CLINICAL INVESTIGATION

Nintedanib: a new treatment for idiopathic pulmonary fibrosis

Nintedanib is an intracellular inhibitor of tyrosine kinases that has recently been approved as a treatment for idiopathic pulmonary fibrosis (IPF) by regulatory authorities in the USA and Europe. Results from the Phase II TOMORROW trial and the two replicate Phase III INPULSIS® trials have shown that nintedanib reduces disease progression in patients with IPF by reducing the annual rate of decline in forced vital capacity by about 50%. Furthermore, in the INPULSIS® trials, nintedanib reduced the risk of adjudicated confirmed or suspected acute exacerbations of IPF by 68%. The adverse events most frequently associated with nintedanib treatment are gastrointestinal in nature, particularly diarrhea. In most patients, such side effects can be managed through treatment interruption, dose reduction and symptomatic therapy.

Keywords: acute exacerbations • antifibrotic • clinical trial • disease progression • forced vital capacity • growth factors • idiopathic pulmonary fibrosis • Phase III • tyrosine kinase

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Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive fibrotic lung disease associated with a radiological and/or histopathological pattern known as usual interstitial pneumonia [1]. The incidence of IPF increases with age, with the disease rarely occurring in individuals under 50 years of age [2]. IPF is characterized by worsening dyspnea and progressive loss of lung function and is ultimately fatal, with a median survival time from diagnosis of 2–3 years [1]. However, the natural history of IPF is highly heterogeneous, with some patients remaining relatively stable for a prolonged period of time, while others progress rapidly [3]. Some patients with IPF experience acute deteriorations in respiratory function. When these acute deteriorations are of unknown cause, they are known as acute exacerbations of IPF [4]. Acute exacerbations are the major cause of hospitalization and death in patients with IPF [5]. IPF has a broad and profound impact on patients' health-related quality of life (HRQL), with impacts on physical health, emotional well-being and independence [6,7].

The diagnosis of IPF requires exclusion of known causes of interstitial lung disease [1]. While the pathogenesis of IPF has not been fully elucidated, the disease is believed to be caused by persistent, multifocal, subclinical injury to the alveolar epithelial cells followed by aberrant wound healing, which ultimately leads to the destruction of the alveolar-capillary basement membrane [8,9]. Characteristic of IPF is fibroblast proliferation and migration and the differentiation of fibroblasts into myofibroblasts, which are responsible for the deposition of extracellular matrix and the structural remodeling that ultimately leads to loss of alveolar function [8,9].

Nintedanib

Nintedanib (OFEV®) is an intracellular inhibitor of tyrosine kinases that has recently been approved for the treatment of IPF in the USA [10] and Europe [11]. Nintedanib was identified as part of a lead optimization program at the pharmaceutical company Boehringer Ingelheim to develop small molecule inhibitors of angiogenesis [12], and has been

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developed both as an anticancer drug (in lung, ovarian and colorectal cancer, renal cell carcinoma and hepatocellular carcinoma) and as an antifibrotic drug. Nintedanib potently blocks PDGF receptor α and β, VEGF receptor 1, 2 and 3, and FGF receptor 1, 2 and 3, as well as FLT3 and the non-receptor tyrosine kinases Src, Lyn and Lck [13]. Overall, over 12 tyrosine kinase receptors and signaling molecules are inhibited by nintedanib, which suggests effects on multiple signaling pathways with potential redundancy.

Tyrosine kinases, including FGF and PDGF, play a key role in the development and progression of fibrosis [14–16]. For example, the effects of TGF-β, a critical intermediary in lung fibrosis, are mediated in part by FGF-2 release and upregulation of FGF receptor 1 and 2 expression [14,15]. PDGF, which stimulates the proliferation of lung fibroblasts, is released at concentrations four times higher by alveolar macrophages from patients with IPF than those from healthy individuals [16]. In studies using fibroblasts from patients with IPF, nintedanib has been shown to interfere with processes active in fibrosis, such as fibroblast proliferation, migration and differentiation to myofibroblasts and the secretion of extracellular matrix [17–21] (Figure 1). In addition, preventative and therapeutic treatment with nintedanib has shown antifibrotic and antiinflammatory effects in animal models of bleomycin- and silica-induced lung fibrosis [18].

Pharmacokinetics of nintedanib

The key pharmacokinetic characteristics of nintedanib are summarized in Table 1. Nintedanib demonstrates linear dose-proportional pharmacokinetics at doses up to 350 mg twice daily. Maximum plasma concentrations are achieved approximately 2–4 h after oral administration with food [10]. The half-life of nintedanib is 9.5 h. Steady state plasma concentrations of nintedanib are achieved within 1 week, with trough concentrations remaining stable for >1 year. The absolute bioavailability of nintedanib 100 mg is 4.7% [10].

The major metabolic pathway for nintedanib is hydrolytic cleavage by esterases followed by glucuronidation [10]. CYP450, primarily CYP3A4, plays a minor role in the biotransformation of nintedanib. *In vitro*, approximately 5% of nintedanib metabolism is cytochrome-dependent, while ester cleavage accounts for approximately 25% [10].

