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Safety of Nintedanib Added to Pirfenidone Treatment for Idiopathic Pulmonary Fibrosis

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"Take home" message: Combined pirfenidone and nintedanib was tolerated by the majority of patients with IPF, encouraging further study

ABSTRACT

We assessed safety and tolerability of treatment with pirfenidone (1602–2403 mg/day) and nintedanib (200–300 mg/day) in patients with idiopathic pulmonary fibrosis (IPF).

This 24-week, single-arm, open-label Phase IV study (NCT02598193) enrolled patients with IPF with forced vital capacity (FVC) ≥50% and carbon monoxide diffusing capacity (DLco) ≥30%. Before initiating nintedanib, patients had received pirfenidone for ≥16 weeks and tolerated a stable dose of ≥1602 mg/day for ≥28 days. The primary endpoint was proportion of patients who completed 24 weeks of combination treatment on pirfenidone (1602–2403 mg/day) and nintedanib (200–300 mg/day). Investigators recorded treatment-emergent adverse events (TEAEs), attributing them to pirfenidone, nintedanib, both or neither.

Eighty-nine patients were enrolled; 73 completed 24 weeks of treatment (69 meeting the primary endpoint) and 16 discontinued treatment prematurely (13 due to TEAEs). Seventy-four patients had 418 treatment-related TEAEs, of which diarrhoea, nausea and vomiting were the most common. Two patients had serious treatment-related TEAEs.

Combined pirfenidone and nintedanib use for 24 weeks was tolerated by the majority of patients with IPF and associated with a similar pattern of TEAEs expected for either treatment alone. These results encourage further study of combination treatment with pirfenidone and nintedanib in patients with IPF.

Key words [5/6]: idiopathic pulmonary fibrosis; pirfenidone; nintedanib; antifibrotic; combination treatment

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive, irreversible, fatal, fibrosing lung disease of unknown cause [1, 2], with a survival rate lower than that reported for many common cancer types [1, 3-5]. Pirfenidone and nintedanib are approved as monotherapies for treatment of IPF [6, 7], and both received a conditional recommendation for use in the 2015 update to American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) clinical practice guidelines [8]. Although pirfenidone and nintedanib have both demonstrated efficacy in reducing rates of disease progression compared with placebo, the disease is neither stopped nor reversed, and patients continue to experience lung function decline while on treatment [9-11].

The differing putative mechanisms of action of pirfenidone and nintedanib [12-14] provide a physiological rationale for combining these two agents in an attempt to further reduce lung function decline in patients with IPF [15]. Even though both agents target the fibrotic cascade, decreasing fibroblast and myofibroblast production, and accumulation of extracellular matrix [12-14, 16, 17], evidence suggests that they may target distinct aspects of the fibrotic cascade. Although its mechanism of action has not been fully established, pirfenidone has been shown to act on multiple targets *in vitro*, including transforming growth factor-beta-triggered events, mediated through glioma-associated oncogene homolog 2 [12, 13]. Nintedanib is a tyrosine kinase inhibitor that blocks intracellular signalling of platelet-derived growth factor receptors, fibroblast growth factor receptors and vascular endothelial growth factor receptor [14].

Pirfenidone and nintedanib are both associated with gastrointestinal (GI) adverse events (AEs), with pirfenidone mainly associated with nausea and nintedanib mainly associated with diarrhoea [9, 10, 18]. A small Japanese randomised, double-blind, Phase II dose-escalation

trial of nintedanib (100–300 mg/day) added to ongoing pirfenidone treatment (≤1800 mg/day) for ≤28 days, and its 1-year, open-label extension, indicated that safety and tolerability of combination treatment in patients with IPF was in line with AE profiles for each drug alone [19, 20]. Similarly, the recent INJOURNEY trial, an open-label, randomised trial of pirfenidone (≤2403 mg/day) added to nintedanib treatment (≤300 mg/day) for 12 weeks, also found that the safety and tolerability profile of combination treatment was comparable with that of the individual drugs [21]. However, there are limited data on long-term safety of combination treatment. Here, we report results from a 24-week study investigating safety and tolerability of adding nintedanib to stable pirfenidone treatment in patients with IPF.

METHODS

Patients

Eligible patients were aged 40–80 years at start of screening, with IPF based on the ATS/ERS/JRS/ALAT 2011 guideline. Patients had received pirfenidone for ≥16 weeks and tolerated a stable dose of 1602–2403 mg/day for ≥28 days without experiencing any moderate or severe adverse reactions considered by the investigator to be related to pirfenidone, or a pirfenidone treatment interruption for >7 days for any reason. Patients also had percent predicted FVC ≥50% and carbon monoxide diffusing capacity (DLco) ≥30% at screening. Informed consent was obtained from each patient before any study activity or treatment was undertaken. Other inclusion and exclusion criteria are listed in Supplementary Table 1.

Study design

This was an international, single-arm, open-label, Phase IV study (NCT02598193) that assessed safety and tolerability of 24 weeks of treatment with pirfenidone (1602–

2403 mg/day) and nintedanib (200–300 mg/day) in patients with IPF (Figure 1). Patients started nintedanib treatment that was added to stable pirfenidone treatment on Day 1 of the study. Combination treatment administration is further described in Supplementary Appendix 1.

Medications prohibited during the study are described in Supplementary Table 2.

Assessments

The primary objective was to investigate safety and tolerability of adding nintedanib to stable pirfenidone treatment in patients with IPF. This was assessed with the following endpoints: (1) primary endpoint: proportion of patients who completed 24 weeks of combination treatment on pirfenidone (1602–2403 mg/day) and nintedanib (200–300 mg/day); (2) secondary endpoints: (a) proportion of patients who discontinued pirfenidone, nintedanib or both treatments before Week 24 due to treatment-emergent AEs (TEAEs; AEs occurring after initiation of combination treatment until 28 days after the last dose of pirfenidone and nintedanib; (b) total patient days of combination treatment; (c) total duration in days from initiation of combination treatment to discontinuation of pirfenidone, nintedanib or both treatments; (d) frequency and timing of TEAEs and serious TEAEs. Changes from baseline in FVC, DLco and King's Brief Interstitial Lung Disease questionnaire (K-BILD) [22] score were assessed as exploratory endpoints. Further details on study assessments are described in Supplementary Appendix 1.

Statistical analysis

This study planned to enrol 80 patients based on the sample size prediction described in Supplementary Appendix 1.

