Nintedanib in patients with idiopathic pulmonary fibrosis: Combined evidence from the TOMORROW and INPULSIS® trials

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A R T I C L E I N F O

A B S T R A C T

Background and purpose: The Phase II TOMORROW trial and two Phase III INPULSIS® trials investigated the efficacy and safety of nintedanib versus placebo in patients with idiopathic pulmonary fibrosis (IPF). To obtain an overall estimate of the treatment effect of nintedanib 150 mg twice daily (bid), pooled and meta-analyses of data from these three trials were conducted.
Methods: Pooled and meta-analyses were conducted for annual rate of decline in forced vital capacity (FVC), time to first acute exacerbation, change from baseline in St George's Respiratory Questionnaire (SGRQ) total score and mortality over 52 weeks.
Results: 1231 patients (nintedanib n = 723, placebo n = 508) were included in the pooled analysis. Adjusted annual rate of decline in FVC was −112.4 mL/year with nintedanib and −223.3 mL/year with placebo (difference: 110.9 mL/year [95% CI: 78.5, 143.3]; p < 0.0001). The hazard ratio for time to first acute exacerbation was 0.53 (95% CI: 0.34, 0.83; p = 0.0047). Adjusted mean change from baseline in SGRQ score at week 52 was 2.92 with nintedanib and 4.97 with placebo (difference: −2.05 [95% CI: −3.59, −0.50]; p = 0.0095). Hazard ratios for time to all-cause and on-treatment mortality were 0.70 (95% CI: 0.46, 1.08; p = 0.0954) and 0.57 (95% CI: 0.34, 0.97; p = 0.0274), respectively, in favour of nintedanib. The meta-analysis was generally consistent with the pooled analysis. Diarrhoea was the most frequent adverse event in the nintedanib group (61.5% of patients treated with nintedanib versus 17.9% of patients treated with placebo).
Conclusion: Nintedanib has a beneficial effect on slowing disease progression in patients with IPF.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disease characterised by worsening dyspnoea, decline in forced vital capacity (FVC) and deterioration in patients' health-related quality of life (HRQL) [1–4]. While IPF is ultimately fatal, its clinical course is variable and unpredictable, with some patients experiencing a rapid decline in lung function while others progress much more slowly [3,5]. Some patients with IPF experience sudden deteriorations in symptoms and respiratory function during periods of relative stability, which are known as acute exacerbations when

the cause of the acute deterioration is unknown [6].

Nintedanib, an intracellular inhibitor of tyrosine kinases including the fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR) and vascular endothelial growth factor receptor (VEGFR) [7], has been approved for the treatment of IPF in the US [8] and EU [9]. The efficacy and safety of nintedanib in patients with IPF have been investigated in three international Phase II/III trials with similar design. The TOMORROW trial (period 1) was a Phase II randomised, placebo-controlled, 52-week, dose-finding trial of nintedanib in 428 patients with IPF [10]. Patients were randomised to one of four doses of nintedanib or placebo using a stepwise increasing dose approach. The primary endpoint was the annual rate of decline in FVC; secondary endpoints included change from baseline in total score on the St George's Respiratory Questionnaire (SGRQ) over 52 weeks, an instrument originally developed for patients with obstructive lung disease, but frequently used to evaluate HRQL in patients with IPF [11], and the incidence of and time to first investigator-reported acute exacerbation. Compared with placebo, nintedanib 150 mg bid was associated with a reduced annual rate of decline in FVC, a decrease in SGRQ total score, and a lower incidence of acute exacerbations and had an acceptable safety and tolerability profile [10]. Based on the findings of the TOMORROW trial, nintedanib 150 mg bid was investigated in two replicate, randomised, placebo-controlled, 52-week, Phase III trials: the INPULSIS® trials [12]. As in the TOMORROW trial, the primary endpoint in the INPULSIS® trials was the annual rate of decline in FVC. Time to first investigator-reported acute exacerbation and change from baseline in SGRQ total score, both analysed over 52 weeks, were key secondary endpoints. Compared with placebo, nintedanib significantly reduced the annual rate of decline in FVC in both INPULSIS® trials. In INPULSIS®-2, there was a significant difference in favour of nintedanib on time to first acute exacerbation and change from baseline in SGRQ total score, while there was no significant difference between the nintedanib and placebo groups for either key secondary endpoint in INPULSIS®-1. Nintedanib had a tolerability profile that was manageable for most patients, with diarrhoea being the most frequently reported adverse event [12]. All-cause, on-treatment and respiratory mortality were secondary endpoints in the TOMORROW and INPULSIS® trials; however, none of these trials was powered to show a difference in mortality between nintedanib and placebo.