The major route of elimination of nintedanib is fecal/biliary excretion (93.4% of dose). The contribution

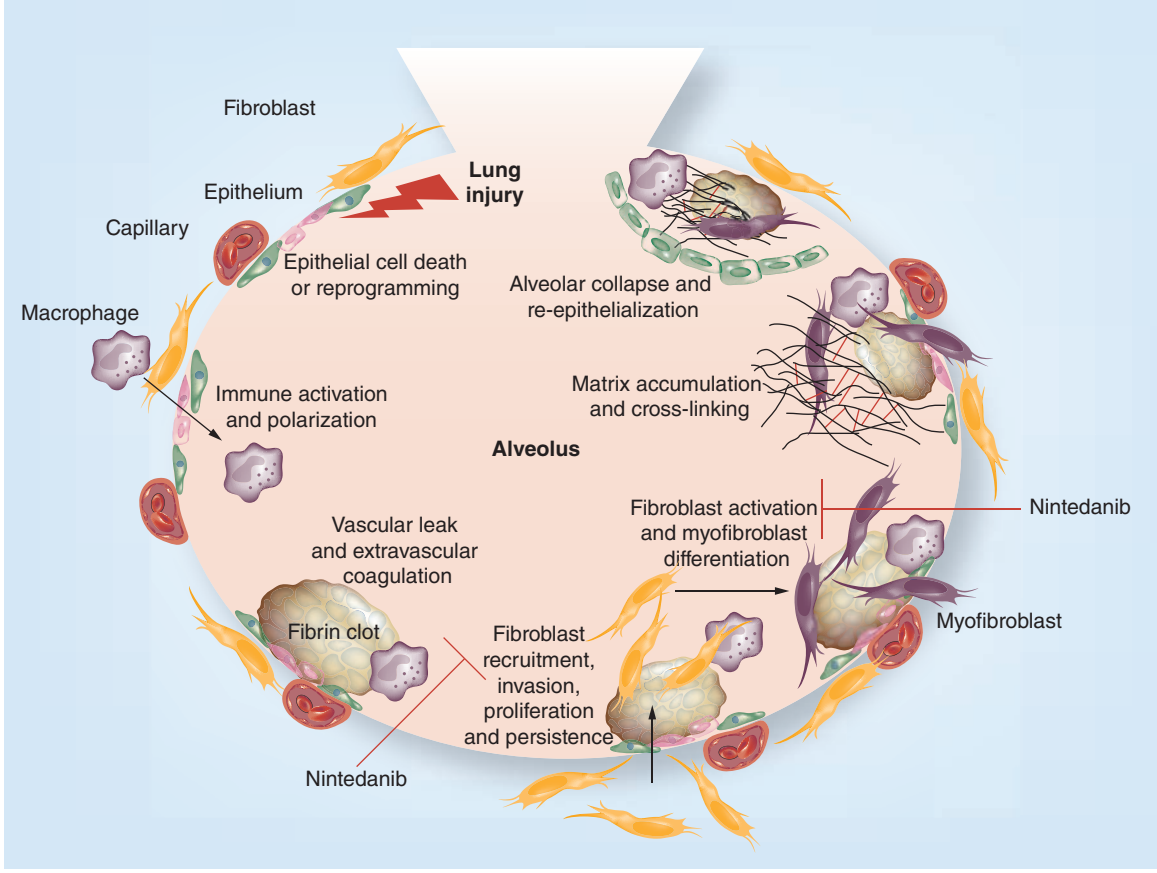

Figure 1. Pathogenic pathways in IPF blocked by nintedanib.
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Table 1. Key pharmacokinetic characteristics of nintedanib.	
Bioavailability	4.7% (for 100 mg tablets)
Time to maximum plasma concentration	~2–4 h after oral administration with food
Half-life	9.5 h
Time to steady state plasma concentrations	1 week
Metabolism	25% by esterases then glucuronidation 5% by CYP3A4
Elimination	Fecal/biliary (93.4% of dose) Renal (0.65% of dose)
PK interactions	Co-administration with ketoconazole or other P-gp and CYP3A4 inhibitors increases exposure to nintedanib Co-administration with rifampicin or other P-gp and CYP3A4 inducers decreases exposure to nintedanib Co-administration with pirfenidone reduces exposure to nintedanib

of renal excretion to total clearance is low (0.65% of dose). Overall recovery is complete (>90%) within 4 days after dosing [10].

Co-administration of nintedanib with ketoconazole, a P-gp and CYP3A4 inhibitor, increases exposure to nintedanib by 60%; therefore, patients receiving nintedanib concomitantly with P-gp and CYP3A4 inhibitors should be monitored closely for tolerability. Co-administration of nintedanib and rifampicin, a P-gp and CYP3A4 inducer, decreases exposure to nintedanib by 50%; therefore, concomitant use of nintedanib and P-gp and CYP3A4 inducers should be avoided [10].

In a study in 50 Japanese patients with IPF, co-administration of nintedanib and pirfenidone reduced exposure to nintedanib, possibly reflecting reduced absorption, but had no effect on the pharmacokinetics of pirfenidone [22]. Due to the low number of patients and the short treatment duration in this study, no definite conclusions on the safety and tolerability of a combination of nintedanib and pirfenidone in the treatment of IPF can be drawn; however, more patients reported nausea and vomiting when nintedanib was added to pirfenidone than when it was given alone.

Clinical data

Phase II: the TOMORROW trial

The TOMORROW trial was a Phase II dose-finding study in which 432 patients with IPF were randomized to receive nintedanib 50 mg once daily, 50 mg twice daily, 100 mg twice daily or 150 mg twice daily or placebo for 12 months [23]. The primary end point was the annual rate of decline in forced vital capacity (FVC; ml/year). A decline in FVC in patients with IPF is consistent with disease progression and is associated with reduced survival time [1,24–26].