The safety population was defined as the population of all patients enrolled who received at least one dose of pirfenidone or nintedanib at baseline. Percentages were calculated based on

number of patients with non-missing data. Confidence intervals were based on a binomial distribution. This was a safety and tolerability study, with only one treatment group, which was not designed to assess efficacy of combination treatment. Thus, no formal statistical hypotheses were assessed, and analyses were limited to descriptive statistics with no adjustments for multiplicity of endpoints or within-subgroup comparisons.

RESULTS

Overall, 89 patients were enrolled from 36 centres in Canada, Denmark, France, Germany, Italy, the Netherlands, Spain and the USA between January and November 2016; baseline patient demographics and characteristics are shown in Table 1. Patients had a mean (standard error [SE]) percent predicted FVC of 71.8% (1.7) and mean (SE) percent predicted DLco of 48.4% (1.3) at baseline (Table 1). Measurements of FVC and DLco closest to 6 months before start of screening were 72.6% (1.7) and 50.0% (1.4) (Table 1).

The most commonly reported medical history preferred terms (>10% of patients) were: gastro-oesophageal reflux disease (49 patients [55%]), hypertension (44 [49%]), hyperlipidaemia (20 [23%]), cough (18 [20%]), seasonal allergy (17 [19%]), IPF (16 [18%]; entering IPF as medical history was optional), sleep apnoea syndrome (16 [18%]), hypercholesterolaemia (14 [16%]), diabetes mellitus (13 [15%]), osteoarthritis (12 [14%]), allergic rhinitis (11 [12%]), hypothyroidism (11 [12%]), depression (10 [11%]), anxiety (9 [10%]), insomnia (9 [10%]), benign prostatic hyperplasia (9 [10%]) and obesity (9 [10%]).

Table 1. Demographic and baseline characteristics (safety population)

Demographic parameter	**Total (N=89)**
Mean age, years (SD)	68.2 (6.8)
Male, n (%)	71 (80)
Race, n (%)	
White	84 (94)
Black or African American	3 (3)
Other*	2 (2)
Mean weight, kg (SD)	84.9 (15.5)
Mean BMI, kg/m^2 (SD)	28.6 (4.6)
Previous tobacco use, n (%)	61 (69)
Mean duration of previous pirfenidone treatment, months (SD)	20.4 (12.3)
Mean percent predicted FVC (SE)	
Historical value closest to 6 months prior to screening†	72.6 (1.7)
At baseline	71.8 (1.7)
Patients categorised by baseline FVC, n (%)	
<65%	32 (36)
65 to <80%	31 (35)
≥80%	26 (29)
Mean percent predicted DLco (SE)	
Historical value closest to 6 months prior to screening‡	50.0 (1.4)
At baseline	48.4 (1.3)

*Includes Asian and mixed Asian/White.

†Mean time from assessment of historical value to screening (SD) was 3.0 (1.9) months (N=87).

‡Mean time from assessment of historical value to screening (SD) was 3.3 (2.6) months (N=87).

BMI, body mass index; DLco, carbon monoxide diffusing capacity; FVC, forced vital capacity; SD, standard deviation; SE, standard error.

The most commonly reported concomitant medications (>25% of patients) were: proton-pump inhibitors (66 patients [74%]), bronchodilators and antiasthmatics (e.g. salbutamol, ipratropium, budesonide; 52 [58%]), statins (41 [46%]), vitamins and minerals (41 [46%]), steroids (38 [43%]), salicylates (35 [39%]), antidiarrhoeals (28 [32%]), antihistamines (26 [29%]), herbal, homeopathic and dietary supplements (24 [27%]) and non-steroidal anti-inflammatories (23 [26%]).

Overall, 73/89 (82%; 95% confidence interval 72.5, 89.4) patients completed 24 weeks of treatment plus follow-up, and 69/89 patients (78%; 95% confidence interval 67.4, 85.7) met the primary endpoint (completion of 24 weeks of combination treatment at doses of pirfenidone 1602–2403 mg/day and nintedanib 200–300 mg/day; Figure 2). For the 16 patients who discontinued treatment prematurely, 13 patients discontinued due to TEAEs, one patient withdrew herself from the study and two patients discontinued for other reasons (one patient did not want to continue nintedanib, and the other was listed for a lung transplant) (Figure 2).

Mean (standard deviation [SD]) daily doses taken during combination treatment were pirfenidone 2339.3 (183.7) mg/day and nintedanib 255.4 (43.7) mg/day (including nintedanib titration period doses). Although 78 patients (88%) received the target dose of >1602 mg/day pirfenidone and >200 mg/day nintedanib, 61 patients (69%) received less than the full dose of pirfenidone (2403 mg/day) and/or nintedanib (287 mg/day when including nintedanib titration period doses) overall during the study; the majority of patients did so because of temporary dose reductions and/or interruptions following TEAEs. Total patient days of combination treatment with pirfenidone and nintedanib was 13 304 days, excluding dose interruptions (the expected patient days on treatment being 14 952 days). Mean (SD) duration of treatment during the study period was 21.3 (6.3), 20.8 (6.2) and 21.4 (6.3) weeks for pirfenidone, nintedanib and combination treatment, respectively, excluding dose

interruptions. Since the exposure analysis considered treatments administered from start of combination treatment until study drug completion/early discontinuation from combination treatment period (as per the electronic case report form), interruptions of either drug before completion of the combination treatment period caused the mean duration of individual treatments to be shorter than that recorded for combination treatment.

A total of 23 patients (26%) had treatment interruptions: one patient (1%) had one interruption of pirfenidone alone, 16 patients (18%) had 28 interruptions of nintedanib alone and six patients (7%) had one interruption each of combination treatment (pirfenidone and nintedanib simultaneously interrupted); interruptions of combination treatment lasted a mean duration of 4.3 days. Mean length of all pirfenidone and nintedanib interruptions was 7.6 and 10.3 days, respectively.

Overall, 88 patients (99%) experienced 670 TEAEs; these were considered to be related to treatment in 74 patients (83%; 418 treatment-related TEAEs) (Table 2). Median (interquartile range) duration of TEAEs was 1.9 (0.3–11.3) weeks, 0.4 (0.1–7.1) weeks and 0.5 (0.1–6.4) weeks for TEAEs considered related to pirfenidone, nintedanib and both pirfenidone and nintedanib, respectively. Sixty-seven patients (75%) in total experienced GI treatment-related TEAEs; the majority of GI events were attributed by investigators to nintedanib alone (61 patients). Seven patients (8%) experienced treatment-related photosensitivity or rash TEAEs (Table 2).

A total of 13 patients discontinued treatment due to TEAEs (15%); these TEAEs were attributed to nintedanib alone in 10 patients (11%), both pirfenidone and nintedanib in one patient (1%) and were considered unrelated to either treatment in two patients (2%), as assessed by the investigator (Table 2). Discontinuation of combination treatment occurred throughout the trial, and there was no clear pattern in the timing of early discontinuation over the treatment period (Figure 3).

