mg Twice Daily (*n* = 51)
Maximum AST and/or ALT		
⩾3× ULN	3 (5.7)	0
⩾5× ULN	2 (3.8)	0
⩾8× ULN	0	0
Maximum total bilirubin		
⩾1.5× ULN	0	1 (2.0)
⩾2× ULN	0	1 (2.0)
Maximum alkaline phosphatase		
⩾1.5× ULN	1 (1.9)	0
⩾2× ULN	0	0
Maximum γ-glutamyltransferase		
⩾1× ULN	29 (54.7)	25 (49.0)
⩾3× ULN	7 (13.2)	3 (5.9)
ALT and/or AST ⩾3× ULN and bilirubin ⩾2× ULN	0	0

Definition of abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; ULN = upper limit of normal.
Data are shown as *n* (%). No cases of Hy's law were observed. Cases of Hy's law were defined as AST or ALT at least three times the ULN, total bilirubin at least twice the ULN measured in the same blood draw sample, and no other reason found to explain the combination of increased hepatic transaminases and bilirubin, such as viral hepatitis A, B, or C; preexisting or acute hepatic disease; or the use of another drug capable of causing the observed injury.

occurred within the first 3 months (14, 15). The safety/tolerability findings from the INJOURNEY trial were consistent with the findings of the phase II dose escalation trial of nintedanib stratified by pirfenidone use at baseline in Japanese patients with IPF (11). In that trial, 24 patients received nintedanib 150 mg twice daily for 28 days, of whom 13 patients had been taking chronic pirfenidone therapy (at different doses). Nausea and vomiting were the most commonly reported adverse events. These were reported more commonly in the 13 patients who received nintedanib 150 mg twice daily on top of pirfenidone background therapy (in 4 and 5 patients, respectively) compared with the 11 patients who received nintedanib 150 mg twice daily only (in 1 and no patients, respectively) (11). An interim analysis of data from a 24-week single-arm study assessing the safety and tolerability of pirfenidone with add-on nintedanib in patients treated for at least 12 weeks (n = 41) also demonstrated that diarrhea and nausea were the most frequent adverse events, reported in 46.3% and 41.5% of patients, respectively (16).

Reversible elevations in hepatic enzymes have been observed in patients receiving nintedanib and pirfenidone monotherapy (3, 5). In our study, hepatic enzyme elevations at least three times the ULN were reported in three patients (5.7%) treated with nintedanib with add-on pirfenidone and none treated with nintedanib alone. The prescribing information for nintedanib and pirfenidone recommends close monitoring for adverse events during treatment, including monitoring for hepatic enzyme elevations (3, 5). Patients with transaminases at least 1.5 times the ULN at baseline were excluded from this trial, similar to the phase III INPULSIS trials.

In the INJOURNEY trial, two-thirds of patients completed the 12-week treatment period with both drugs, and one-third prematurely discontinued pirfenidone. In the INPULSIS and ASCEND trials, 25% and 20% of patients, respectively, prematurely discontinued treatment with nintedanib and pirfenidone over 52 weeks, predominantly because of adverse events. In the combination therapy group of the INJOURNEY trial, permanent discontinuations of pirfenidone were more frequent than permanent discontinuations of nintedanib. This might partially be attributed to the protocol recommendation to reduce the dose of pirfenidone before reducing the dose of nintedanib in the case of adverse events other than diarrhea. In addition, it is likely that investigators attributed more treatment-emergent adverse events in the combination therapy group to the newly introduced pirfenidone rather than to nintedanib, which the patients had already shown they could tolerate. Furthermore, inherent to the design of this trial, only patients who had already tolerated nintedanib in a 4- to 5-week run-in period were randomized. This likely reduced the rates of permanent discontinuations and dose adjustments of nintedanib during the randomized period. It should also be noted that 41% of patients were already being treated with nintedanib at study entry. Although this trial was not designed to inform the best treatment strategy for combination treatment (i.e., concurrent or sequential), the trial design took into account a pragmatic clinical approach in which physicians would give a second antifibrotic drug only to patients who could tolerate one antifibrotic drug, given the known overlapping adverse event profiles of nintedanib and pirfenidone.