In the TOMORROW study, the annual rate of decline in FVC was 0.06 l/year with nintedanib 150 mg twice daily versus 0.19 l/year with placebo. In the primary analysis, in which a closed testing procedure was used to correct for multiplicity, the primary end point approached statistical significance for nintedanib 150 mg twice daily versus placebo ($p = 0.06$). Using a prespecified hierarchical test, without correction for multiplicity, the difference in the annual rate of decline in FVC was significantly superior for nintedanib 150 mg twice daily versus placebo ($p = 0.01$) [23]. Furthermore, nintedanib 150 mg twice daily significantly reduced the proportion of patients with a decrease in FVC >10% or >200 ml compared with placebo (23.8 vs 44.0%; $p = 0.004$). There were no significant differences between the lower doses of nintedanib and placebo in the annual rate of decline in FVC.

Nintedanib 150 mg twice daily preserved HRQL compared with placebo, as measured by change in the St George's Respiratory Questionnaire (SGRQ) score (-0.66 vs +5.46 points; $p = 0.007$), and significantly reduced the incidence of investigator-reported acute exacerbations compared with placebo (2.4 vs 15.7 per 100 patient-years; $p = 0.02$), with a trend towards fewer deaths from respiratory causes (2 vs 8; $p = 0.06$) [23]. Gastrointestinal adverse events such as diarrhea, nausea and vomiting were reported by a greater proportion of patients treated with nintedanib 150 mg twice daily than placebo and led to more treatment discontinuations. Elevations in liver transaminases were also more frequently reported in patients treated with nintedanib 150 mg twice daily than placebo, but led to only one premature treatment discontinuation [23].

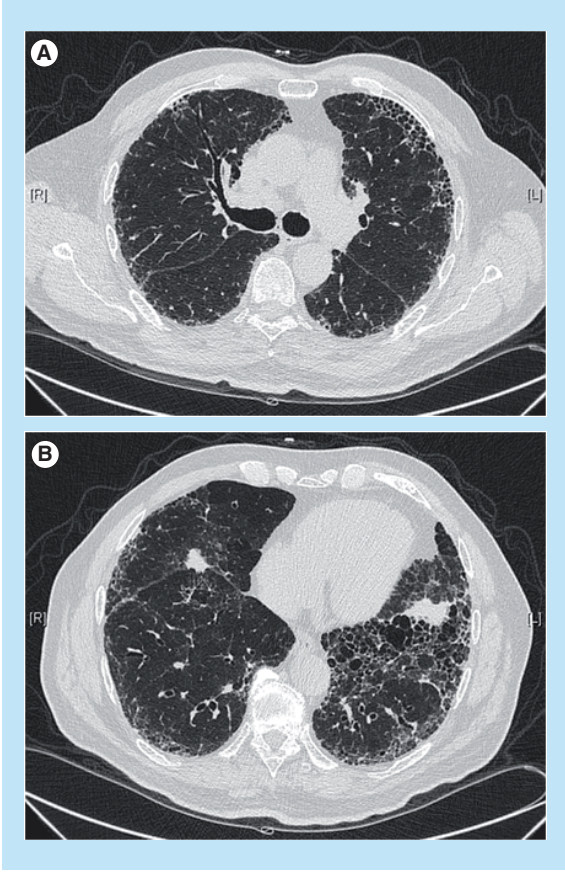

Figure 2. High resolution computed tomography scan of the chest of a patient with idiopathic pulmonary fibrosis, demonstrating a typical pattern of usual interstitial pneumonia with reticulation, subpleural and basal predominance of lesions, traction bronchiectasis and honeycombing. **(A)** Level of the carina; **(B)** level of the lower lobes.

Based on the results of the TOMORROW study, a nintedanib dose of 150 mg b.i.d. was selected for the Phase III program.

Phase III: the INPULSIS® trials

Study design

The INPULSIS® trials were two replicate, randomized, parallel group, Phase III trials of nintedanib 150 mg twice daily versus placebo [27,28]. A total of 1066 patients were randomized 3:2 to receive nintedanib or placebo for 52 weeks. Temporary interruption of treatment, dose reduction to 100 mg twice daily and the use of symptomatic therapies for the relief of diarrhea were recommended for the management of adverse events. Specific recommendations were provided to the investigators for the management of hepatic enzyme elevations. Concomitant therapy with prednisone ≤15 mg/day or equivalent was permitted if the dose had been stable for ≥8 weeks prior to screening. After 6 months, patients were permitted to receive azathioprine, cyclophosphamide, cyclosporine A, *N*-acetylcysteine or prednisone >15 mg/day or equivalent if deemed appropriate by the investigator. In cases of acute exacerbation, any treatments could be freely initiated or increased by the investigator, except for pirfenidone and investigational treatments for IPF, which were not allowed at any time.

Study population

To be eligible for inclusion in the INPULSIS® trials, patients must have been diagnosed with IPF within 5 years prior to randomization, have an FVC of ≥50% predicted, have a carbon monoxide diffusion capacity (DL_{CO}) of 30–79% predicted and to have had a chest high resolution computed tomography [HRCT] scan within 12 months before screening. A diagnosis of IPF was confirmed centrally by a single radiologist based on the HRCT scan (and by a single pathologist if a surgical lung biopsy specimen was available). To be eligible for inclusion, a patient's HRCT scan had to show honeycombing and/or a combination of reticular abnormality and traction bronchiectasis, without nodules or consolidation or features suggestive of alternative causes. Examples of HRCT scans showing these features are shown in Figures 2 & 3. Patients had to have a forced expiratory volume in 1 s (FEV_1)/FVC ratio of ≥0.7, but patients with an HRCT scan showing emphysema were not excluded. Indeed emphysema, which is a common comorbidity in patients with IPF [29] and associated with smaller changes in lung function over time [30], was present in 40% of patients in the INPULSIS® trials [31]. The study population in the INPULSIS® trials was well defined (Table 2) and represented a wide range of patients with IPF, including patients with relatively preserved FVC, as well as patients with moderate impairment of lung function. However, patients at increased risk of bleeding, for example, those receiving full-dose anticoagulation, high-dose platelet therapy or fibrinolysis were excluded from the trials, as were patients with liver transaminases or bilirubin above 1.5-fold upper limit of normal, and patients with myocardial infarction within 6 months or unstable angina within 1 month of randomization [27].