Table 2. Summary of common TEAEs and TEAEs leading to discontinuation (safety population)

N=89	Patients with at least one TEAE* n (%)	Patients with at least one TEAE related to pirfenidone only† n (%)	Patients with at least one TEAE related to nintedanib only† n (%)	Patients with at least one TEAE related to both pirfenidone and nintedanib† n (%)
TEAEs occurring in ≥5% of patients				
≥1 TEAE	88 (99)	–	–	–
≥1 treatment-related TEAE	74 (83)	15 (17)	67 (75)	26 (29)
Diarrhoea	44 (49)	2 (2)	38 (43)	5 (6)
Nausea	41 (46)	3 (3)	31 (35)	12 (14)
Vomiting	21 (24)	1 (1)	16 (18)	7 (8)
Decreased appetite	14 (16)	2 (2)	7 (8)	5 (6)
Fatigue	11 (12)	0	8 (9)	3 (3)
Dyspepsia	8 (9)	1 (1)	6 (7)	1 (1)
Headache	8 (9)	0	7 (8)	1 (1)
Weight decreased	6 (7)	1 (1)	3 (3)	2 (2)
Photosensitivity or rash TEAEs	7 (8)	4 (5)	2 (2)	1 (1)
Abdominal pain upper	5 (6)	1 (1)	2 (2)	2 (2)
Dizziness	5 (6)	0	4 (5)	1 (1)
TEAEs leading to discontinuation				
≥1 TEAE	13 (15)	–	–	–
≥1 treatment-related TEAE	11 (12)	0	10 (11)	1 (1)
Nausea	4 (5)	0	3 (3)	1 (1)
Diarrhoea	4 (5)	0	3 (3)	1 (1)
Fatigue	2 (2)	0	2 (2)	0
Weight decreased	2 (2)	0	2 (2)	0
Deep vein thrombosis	1 (1)	0	1 (1)	0
Epigastric discomfort	1 (1)	0	1 (1)	0

Malaise	1 (1)	0	1 (1)	0
Migraine	1 (1)	0	1 (1)	0
Vomiting	1 (1)	0	1 (1)	0

*Each of the patients could have experienced ≥1 treatment-related TEAE, with the potential for different events to be related to different treatments.

†Assessed by investigators for each therapy using their previous experience with pirfenidone and/or nintedanib, knowledge of the patient, the circumstances surrounding the event and an evaluation of any potential alternative causes.

TEAE, treatment-emergent adverse event.

Eighteen patients (20%) experienced severe (Common Terminology Criteria for Adverse Events Grade ≥3) TEAEs; these were considered treatment-related in six patients (7%) (Table 3). Sixteen patients (18%) experienced 18 serious TEAEs (Table 3 and Supplementary Table 3); two patients (2%) experienced one serious treatment-related TEAE each, both of which were attributed to nintedanib alone: one patient experienced a transient ischaemic attack but continued combination treatment without dose modification, and one patient experienced deep vein thrombosis and discontinued nintedanib but continued pirfenidone treatment. No fatal TEAEs were reported during the study.

Treatment-related hepatic TEAEs were reported in six patients (7%); these were attributed to nintedanib alone in five patients (Table 3). All events were Grade 1 (n=4) or Grade 2 (n=1) elevations in liver enzymes or Grade 1 abnormal hepatic function (n=1).

Table 3. Summary of severe, serious and hepatic TEAEs (safety population)

N=89	Patients with at least one TEAE* n (%)	Patients with at least one TEAE related to pirfenidone only† n (%)	Patients with at least one TEAE related to nintedanib only† n (%)	Patients with at least one TEAE related to both pirfenidone and nintedanib† n (%)
Severe TEAEs‡				
≥1 TEAE	18 (20)	–	–	–
≥1 treatment-related TEAE	6 (7)	0	5 (6)	1 (1)
Diarrhoea	2 (2)	0	1 (1)	1 (1)
Nausea	2 (2)	0	2 (2)	0
Fatigue	1 (1)	0	1 (1)	0
Muscle spasms	1 (1)	0	1 (1)	0
Weight decreased	1 (1)	0	1 (1)	0
Deep vein thrombosis	1 (1)	0	1 (1)	0
Serious TEAEs§				
≥1 TEAE	16 (18)	–	–	–
≥1 treatment-related TEAE	2 (2)	0	2 (2)	0
Transient ischaemic attack	1 (1)	0	1 (1)	0
Deep vein thrombosis	1 (1)	0	1 (1)	0
Hepatic TEAEs				
≥1 TEAE	7 (8)	–	–	–
≥1 treatment-related TEAE	6 (7)	0	5 (6)	1 (1)
GGT increased	2 (2)	0	2 (2)	0
ALT increased	2 (2)	0	2 (2)	0
AST increased	1 (1)	0	1 (1)	0
Aminotransferase increased	1 (1)	0	1 (1)	0
Blood ALP increased	1 (1)	0	1 (1)	0
Hepatic function abnormal	1 (1)	0	1 (1)	0

Elevated liver function test	1 (1)	0	1 (1)	0
Elevated liver enzymes	1 (1)	0	0	1 (1)

*Each of the patients could have experienced ≥1 treatment-related TEAE, with the potential for different events to be related to different treatments.

†Assessed by investigators for each therapy using their previous experience with pirfenidone and/or nintedanib, knowledge of the patient, the circumstances surrounding the event and an evaluation of any potential alternative causes.

‡Grade ≥3 using the adverse event severity grading scale for the Common Terminology Criteria for Adverse Events (version 4.03) [23].

§Meet any of the following criteria: are fatal or life-threatening, require or prolong inpatient hospitalisation, result in persistent or significant disability or incapacity, are congenital anomalies or birth defects in a neonate or infant born to a mother exposed to study drug or are significant medical events in the investigator's judgement.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; TEAE, treatment-emergent adverse event.

In an exploratory analysis of efficacy, mean (SE) percent predicted FVC and DLco declined by 0.8% (0.6) and 1.4% (0.8), respectively, from historical values to baseline and by 0.4% (0.5) and 1.9% (0.8), from baseline to Week 24 in patients with available data (Supplementary Figure 1). An exploratory analysis of K-BILD from baseline to Week 24 found that mean (SD) total score decreased by 1.3 (8.7) and individual subscores decreased by 2.4 (14.3) for psychological domain, 0.7 (15.9) for breathlessness and activities and 3.1 (17.0) for chest symptoms in patients completing 24 weeks of combination treatment; these changes might be due to chance, as the standard deviations are larger than the decreases (Supplementary Figure 2).