In order to obtain an overall estimate of the treatment effect of nintedanib 150 mg bid, data from the nintedanib 150 mg bid and placebo groups of the TOMORROW and INPULSIS® trials were pooled. The similarity of the trial designs and the consistent results observed on the primary endpoint justified the data from these three trials being pooled. Due to some differences in data collection and efficacy analyses between the TOMORROW and INPULSIS® trials, a *meta*-analysis was also conducted. Safety data from the trials were pooled to obtain a more precise estimate of the incidence of adverse events.

2. Materials and methods

2.1. Pooled analysis

A pooled analysis of data from the nintedanib 150 mg bid and placebo groups from the TOMORROW and INPULSIS® trials was conducted on the primary and key secondary endpoints in the INPULSIS® trials (annual rate of decline in FVC, time to first investigator-reported acute exacerbation, change from baseline in SGRQ total score), plus change from baseline in FVC % predicted over 52 weeks, and all-cause, on-treatment and respiratory mortality.

Small differences in data collection, time windowing and censoring rules between the TOMORROW and INPULSIS® trials were addressed as follows. In the TOMORROW trial, FVC data were collected in litres; these were converted into millilitres for the pooled analysis. In the TOMORROW trial, FVC data collected after premature discontinuation of trial drug were not used in the primary analyses and if ≥1 FVC measurement was allocated to the same visit, only the first assessment was used. Conversely, in the INPULSIS® trials, data collected after premature discontinuation of trial drug were used in the primary analysis and if ≥1 measurement was allocated to the same visit, time windowing was used to select the assessment closest to the planned visit. For the pooled analysis, data collected after premature discontinuation of trial drug in TOMORROW were included and time windowing was applied as per the INPULSIS® trials. Similarly, unlike in the INPULSIS® trials, in the TOMORROW trial, SGRQ data were not collected after premature discontinuation of trial drug or during the post-treatment follow-up period and if ≥1 SGRQ assessment was allocated to the same visit, only the first assessment was used. For the pooled analysis, all the data from the TOMORROW and INPULSIS® trials up to 372 days (plus 7-day margin) after randomisation were included and time windowing was applied as per the INPULSIS® trials. There were small differences in the definition of an acute exacerbation between the TOMORROW and INPULSIS® trials [10,12]. In the TOMORROW and INPULSIS® trials, time to first acute exacerbation was analysed using data collected up to 366 and 372 days (plus 7-day margin) after randomisation, respectively; patients who did not experience an event were then censored. For the pooled analysis, data collected up to 372 days (plus 7-day margin) in all three trials were used.

For mortality endpoints, a blinded adjudication committee reviewed medical documentation to adjudicate the primary cause of deaths in the TOMORROW and INPULSIS® trials. Results for respiratory mortality were based on results of this adjudication. Analyses for all-cause and respiratory mortality were based on data collected between randomisation and up to 372 days after randomisation. On-treatment mortality was defined as deaths that occurred between randomisation and the end of the post-treatment follow-up period (28 days in the INPULSIS® trials and up to 14 days in the TOMORROW trial).

The statistical models used in the pooled analysis were the same as those used in the INPULSIS® trials [12] except for the addition of trial as a fixed effect.

Safety was assessed by means of clinical and laboratory evaluation at study visits and the recording of adverse events using the Medical Dictionary for Regulatory Activities (MedDRA) (version 16.1). Safety analyses were descriptive.

All pooled analyses were based on data from patients who received ≥1 dose of trial drug (treated set).

2.2. Meta-analysis

A *meta*-analysis was performed on the primary and key secondary endpoints in the INPULSIS® trials, plus change from baseline in FVC % predicted over 52 weeks, and all-cause and respiratory mortality, using data from the nintedanib 150 mg bid and placebo groups from the three trials. The nintedanib versus placebo estimates from the primary analyses conducted in the three trials were used to obtain estimates of the overall treatment effect. Efficacy analyses were based on patients who were randomised in the TOMORROW trial and patients who received ≥1 dose of trial drug (treated set) in the INPULSIS® trials. Standard *meta*-analysis methodology was used (see Supplementary Material for further details).