End points

The primary end point in the INPULSIS® trials was the annual rate of decline in FVC (Figure 4). Key secondary end points were the time to first investigator-reported acute exacerbation and change from baseline in SGRQ total score, both assessed over 52 weeks [27]. Investigators were provided with a definition for acute exacerbations in the trial protocol [27]. Pooled analyses of data from both INPULSIS® trials on the primary and key secondary end points and on adverse events were prespecified.

Results: lung function

In both trials, the annual rate of decline in FVC was significantly lower in the nintedanib group than in the placebo group. Pooled data from both trials showed an annual rate of decline in FVC of -113.6 ml/year in the nintedanib group vs -223.5 ml/year in the placebo group (difference vs placebo: 109.9 l/year; 95% CI: 75.9–144.0; p < 0.001) (Figure 5A) [27]. Prespecified subgroup analyses showed that the effect of nintedanib on the annual rate of decline in FVC was independent of the following baseline characteristics: sex, age (<65 and ≥65 years), race (white and Asian), severity of lung impairment (FVC >70% and ≤70% predicted), SGRQ total score (≤40 and >40), smoking status (never and ex/current), bronchodilator use (yes/no) and corticosteroid use (yes/no) [32]. A *post hoc* analysis showed that the treatment effect of nintedanib was independent of the presence (yes/no) of emphysema at baseline [31]. A further *post hoc* analysis demonstrated that nintedanib reduced the annual rate of decline in FVC in patients with an FEV_1/FVC ratio >0.8 (difference vs placebo: 126.1 ml/year; 95% CI: 81.6–170.6) and in patients with an FEV_1/FVC ratio ≤0.8 (difference vs placebo: 95.5 ml/year; 95% CI: 41.9–149.1) with a significant treatment-by-subgroup interaction (p = 0.0124) [33].

The effects of nintedanib on prespecified secondary lung function end points were consistent with the primary analysis (Figure 5B). The absolute mean changes in FVC% predicted at week 52 were -2.9% in the nintedanib group and -6.1% in the placebo group (difference vs placebo: 3.2%; 95% CI: 2.4–4.0; p < 0.001) [27]. An absolute decline in FVC% predicted of ≥5% over 6–12 months is associated with increased mortality in patients with IPF [24–26]. A significantly higher proportion of patients in the nintedanib group than in the placebo group had an FVC response at week 52, defined as no absolute decline in FVC >5% predicted (53.0 vs 38.8%; odds ratio [OR]: 1.8; 95% CI: 1.4–2.4) or >10% predicted (70.1 vs 60.5%; OR: 1.6; 95% CI: 1.2–2.1) [27]. In a *post hoc* analysis, disease progression was defined as absolute and relative declines in FVC >5% or >10% predicted at week 52. Nintedanib significantly reduced the proportions of patients with absolute and relative declines in FVC >10% predicted compared with placebo (29.9 vs 39.5% and 35.6 vs 48.7%, respectively) and with absolute and relative declines in FVC >5% predicted (47.0 vs 61.2% and 51.1 vs 64.5%, respectively) [34]. Assessing the decline in FVC% predicted as a relative change may maximize the chance of identifying a ≥10% decline in FVC% predicted without sacrificing prognostic accuracy [24].

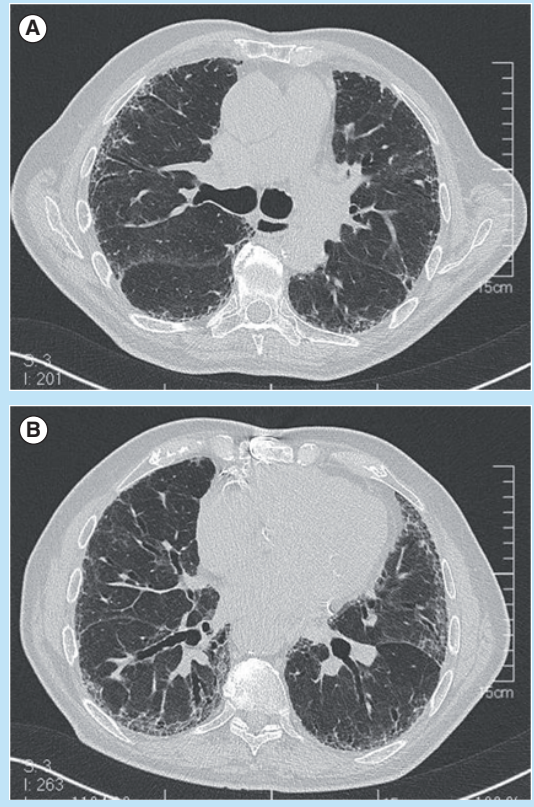

Figure 3. High resolution computed tomography scan of the chest of a patient with idiopathic pulmonary fibrosis, demonstrating a pattern of possible usual interstitial pneumonia with reticulation, subpleural and basal predominance of lesions, traction bronchiectasis with no evident honeycombing.
A pattern of usual interstitial pneumonia was found at lung biopsy. **(A)** Level of the carina; **(B)** level of the lower lobes.