DISCUSSION

This study found that combined treatment with pirfenidone (1602–2403 mg/day) and nintedanib (200–300 mg/day) for 24 weeks in 89 patients with IPF was completed by 78% of patients. The safety profile of combination treatment did not reveal a different pattern of TEAEs to that expected with either treatment alone. Most TEAEs affected the GI system and were mild to moderate in severity. Furthermore, combination treatment taken for 24 weeks was not associated with increased risk of liver toxicity or photosensitivity. However, frequency of TEAEs (99%) was high for a 6-month study, comparable to frequencies observed in the 12-month pirfenidone and nintedanib monotherapy trials [18, 24]; although common GI TEAEs occurred less frequently after 6 months of pirfenidone or nintedanib monotherapy in these studies [25, 26].

Results of this 24-week study are in line with those of the recent 12-week INJOURNEY trial in terms of overall TEAE frequency [21]. Both studies found that combination treatment with nintedanib and pirfenidone had a similar safety profile to that of pirfenidone or nintedanib monotherapy in terms of proportion of patients experiencing TEAEs and types of TEAEs

reported. In the current study, patients were already tolerating a stable dose of pirfenidone prior to initiation of nintedanib, which may explain the higher incidence of TEAEs attributed to nintedanib versus pirfenidone by investigators. Similarly, the INJOURNEY trial (in which patients had already shown tolerability to nintedanib prior to initiating pirfenidone) found that more patients in the combination therapy group discontinued pirfenidone than nintedanib, although it should be noted that the study protocol recommended reducing pirfenidone dose before nintedanib dose for management of AEs other than diarrhoea [21].

In this study, treatment-related diarrhoea (49% of patients) was reported more frequently than any diarrhoea TEAEs in previous studies of pirfenidone monotherapy (25%) [24] and for combination treatment in the INJOURNEY trial (38%) [21] but less frequently than any diarrhoea TEAEs in previous studies of nintedanib monotherapy (62%) [18]. Moreover, treatment-related nausea (46% of patients) was reported by more patients than any nausea TEAEs in previous studies of pirfenidone or nintedanib monotherapy (36% and 24%, respectively) [18, 24] and was comparable with nausea TEAEs reported in the INJOURNEY trial (42%) [21], although the durations of the two studies were different, making such comparisons difficult.

Although the frequency of some TEAEs was higher in this 24-week study than in studies of each therapy alone, discontinuation rates (18% overall and 15% due to TEAEs) were numerically lower than those over 12 weeks in the INJOURNEY trial and over 52 weeks in the INPULSIS trials, and numerically similar to those over 52 weeks or more in the ASCEND and CAPACITY trials [9-11, 21]. Real-world data from the USA suggest that discontinuation rates for pirfenidone and nintedanib are higher in clinical practice (24% for pirfenidone and 34% for nintedanib; mean follow-up of 8–9 months) than in clinical trials [6, 7, 27]. Therefore, it will be important to further investigate tolerability of combination treatment and develop strategies to help reduce the burden of GI TEAEs. Current strategies to

reduce nausea associated with pirfenidone include taking each dose with food; for reducing diarrhoea or nausea associated with nintedanib, ensuring adequate hydration and use of antidiarrhoea or antiemetic medications are recommended [6, 7, 28, 29]. Dose adjustments are also recommended for management of AEs with both pirfenidone and nintedanib [6, 7], and available data suggest that dose adjustments have a positive impact on treatment persistence [30] while maintaining the benefit of treatment on FVC decline [31]. In this study, 26% of patients had an interruption of combination treatment but only 7% had both treatments simultaneously interrupted (for an average interruption length of approximately 4 days). This overall rate is similar to other clinical trial data for pirfenidone monotherapy (25%) [31].

The exploratory efficacy analyses found that there was little decline in lung function during treatment with combined pirfenidone and nintedanib, which is similar to results in the INJOURNEY trial [21]. However, with the absence of a control group and larger sample size, no firm conclusions can be drawn regarding efficacy of combination treatment in patients with IPF. Quality of life, measured using the K-BILD questionnaire, did not worsen in patients who completed 24 weeks of treatment, which is in line with quality of life findings from the EuroQoL-5D questionnaire used in the INJOURNEY trial [21].

The benefits of combining therapies with different mechanisms of action have been demonstrated in a variety of chronic diseases, including chronic obstructive pulmonary disease, asthma and pulmonary arterial hypertension (PAH) [32, 33]. Evidence from long-term studies in PAH has demonstrated that combination treatments targeting endothelin, nitric oxide and/or prostacyclin pathways have the potential to significantly delay disease progression [33]. Indeed, the treatment strategy for PAH is shifting towards use of first-line combination therapy [32]. Results of the current study suggest that combination treatment with pirfenidone and nintedanib could provide a viable future option for patients with IPF.

However, combination therapy might not be suitable for all patients, and further research will be necessary to study long-term benefits and risks of combination treatment in a controlled study with treatment duration of >6 months.

Limitations of this study include the lack of control or comparator group and small sample size, which are due to the exploratory nature of this study. Furthermore, only patients who tolerated pirfenidone were included, which may introduce a bias towards patients less likely to experience TEAEs; and patients could have treatment interrupted for <28 consecutive days and still be considered to have completed 24 weeks of combination treatment. Thus, tolerance to treatment in the real world might be less than that reflected in the completion rate. Given that pirfenidone and nintedanib treatment can result in similar AEs [9, 10, 18], there may have been uncertainty regarding whether some TEAEs were related specifically to pirfenidone or nintedanib. Since nintedanib was added to stable pirfenidone treatment in this study, conclusions cannot be drawn for pirfenidone added to stable nintedanib treatment or when both treatments are started simultaneously. Although patients with more advanced IPF (percent predicted FVC <50% and DLco <30%) might also be expected to benefit from combination treatment, these patients were excluded from the trial. However, eligibility criteria were similar to the pivotal trials [9-11], allowing comparison of safety data between this study and clinical trials of pirfenidone monotherapy. Finally, changes in FVC, DLco and K-BILD were tested as exploratory endpoints, and the study was not designed to formally assess efficacy of combination treatment; historical values were used to compare pre-treatment changes in FVC and DLco.

Summary

Combined use of pirfenidone and nintedanib for 24 weeks was tolerated by the majority of patients with IPF, and associated with similar types of TEAEs and discontinuation rates

expected with either treatment alone. Results of this trial add to the limited safety data of combination treatment taken for >3 months and encourage further study to determine efficacy and safety of pirfenidone and nintedanib taken as combination treatment versus monotherapy in patients with IPF.