3. Results

3.1. Patients

The pooled data set included 723 patients treated with nintedanib and 508 patients treated with placebo; baseline characteristics were similar between the nintedanib and placebo groups (Table 1). Baseline characteristics were generally similar across the individual trials except for a higher proportion of Asian patients in INPULSIS®-2 (Supplementary Table S1).

3.2. Exposure

Mean (SD) total duration of exposure was 10.2 (3.4) months in patients treated with nintedanib and 10.8 (2.9) months in patients treated with placebo. Median total duration of exposure was 11.9 months in both groups.

3.3. Pooled analysis

3.3.1. Annual rate of decline in FVC and change from baseline in FVC % predicted

In the pooled analysis, the adjusted annual rate of decline in FVC was −112.4 mL/year (95% CI: −133.2, −91.5) with nintedanib and −223.3 mL/year (95% CI: −248.1, −198.5) with placebo (difference: 110.9 mL/year [95% CI: 78.5, 143.3]; p < 0.0001) (Fig. 1). Observed changes in FVC over time in the pooled analysis are presented in Fig. 2. The adjusted absolute mean change from baseline in FVC % predicted at week 52 was −2.8% (95% CI: −3.3, −2.2) in the nintedanib group and −6.0% (95% CI: −6.6, −5.3) in the placebo group (difference: 3.2% [95% CI: 2.5, 4.0]; p < 0.0001).

3.3.2. Time to first investigator-reported acute exacerbation

In the pooled analysis, the hazard ratio (HR) for time to first acute exacerbation was 0.53 ([95% CI: 0.34, 0.83]; p = 0.0047), in favour of nintedanib (Fig. 3). The proportion of patients with ≥1 acute exacerbation was 4.6% in the nintedanib group and 8.7% in the placebo group.

3.3.3. SGRQ total score

In the pooled analysis, the adjusted mean change from baseline in SGRQ total score at week 52 was 2.92 (95% CI: 1.83, 4.01) in the nintedanib group and 4.97 (95% CI: 3.75, 6.19) in the placebo group
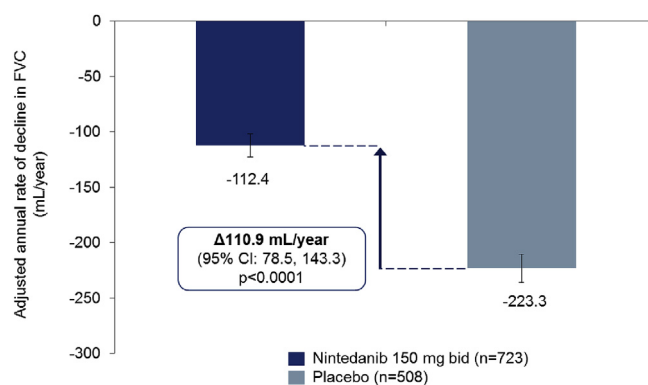

Fig. 1. Annual rate of decline in FVC: pooled data from the TOMORROW and INPULSIS® trials.

(difference: −2.05 [95% CI: −3.59, −0.50]; p = 0.0095) in favour of nintedanib (Fig. 4).

3.3.4. Mortality

A 30% reduction in the risk of all-cause mortality was observed with nintedanib versus placebo over 52 weeks (HR 0.70 [95% CI: 0.46, 1.08]; p = 0.0954). The proportion of patients who died from any cause over 52 weeks was 5.8% in the nintedanib group and 8.3% in the placebo group. Nintedanib significantly reduced the risk of on-treatment mortality versus placebo (HR 0.57 [95% CI: 0.34, 0.97]; p = 0.0274). The proportion of patients who died during the on-treatment period was 3.5% in the nintedanib group and 6.7% in the placebo group. A 38% reduction in the risk of respiratory mortality was observed with nintedanib versus placebo over 52 weeks (HR 0.62 [95% CI: 0.37, 1.06]; p = 0.0779). The proportion of patients who died due to a respiratory cause over 52 weeks was 3.6% in the nintedanib group and 5.7% in the placebo group.