Results: key secondary end points

The results of the two INPULSIS® trials were discordant with regard to the key secondary end points of time to first investigator-reported acute exacerbation, with no significant difference between the nintedanib and placebo groups in INPULSIS®-1 (hazard ratio [HR]: 1.15; 95% CI: 0.54–2.42; p = 0.67), but a significant benefit of nintedanib versus placebo in INPULSIS®-2 (HR: 0.38; 95% CI: 0.19–0.77; p = 0.005). In the pooled analysis, there was no significant difference in the time to first investigator-reported acute exacerbation between the nintedanib and placebo groups (HR: 0.64; 95% CI: 0.39–1.05; p = 0.08) [27]. The discrepancy between the trials was not explained by imbalances in the races or geographical distribution of the study populations. A subgroup analysis demonstrated that the majority of acute exacerbations were observed in patients with FVC ≤70% predicted at baseline and

Table 2. Demographics and baseline characteristics of patients in the INPULSIS® trials.

Demographics and baseline characteristics	INPULSIS®-1		INPULSIS®-2	
	Nintedanib 150 mg twice daily (n = 309)	Placebo (n = 204)	Nintedanib 150 mg twice daily (n = 329)	Placebo (n = 219)
Male, n (%)	251 (81.2)	163 (79.9)	256 (77.8)	171 (78.1)
Age (years)	66.9 ± 8.4	66.9 ± 8.2	66.4 ± 7.9	67.1 ± 7.5
Weight (kg)	82.0 ± 16.8	81.2 ± 16.3	76.6 ± 15.9	76.3 ± 16.5
BMI (kg/m^2)	28.6 ± 4.5	28.1 ± 4.6	27.6 ± 4.6	27.2 ± 4.5
Smoking status, n (%):				
– Never smoker	71 (23.0)	51 (25.0)	103 (31.3)	71 (32.4)
– Former/current smoker	238 (77.0)	153 (75.0)	226 (68.7)	148 (67.6)
Time since diagnosis of IPF (years)	1.7 ± 1.4	1.6 ± 1.4	1.6 ± 1.3	1.6 ± 1.3
Lung biopsy specimen available, n (%)	60 (19.4)	33 (16.2)	84 (25.5)	52 (23.7)
Receiving systemic corticosteroids, n (%)	68 (22.0)	43 (21.1)	68 (20.7)	46 (21.0)
FVC:				
– Mean (ml)	2757 ± 735	2845 ± 820	2673 ± 776	2619 ± 787
– % predicted	79.5 ± 17.0	80.5 ± 17.3	80.0 ± 18.1	78.1 ± 19.0
FEV_1: FVC (%)	81.5 ± 5.4	80.8 ± 6.1	81.8 ± 6.3	82.4 ± 5.7
DLco (% predicted)	47.8 ± 12.3	47.5 ± 11.7	47.0 ± 14.5	46.4 ± 14.8[†]
SpO_2 (%)	95.9 ± 2.0	95.9 ± 1.9	95.8 ± 2.6	95.7 ± 2.1
SGRQ total score[‡]	39.6 ± 17.6	39.8 ± 18.5	39.5 ± 20.5	39.4 ± 18.7

Values are mean ± standard deviation, unless otherwise stated.
[†]n = 218.
[‡]INPULSIS®-1 nintedanib: n = 298; placebo: n = 202; INPULSIS®-2 nintedanib: n = 326; placebo: n = 217.
DLco: Carbon monoxide diffusion capacity; FEV_1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; IPF: Idiopathic pulmonary fibrosis; SGRQ: St George's Respiratory Questionnaire; SpO_2: Oxygen saturation.
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suggested that the effect of nintedanib may be more pronounced in this patient population [32].

An adjudication committee of three experts in IPF reviewed medical documentation on all the investigator-reported exacerbations and classified every event as a confirmed acute exacerbation, suspected acute exacerbation or not an acute exacerbation. In a prespecified sensitivity analysis of pooled data from both INPULSIS® trials, a significant benefit of nintedanib was observed on time to first adjudicated confirmed or suspected acute exacerbation compared with placebo (HR: 0.32; 95% CI: 0.16–0.65; p = 0.001) (Figure 6) [27]. Recently it has been proposed that the differences in results observed for all investigator-reported exacerbations and adjudicated confirmed/suspected exacerbations may be explained statistically by the phenomenon of treatment effect dilution, that is, the random inclusion of 'false' acute exacerbations in the analysis of investigator-reported acute exacerbations may have introduced inaccuracy into this outcome measure, leading to a dilution of the difference between the nintedanib and placebo groups such that statistical significance was not reached [35].

No difference between the nintedanib and placebo groups in mean change from baseline in SGRQ total score was observed in INPULSIS®-1 (difference: -0.05 points; 95% CI: -2.50–2.40; p = 0.97), but a significantly smaller increase (indicating benefit) in SGRQ total score occurred in the nintedanib group in INPULSIS®-2 (difference vs placebo: -2.69; 95% CI: -4.95 to -0.43; p = 0.02) [27]. In the pooled analysis, there was no significant difference in adjusted mean change from baseline in SGRQ total score between the nintedanib and placebo groups (difference: -1.43 points; 95% CI: -3.09–0.23; p = 0.09). Changes in the individual SGRQ domain scores were consistent with these results [27].

Results: mortality

The INPULSIS® trials were not powered to show a reduction in mortality with nintedanib versus placebo. However, pooled data from the two INPULSIS® trials showed a trend towards a reduction in mortality in patients receiving nintedanib compared with placebo (all-cause mortality 5.5 vs 7.8%; HR: 0.70; 95% CI: 0.43–1.12; p = 0.14; death from respiratory causes 3.8 vs 5.0%; HR: 0.74; 95% CI: 0.41–1.34; p = 0.34) [27].