Declarations

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Conflicts of interests

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Author contributions

All authors were involved in the design of this study and the interpretation of study results, contributed to the manuscript from the outset, and read and approved the final draft. All authors vouch for the accuracy of the content included in the final manuscript.

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Figure legends

Figure 1. Study design

*Patients receiving prohibited medication discontinued that medication during washout; other patients entered directly into screening. †Taking place 28–35 days after the end of combination treatment for patients who completed the 24-week combination treatment period, or 28–35 days after the decision to discontinue nintedanib for patients who discontinued prematurely or had treatment interrupted for ≥28 consecutive days.
ICF, informed consent form signed.

Figure 2. Patient disposition

*Combined pirfenidone and nintedanib taken at any dose.

†One patient was listed in the active lung transplant list, and one patient did not wish to take nintedanib. TEAE, treatment-emergent adverse event.

Figure 3. Time to discontinuation* (safety population)

*Includes time to early discontinuation or study completion. †Forty patients completed the planned 24 weeks of combination treatment before study Day 168 and were, therefore, censored on the Kaplan–Meier curve (represented by an x).

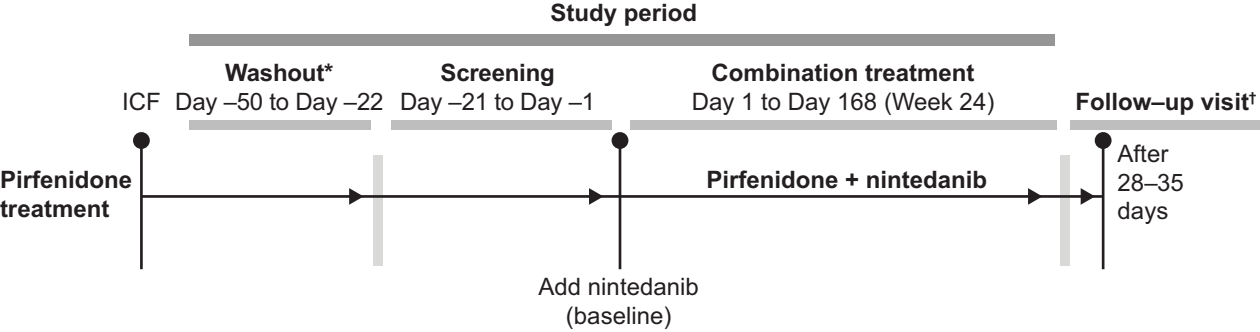

Study period
Washout*
Day –50 to Day –22
Screening
Day –21 to Day –1
Combination treatment
Day 1 to Day 168 (Week 24)
Follow–up visit†
ICF
Pirfenidone treatment
Pirfenidone + nintedanib
After 28–35 days
Add nintedanib (baseline)

Figure 2

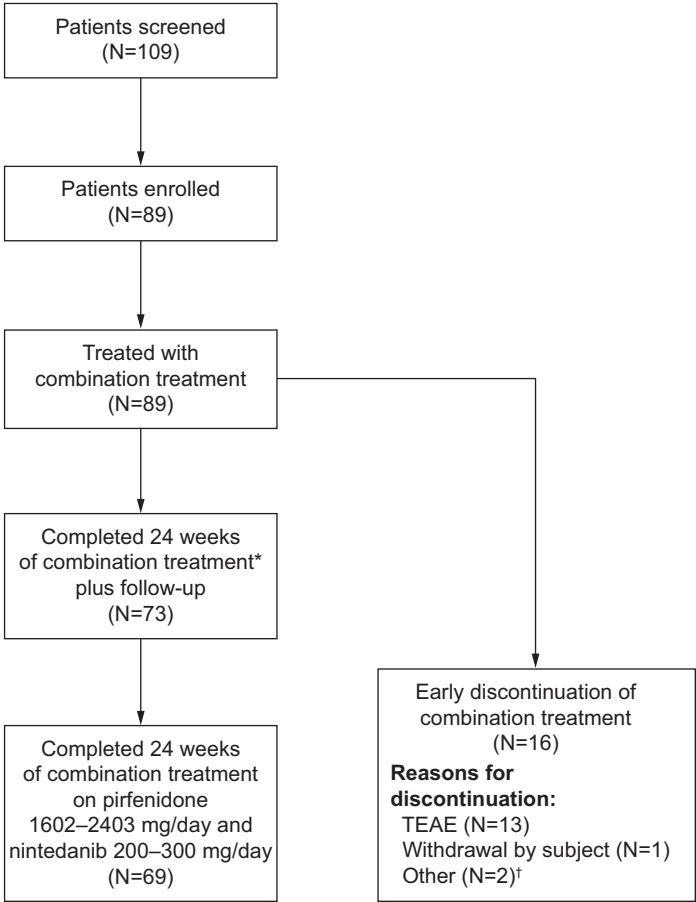
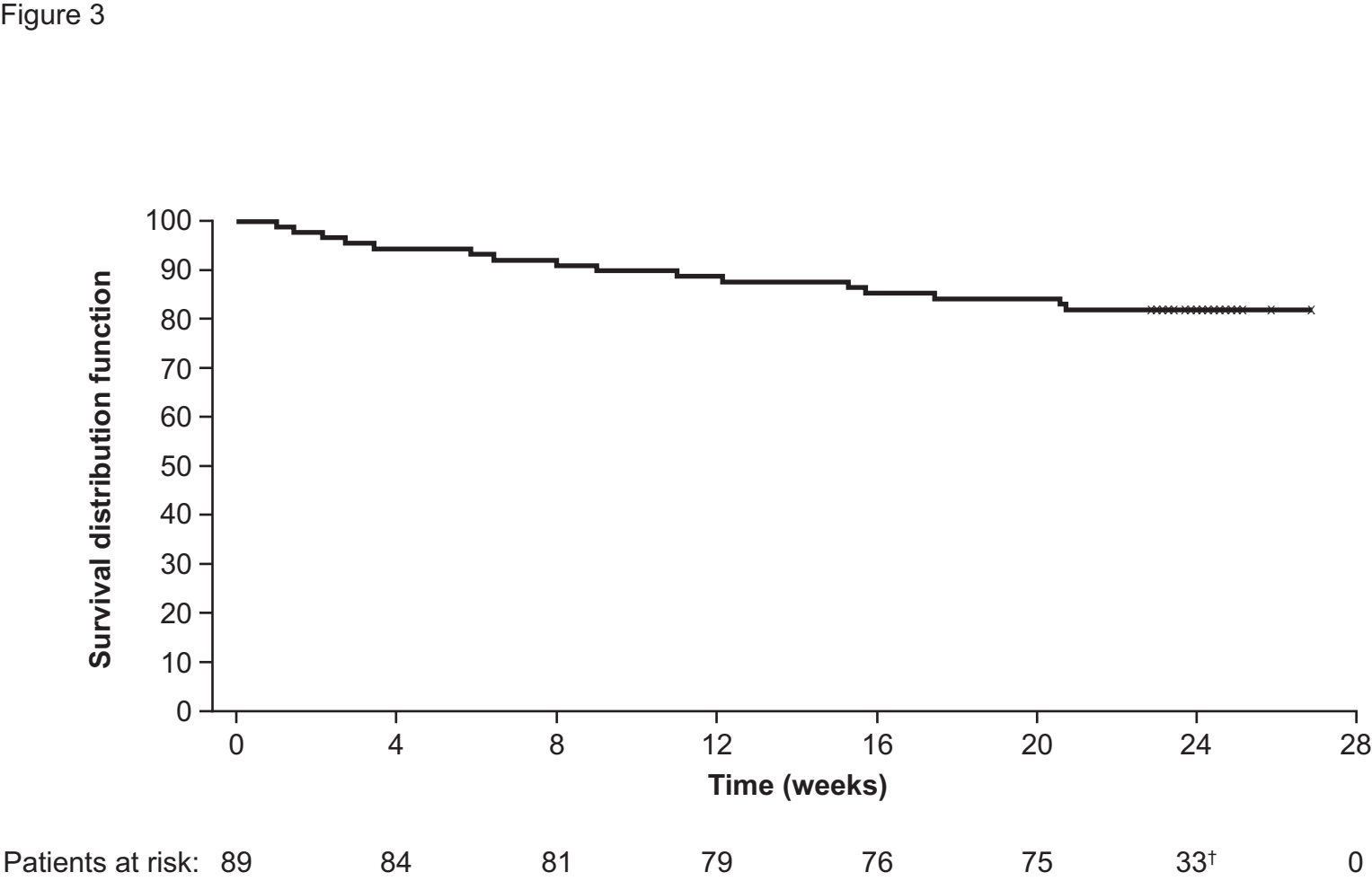