3.3.5. Adverse events

A summary of pooled data on adverse events is presented in Table 2. Data on adverse events in the individual trials are shown in Supplementary Table S2. Adverse events led to premature treatment discontinuation in 20.6% of patients in the nintedanib group versus 15.0% of patients in the placebo group. The most frequently reported adverse event in patients treated with nintedanib was diarrhoea, which was reported in 61.5% of patients in the

Table 1
Baseline characteristics: pooled data from the TOMORROW and INPULSIS® trials.

	Nintedanib 150 mg bid (n = 723)	Placebo (n = 508)
Age, years, mean (SD)	66.5 (8.1)	66.6 (8.0)
Male, n (%)	572 (79.1)	397 (78.1)
Race, n (%)		
White	421 (58.2)	313 (61.6)
Asian	218 (30.2)	148 (29.1)
Black	2 (0.3)	0 (0.0)
Missing[a]	82 (11.3)	47 (9.3)
Weight, kg, mean (SD)	78.7 (16.4)	78.4 (16.0)
Current or ex-smoker, n (%)	524 (72.5)	358 (70.5)
Time since diagnosis, years, mean (SD)	1.6 (1.3)	1.6 (1.3)
FVC, mL, mean (SD)	2714 (762)	2738 (803)
FVC, % predicted, mean (SD)	79.7 (17.7)	79.7 (18.1)
FEV_1/FVC ratio, %, mean (SD)	81.6 (6.0)	81.7 (5.9)
DL_{CO}, % predicted, mean (SD)	47.4 (13.2)	47.2 (13.3)
SGRQ total score, mean (SD)[b]	39.7 (19.1)	40.0 (18.5)

Treated set (patients treated with ≥1 dose of trial drug).
 [a] In France, regulation did not permit the collection of data on race.
 [b] n = 708 in the nintedanib group and n = 504 in the placebo group.
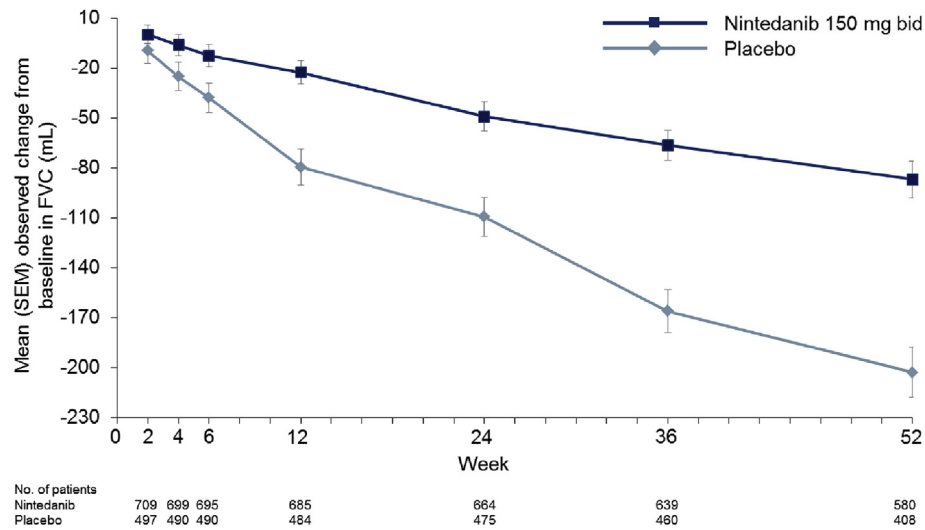
Fig. 2. Changes in FVC over time: pooled data from the TOMORROW and INPULSIS® trials.
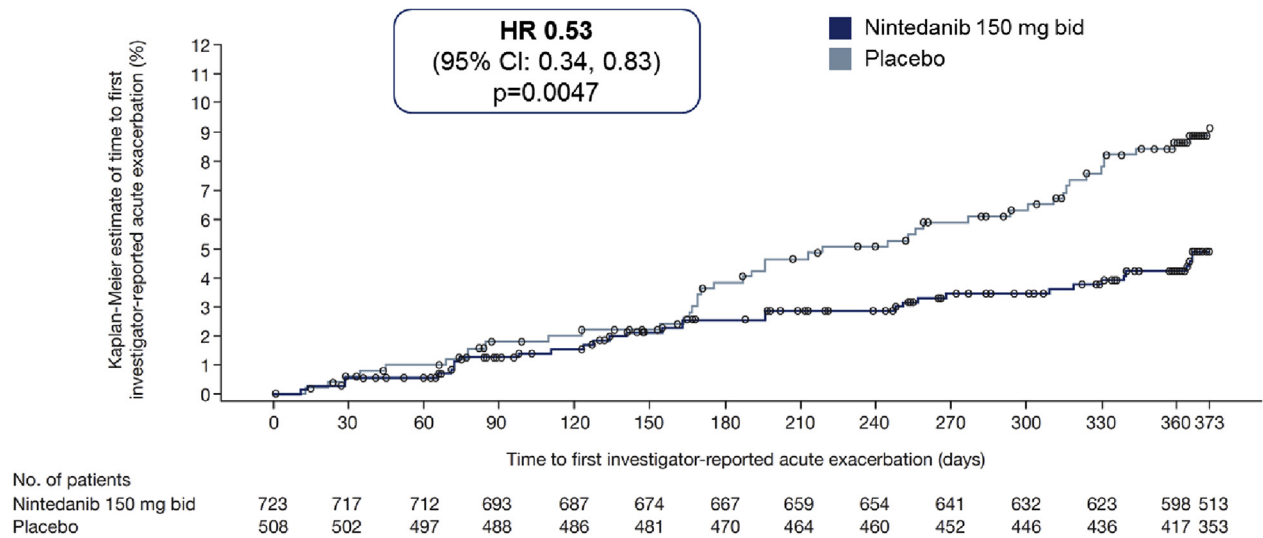