An analysis of pooled data from the TOMORROW and INPULSIS® trials was conducted to obtain a more precise estimate of the effect of nintedanib 150 mg twice daily on mortality. The HR for all-cause mortality was 0.70 (95% CI: 0.46–1.08; p = 0.0954) and the HR for mortality from respiratory causes was 0.62 (95% CI: 0.37–1.06; p = 0.0779) [36]. In a further analysis of deaths that occurred between randomization and the end of the follow-up period (28 days after last study drug intake in the INPULSIS® trials and a maximum of 14 days after last study drug intake in the TOMORROW trial), there was a significant 43% reduction in risk favoring nintedanib (HR: 0.57; 95% CI: 0.34–0.97; p = 0.0274).

Safety & tolerability

Nintedanib had a side-effect profile that was manageable for most patients. The most frequently reported adverse events in patients receiving nintedanib were gastrointestinal (Table 3) [27]. Almost all such adverse events were mild or moderate in intensity. Adverse events led to permanent treatment discontinuation in 19.3% of patients in the nintedanib group versus 13.0% of patients treated with placebo. Diarrhea was reported by 62.4% of patients in the nintedanib group (compared with 18.4% of patients in the placebo group) but led to permanent treatment discontinuation in only 4.4% of patients, suggesting that management of diarrhea through treatment interruption, dose reduction and the use of antidiarrheal therapies were successful in enabling patients to remain on treatment.

Elevations in liver enzymes (alanine aminotransferase and/or aspartate aminotransferase ≥3× upper limit of normal) were reported in 5.0% of patients in the nintedanib group and 0.7% of patients in the placebo group. No patients with moderate or severe liver impairment (alanine aminotransferase or aspartate aminotransferase or bilirubin >1.5× upper limit of normal) were enrolled in the INPULSIS® trials and nintedanib is not recommended for use in such patients.

Clinical use of nintedanib

Nintedanib (OFEV®) has been approved for the treatment of IPF in the USA [10] and Europe [11]. The recommended dose is 150 mg b.i.d., with the two doses administered approximately 12 h apart with food [10]. For the management of adverse events, temporary treatment interruption or dose reduction to 100 mg b.i.d. are recommended. Patients who experience gastrointestinal adverse events should be treated with antidiarrheal therapy, antiemetics and adequate hydration as soon as symptoms occur [10]. Liver enzymes should be monitored before and periodically during nintedanib treatment and liver enzyme elevations managed through treatment interruption or dose reduction. As inhibition of VEGFR by nintedanib may potentially increase the risk of bleeding or gastrointestinal perforation, patients at known risk for these events should be treated with nintedanib only if the anticipated benefit outweighs the risk [10]. Nintedanib may be used as first-line therapy in patients with IPF or in patients who have

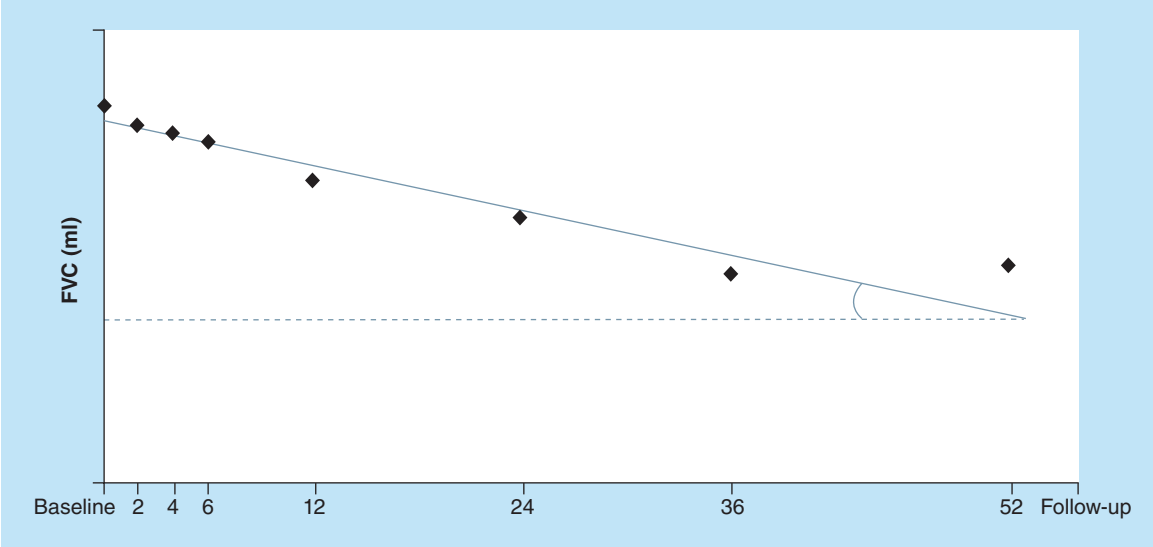

Figure 4. Calculation of the slope of forced vital capacity decline (primary end point) in the INPULSIS® trials. The primary end point was analyzed using a random coefficient regression model including sex, age and height as covariates. All available forced vital capacity values from baseline to week 52 were used in the primary analysis, including data collected following discontinuation of trial drug.
FVC: Forced vital capacity.