Patients screened
(N=109)
Patients enrolled
(N=89)
Treated with
combination treatment
(N=89)
Completed 24 weeks
of combination treatment*
plus follow-up
(N=73)
Completed 24 weeks
of combination treatment
on pirfenidone
1602–2403 mg/day and
nintedanib 200–300 mg/day
(N=69)
Early discontinuation of
combination treatment
(N=16)
Reasons for
discontinuation:
TEAE (N=13)
Withdrawal by subject (N=1)
Other (N=2)†

Figure 3


Survival distribution function
100
90
80
70
60
50
40
30
20
10
0
0
4
8
12
16
20
24
28
Time (weeks)
Patients at risk: 89 84 81 79 76 75 33† 0

Supplementary Appendix 1. Supplementary methods

Combination treatment administration

Over the 24-week combination treatment period, pirfenidone was continued at 1602–2403 mg/day (up to three 267-mg capsules three times daily), taken with food at the same times each day; and nintedanib was administered at 200–300 mg/day, taken with food at the same times each day. Nintedanib was titrated over the first 2 weeks from 100 mg/day during Week 1 (one 100-mg capsule once daily), to 200 mg/day during Week 2 (one 100-mg capsule twice daily [BID]) to a maintenance dose of 300 mg/day from Week 3 onwards (one 150-mg capsule BID). Twice-daily doses were taken approximately 12 hours apart.

For patients with a treatment interruption of <28 consecutive days, study treatment could be restarted at the discretion of the investigator. Patients who had study treatment interrupted for ≥28 consecutive days could not restart treatment in the study and were withdrawn.

Assessments

Physical examination findings, clinical laboratory tests, electrocardiograms, early treatment discontinuation (including reasons) and deaths and cause of deaths were also recorded. A patient diary was used to report TEAEs and investigators sought information on TEAEs at each patient visit. The patient diary was also used to record daily dosing adherence for both pirfenidone and nintedanib, and concomitant medication use from screening to final follow-up. Concomitant medications were coded according to the proprietary Genentech Drug Thesaurus (e.g. bronchodilators and antiasthmatics). Physical examinations were performed at screening, baseline (Day 1 of nintedanib treatment), Weeks 2, 4, 8, 12, 16, 20 and 24 and follow-up (or early discontinuation, if applicable). Clinical laboratory tests were undertaken at screening,

baseline, Weeks 1, 2, 3, 4, 8, 12, 16, 20 and 24 and follow-up (or early discontinuation, if applicable). TEAEs were coded to a preferred term and system organ class using the Medical Dictionary for Regulatory Activities (Version 20.0) and graded using the Common Terminology Criteria for Adverse Events, version 4.03 [1]. Investigators assessed whether each TEAE was related to pirfenidone, nintedanib, both or neither using their knowledge of the patient, the circumstances surrounding the event and an evaluation of any potential alternative causes. This assessment of TEAE causality considered the course of the event, known association of the event with the study drug or similar treatments, and with IPF, presence of risk factors or use of concomitant medications known to increase the occurrence of the event, and presence of non–treatment-related factors known to be associated with the event.

During combination treatment, nintedanib dosage was reduced or interrupted in patients who experienced new diarrhoea, vomiting or nausea TEAEs that persisted despite appropriate supportive care and symptomatic treatment (e.g. adequate hydration, antidiarrhoeal medication, antiemetic medication); whether pirfenidone dosage was maintained, reduced or interrupted was left to the judgement of the investigator. If diarrhoea, vomiting or nausea persisted for ≥28 days or was judged to be intolerable, nintedanib was discontinued and the patient was withdrawn from the study.

FVC and DLco were measured at screening, baseline and Weeks 12 and 24 (or early discontinuation, if applicable). An exploratory assessment of efficacy measured change in percent predicted FVC and DLco (as reported by the investigator) between baseline and Week 24. Historical values of percent predicted FVC and DLco closest to 6 months before start of screening were used as a comparison. Change in K-BILD score from baseline to Week 24 (or early discontinuation, if applicable) was also analysed in an exploratory analysis.

An independent data monitoring committee (iDMC) reviewed safety data and advised on study conduct three times during the study.