Table 3. Predose Plasma Trough Concentrations of Nintedanib

	Nintedanib 150 mg Twice Daily with Add-on Pirfenidone 534 mg or 801 mg Three Times Daily*†		Nintedanib 150 mg Twice Daily	
	n	gMean (gCV%)	*n*	gMean (gCV%)
Predose concentration of nintedanib, ng/ml				
Baseline*	46	7.65 (72.5)	46	7.08 (56.0)
Week 2	35	8.17 (69.8)	41	7.25 (52.7)
Week 4	30	7.13 (63.9)	44	5.92 (73.5)

Definition of abbreviations: gMean = geometric mean; gCV = geometric coefficient of variation.
*Nintedanib 150 mg twice daily alone at baseline.
†Pirfenidone dose titration: 267 mg three times daily from randomization to Week 1, 534 mg three times daily from Week 1 to Week 2, 801 mg three times daily from Week 2.

Table 4. Adverse Events

	Nintedanib 150 mg Twice Daily with Add-on Pirfenidone (*n* = 53)	Nintedanib 150 mg Twice Daily (*n* = 51)
Any adverse events	47 (88.7)	45 (88.2)
Most frequent adverse events*		
Diarrhea	20 (37.7)	16 (31.4)
Nausea	22 (41.5)	6 (11.8)
Vomiting	15 (28.3)	6 (11.8)
Fatigue	10 (18.9)	6 (11.8)
Upper abdominal pain	7 (13.2)	4 (7.8)
Decreased appetite	6 (11.3)	5 (9.8)
Dyspnea	2 (3.8)	8 (15.7)
Headache	7 (13.2)	1 (2.0)
Any serious adverse events†	2 (3.8)	5 (9.8)
Any fatal adverse events	0	0

Data are shown as *n* (%) of patients with at least one such adverse event.
*Adverse events reported in greater than 10% of patients in either treatment group by preferred term in the Medical Dictionary for Regulatory Activities (MedDRA).
†An adverse event that resulted in death, was life threatening, required hospitalization or prolongation of hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or was deemed serious for any other reason.

The PK data obtained in this trial did not replicate the results of the phase II Japanese trial, in which nintedanib plasma concentration tended to be lower after administration with pirfenidone (11). In our trial, plasma trough concentrations of nintedanib were similar when it was administered alone or with add-on pirfenidone. However, neither the present trial nor the phase II Japanese trial was specifically designed to assess a drug–drug interaction between nintedanib and pirfenidone. Nintedanib and pirfenidone are metabolized via different pathways, and therefore no PK interaction between nintedanib and pirfenidone would be expected. Data from a recently conducted dedicated drug–drug interaction study (www.clinicaltrials.gov identifier NCT02606877) will allow robust conclusions to be drawn regarding the PK interactions between nintedanib and pirfenidone.

When given as monotherapy to patients with IPF and mild or moderate impairment in lung function, nintedanib and pirfenidone reduce the rate of decline in lung function by approximately 50% (4, 6). In the present trial, we observed a smaller numerical decline in FVC over 12 weeks in patients treated with nintedanib with add-on pirfenidone than with nintedanib alone. However, because this trial was not powered for this endpoint and was too short for conclusions to be drawn about the efficacy of combination therapy, these findings should be interpreted with caution. Reassuringly, there was no meaningful change in EQ-5D (a generic measure of quality of life) in either treatment group.

In conclusion, in the INJOURNEY trial, treatment with nintedanib and add-on pirfenidone for 12 weeks had a manageable safety and tolerability profile in patients with IPF. Further large controlled studies are needed to confirm the benefit/risk ratio of combination antifibrotic therapy in patients with IPF. ■

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