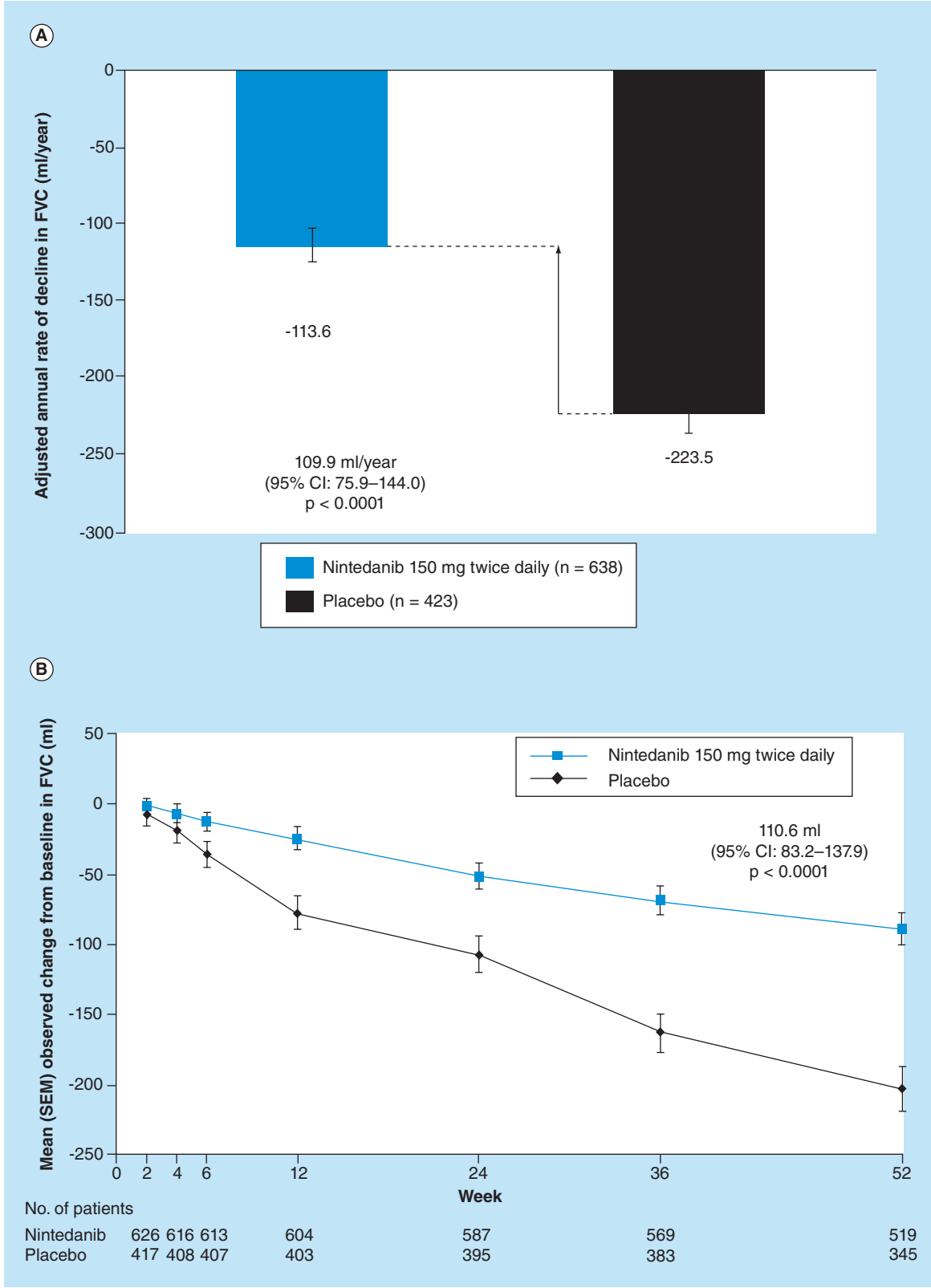

Figure 5. Adjusted annual rate (SE) of decline from baseline in (A) forced vital capacity, and (B) change from baseline in forced vital capacity over time in the INPULSIS® trials (pooled data).
FVC: forced vital capacity.
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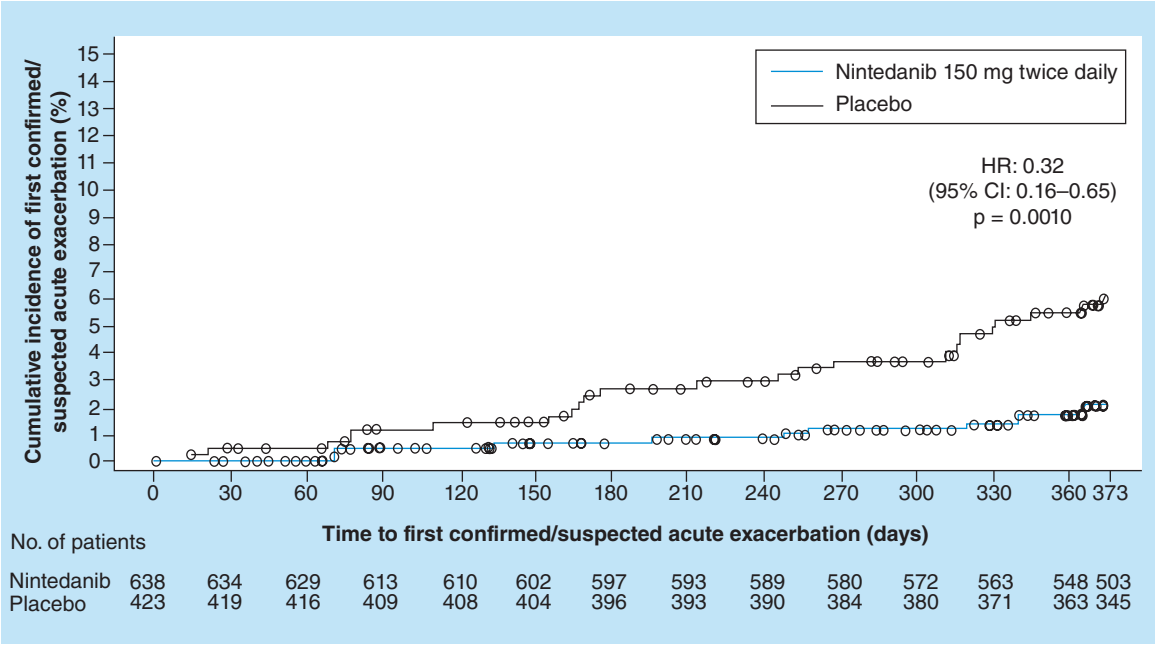