Sample size prediction

A sample size of approximately 80 patients was selected based on AE discontinuation rates after one year observed in the randomised Phase III pirfenidone studies (15%) and randomised Phase II and III nintedanib studies (21%) [2, 3]. Since discontinuation rates after 24 weeks for pirfenidone were 6–8% in the CAPACITY studies, it was estimated that nintedanib discontinuation rates after 24 weeks would be around 10–11%. However, it is possible that addition of nintedanib to ongoing pirfenidone treatment could increase the proportion of patients discontinuing due to TEAEs, since both pirfenidone and nintedanib are associated with increased risk of GI and hepatic AEs. Assuming 85% of the patients completed 24 weeks of combination treatment, a sample size of 80 patients would be expected to yield an actual completion rate of 77.2–92.8% using a 95% confidence interval.

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Supplementary Figure 1. Exploratory analysis of change in percent predicted a) FVC and b) DLco (safety population)

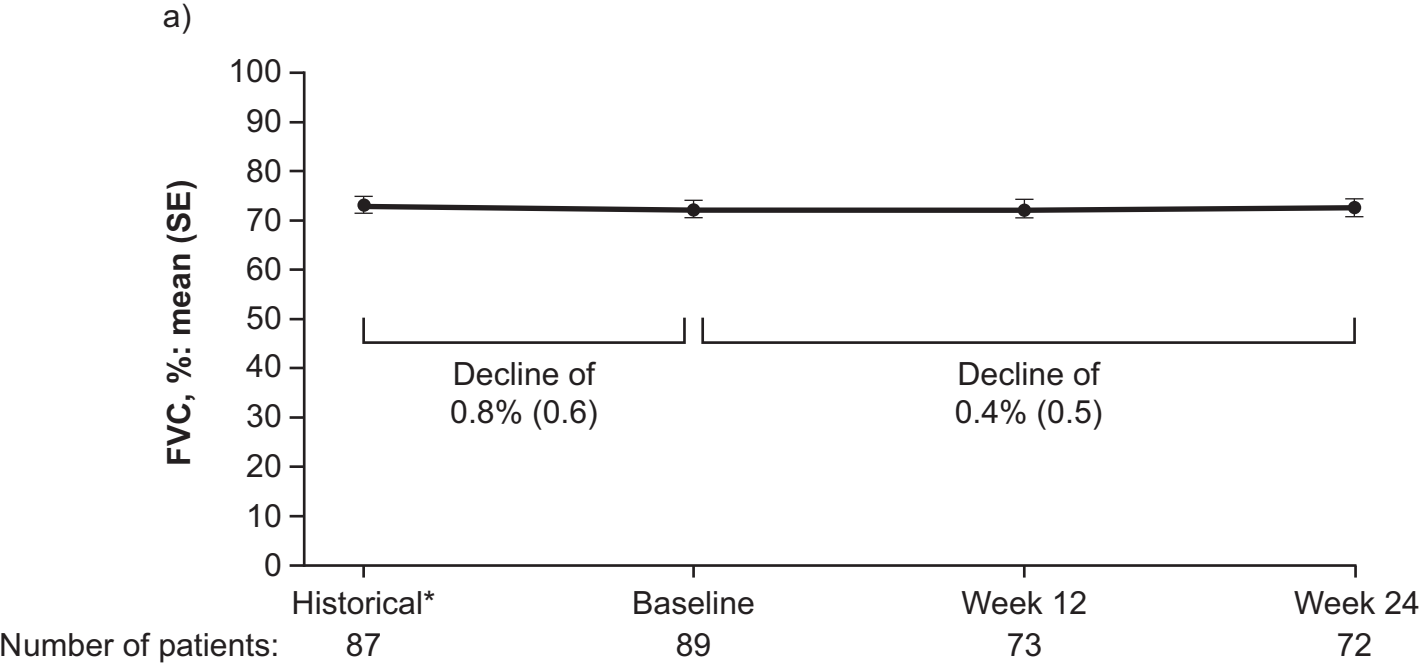
*Pulmonary function values closest to 6 months before start of screening.

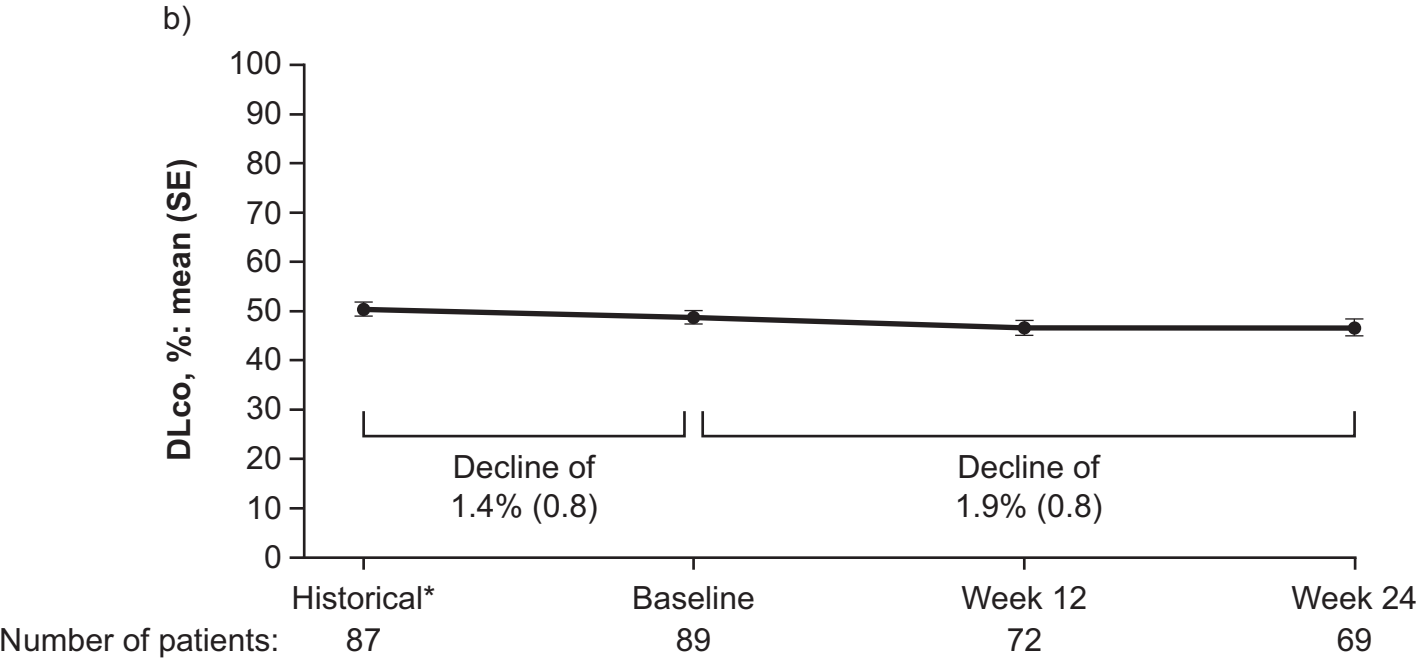
DLco, carbon monoxide diffusing capacity; FVC, forced vital capacity; SE, standard error.