Fig. 3. Time to first investigator-reported acute exacerbation: pooled data from the TOMORROW and INPULSIS® trials.
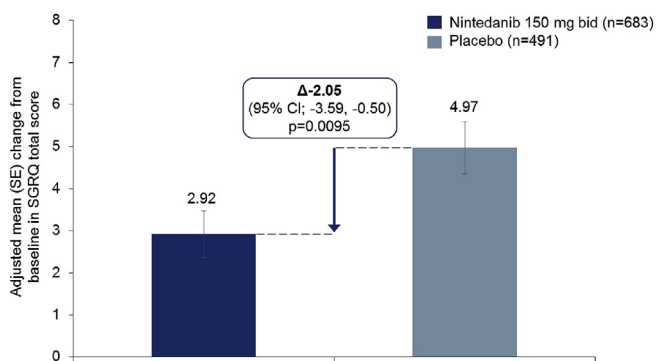

Fig. 4. Change from baseline in SGRQ total score: pooled data from the TOMORROW and INPULSIS® trials.

nintedanib group versus 17.9% of patients in the placebo group and led to premature treatment discontinuation in 5.3% versus 0.2% of patients in these groups, respectively. The proportion of patients

who had ≥1 serious adverse event was comparable between the nintedanib and placebo groups (30.0% and 30.1%, respectively).

3.4. Meta-analysis

In general, the treatment effect sizes observed in the pooled analyses were confirmed in the *meta*-analysis (See Supplementary Material).

4. Discussion

We conducted a pooled analysis of data from the three international randomised, placebo-controlled, 52-week trials of nintedanib in patients with IPF, which was complemented with a *meta*-analysis. In general, the treatment effect sizes were similar across the pooled and *meta*-analyses. Nintedanib consistently slowed disease progression by significantly reducing the annual rate of decline in FVC compared with placebo. The treatment effect of nintedanib on change from baseline in SGRQ total score was modest and consistent across the pooled and *meta*-analyses.

Table 2
Adverse events: Pooled data from the TOMORROW and INPULSIS® trials.

N (%)	Nintedanib 150 mg bid (n = 723)	Placebo (n = 508)
Any adverse event(s)	689 (95.3)	456 (89.8)
Most frequent adverse events[a]		
Diarrhoea	445 (61.5)	91 (17.9)
Nausea	176 (24.3)	36 (7.1)
Nasopharyngitis	93 (12.9)	79 (15.6)
Cough	93 (12.9)	75 (14.8)
Vomiting	85 (11.8)	15 (3.0)
Decreased appetite	81 (11.2)	24 (4.7)
Bronchitis	76 (10.5)	56 (11.0)
Progression of IPF[b]	68 (9.4)	72 (14.2)
Upper respiratory tract infection	65 (9.0)	55 (10.8)
Dyspnoea	55 (7.6)	59 (11.6)
Severe adverse event(s)	193 (26.7)	119 (23.4)
Serious adverse event(s)	217 (30.0)	153 (30.1)
Fatal adverse event(s)	38 (5.3)	43 (8.5)
Adverse event(s) leading to treatment discontinuation[c]	149 (20.6)	76 (15.0)
Diarrhoea	38 (5.3)	1 (0.2)
Nausea	17 (2.4)	0 (0.0)
Progression of IPF[a]	15 (2.1)	27 (5.3)
Decreased appetite	11 (1.5)	1 (0.2)
Weight decreased	8 (1.1)	1 (0.2)
Abdominal pain	7 (1.0)	1 (0.2)
Vomiting	7 (1.0)	1 (0.2)
Pneumonia	6 (0.8)	5 (1.0)

Treated set (patients treated with ≥1 dose of trial drug).
[a] Adverse events reported by >10% of patients in either treatment group.
[b] Corresponds to the MedDRA term 'IPF', which included disease worsening and IPF exacerbations.
[c] Adverse events leading to treatment discontinuation in ≥1% of patients in either treatment group by MedDRA preferred term.

A significant benefit in favour of nintedanib on time to first investigator-reported acute exacerbation was observed in the pooled analysis. In all models, the hazard ratio estimates were associated with wide confidence intervals due to the small number of acute exacerbations observed. In a recent systematic review of published data on the clinical effectiveness of treatments for IPF and *meta*-analysis of key efficacy outcomes, Loveman et al. reported a significant odds ratio of 0.50 (95% CI: 0.31, 0.79) in favour of nintedanib compared with placebo for the proportion of patients experiencing ≥1 investigator-reported acute exacerbation in the TOMORROW and INPULSIS® trials [13]. In this *meta*-analysis, data on the proportion of patients experiencing an acute exacerbation (odds ratio) were used whereas in our *meta*-analysis, data on time to first acute exacerbation (hazard ratio) were used, as per the key secondary endpoint defined in the INPULSIS® trials; however, the results obtained in the two analyses were consistent.

As well as being consistent across the TOMORROW and INPULSIS® trials and across analyses, the treatment effect of nintedanib has been shown to be consistent across patient subgroups. In pre-specified subgroup analyses of pooled data from just the INPULSIS® trials a consistent effect of nintedanib on the annual rate of decline in FVC, time to first investigator-reported acute exacerbation and change from baseline in SGRQ total score was demonstrated across subgroups of patients defined by a variety of baseline characteristics, including sex, age (<65, ≥65 years), race (White, Asian) and baseline FVC % predicted (≤70%, >70%) [14].

Due to relatively low death rates in patients with IPF and mild or moderate impairment of lung function, an adequately powered trial to assess mortality in this population would be challenging [2,15]. However, mortality is a clinically meaningful endpoint in IPF, and pooling the data from three trials allowed for a more precise estimate on the effect of nintedanib on mortality. In this pooled analysis of data from the TOMORROW and INPULSIS® trials, there were trends towards a reduction in the risk of all-cause and respiratory mortality and a significant reduction in the risk of on-treatment mortality. In addition, in the *meta*-analysis of the TOMORROW and INPULSIS® trials conducted by Loveman et al. [13], there was a significantly lower odds ratio for absolute decline in FVC of >10% predicted with nintedanib compared with placebo at week 52. These findings reflect the overall beneficial effects of nintedanib on slowing disease progression and have been used to further support the appropriateness of decline in FVC as a primary endpoint in clinical trials in patients with IPF [16].

The safety and tolerability profile of nintedanib based on the pooled data was as expected based on the results of the individual trials, with gastrointestinal events, particularly diarrhoea, being the most frequently reported adverse events in patients treated with nintedanib but leading to premature treatment discontinuation in around 5% of patients treated with nintedanib.

5. Conclusions

The totality of evidence from the TOMORROW and INPULSIS® trials supports the conclusion that there is a beneficial effect of nintedanib on slowing disease progression in patients with IPF. Estimates of the treatment effect of nintedanib were consistent across analyses.

Conflict of interest statement

The authors have reported to *Respiratory Medicine* the following conflicts of interest:
Luca Richeldi reports receipt of grants and personal fees from Boehringer Ingelheim for being a member of the INPULSIS® steering committee and co-principal investigator of the trials; grants

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2016.02.001.

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