Supplementary Figure 2. Exploratory analysis of K-BILD (safety population)

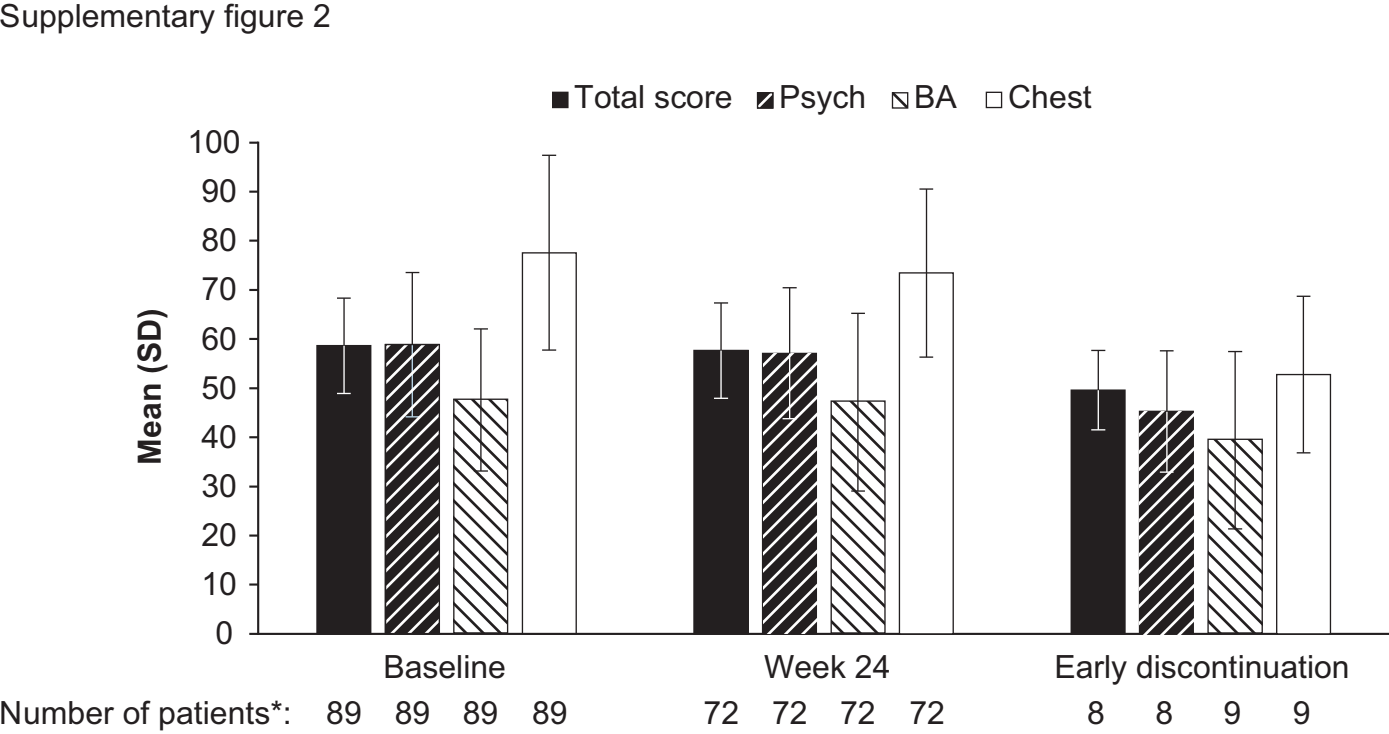
*All patients with non-missing data. BA, breathlessness and activities; Chest, chest symptoms; K-BILD, King's Brief Interstitial Lung Disease questionnaire; Psych, psychological domains; SD, standard deviation.

Supplementary figure 1





Supplementary figure 2



Supplementary Table 1. Additional entry criteria not described within the text

Description of inclusion criteria
• For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use two adequate methods of contraception, including at least one method with a failure rate of <1% per year, during the treatment period and for at least 3 months after the final follow-up visit
• For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm
Description of exclusion criteria
• Clinical evidence of active infection
• Any condition that is likely to result in death in the 12 months after the start of screening
• Lung transplantation anticipated or any planned significant surgical intervention
• Known hypersensitivity to the active substance or any excipient of either pirfenidone or nintedanib
• Hepatic impairment and/or severe renal impairment
• History of GI tract perforation, unstable or deteriorating cardiac or pulmonary disease (other than IPF), long QT syndrome, alcohol or substance abuse, use of any tobacco product, etc
• Bleeding risk
• Pregnancy or lactation

GI, gastrointestinal; IPF, idiopathic pulmonary fibrosis; QT interval, time between Q and T waves.

Supplementary Table 2. Medications prohibited in the 28 days before start of screening and during the study

- Any cytotoxic, immunosuppressive, cytokine-modulating or receptor-antagonist agent
- Strong CYP1A2 inhibitors (e.g. enoxacin, fluvoxamine); moderate CYP1A2 inhibitors could be administered at pre-specified low doses if the patient was closely monitored for AEs
- Inhibitors or inducers of P-glycoprotein or CYP3A4
- Other medications specifically used for treatment of IPF

AE, adverse event; CYP1A2, cytochrome P450 1A2; CYP3A4, cytochrome P450 3A4; IPF, idiopathic pulmonary fibrosis.

Supplementary Table 3. Serious TEAEs (safety population)

N=89	TEAEs, n
Infections and infestations	
Cholecystitis infective	1
Influenza	1
Pneumonia	1
Tracheobronchitis	1
Respiratory, thoracic and mediastinal disorders	
IPF	2
Pneumothorax	3
Pneumomediastinum	1
Neoplasm benign, malign, unspecified	
Invasive ductal breast carcinoma	1
Prostate cancer	1
GI disorders	
Pancreatitis	1
Hepatobiliary disorders	
Cholelithiasis	1
Injury, poisoning and procedural complications	
Concussion	1
Musculoskeletal and CTD	
Lumbar spinal stenosis	1
Nervous system disorders	
TIA*	1
Vascular disorders	
DVT*	1

*Event considered related to treatment (nintedanib only).

CTD, connective tissue disorders; DVT, deep vein thrombosis; GI, gastrointestinal; IPF, idiopathic pulmonary fibrosis; TEAE, treatment-emergent adverse event; TIA; transient ischaemic attack.