Figure 6. Time to first adjudicated confirmed or suspected acute exacerbation in the INPULSIS® trials (pooled data).
HR: Hazard ratio.
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previously been treated with pirfenidone. No head-to-head trials of nintedanib and pirfenidone have been conducted. At present, there are no data to support the use of combination therapy with nintedanib and pirfenidone in patients with IPF.

Ongoing trials

INPULSIS®-ON (NCT01619085), an ongoing open-label extension of the INPULSIS® trials, will report the results of an interim analysis at the American Thoracic Society meeting in May 2015. An open-label extension of the TOMORROW trial (NCT01170065) is also ongoing. A Phase IIIb 52–78-week, randomized, double-blind, placebo-controlled trial with a primary end point of change from baseline in a quantitative lung fibrosis score based on HRCT (NCT01979952) is in the process of recruiting patients.

Conclusion & future perspective

Demonstration of the efficacy of nintedanib in reducing the progression of IPF in the TOMORROW and INPULSIS® trials has created momentum for further studies to increase our understanding of the benefits of this drug in the treatment of patients with IPF. For example, there is a need to improve our knowledge of the effect of nintedanib on patient-reported outcomes, to consolidate data on the prevention of acute exacerbations of IPF, to investigate further effects on disease progression and survival and to investigate the efficacy and safety of nintedanib in situations not explored in the INPULSIS® trials such as in patients with advanced disease. Given the heterogeneity of the clinical course of IPF among individual patients, the identification of biomarkers to predict the benefits of therapy for a given patient early in the course of disease remains one of our most urgent and relevant challenges. Patient registries and post-authorization programs provide the opportunity to collect further data, including evidence regarding long-term safety and tolerability, to provide further guidance on how best to prevent and manage the most frequent side-effects of nintedanib in clinical practice.

Future clinical trials will likely largely comprise add-on trials, in which a new drug is combined with nintedanib [37]. Monoclonal antibodies, several of which are currently in development as treatments for IPF, might ultimately prove valuable for use in combination therapy with nintedanib. Furthermore, there remains a significant unmet need for better treatments for chronic fibrotic lung diseases other than IPF, including interstitial lung disease associated with connective tissue disease, chronic hypersensitivity pneumonitis, combined pulmonary fibrosis and emphysema (CPFE) and unclassifiable fibrosis. Although the scientific rationale for using antifibrotic drugs to treat these conditions is unquestioned, the development of drugs to treat them will need to overcome significant challenges in study design and patient recruitment.

Table 3. Adverse events in the INPULSIS® trials.

Adverse events	Nintedanib 150 mg twice daily (n = 638), n (%)	Placebo (n = 423), n (%)
Any adverse event(s)	609 (95.5)	379 (89.6)
Most frequent adverse events[†]:		
– Diarrhea	398 (62.4)	78 (18.4)
– Nausea	156 (24.5)	28 (6.6)
– Nasopharyngitis	87 (13.6)	68 (16.1)
– Cough	85 (13.3)	57 (13.5)
– Progression of IPF[‡]	64 (10.0)	61 (14.4)
– Bronchitis	67 (10.5)	45 (10.6)
– Dyspnea	49 (7.7)	48 (11.3)
– Decreased appetite	68 (10.7)	24 (5.7)
– Vomiting	74 (11.6)	11 (2.6)
Serious adverse event(s)	194 (30.4)	127 (30.0)
Fatal adverse event(s)	37 (5.8)	31 (7.3)
Adverse event(s) leading to treatment discontinuation[§]:	123 (19.3)	55 (13.0)
– Progression of IPF[‡]	13 (2.0)	21 (5.0)
– Diarrhea	28 (4.4)	1 (0.2)
– Nausea	13 (2.0)	0 (0.0)
– Decreased appetite	9 (1.4)	1 (0.2)

Adverse events with onset after first dose and up to 28 days after the last dose of study drug in patients treated with ≥1 dose of study medication.
[†]Adverse events reported by >10% of patients in either treatment group based on pooled data.
[‡]Corresponds to the Medical Dictionary for Regulatory Activities (MedDRA) term 'idiopathic pulmonary fibrosis', which included disease worsening and idiopathic pulmonary fibrosis exacerbations.
[§]Adverse events leading to treatment discontinuation in >1% of patients in either treatment group based on pooled data.

A number of novel antifibrotic compounds are in development, most of them targeting the wound healing process and downstream events of fibrogenesis [38]. Preclinical data should ideally include several experimental models as well as data obtained in human tissue. Among others, targets of drugs in development include lysyl oxidase-like 2, CTGF, IL-13 and/or IL-4, integrin αVβ6 and the lysophosphatidic acid receptor. Some pleiotropy in drug activity may be beneficial in the treatment of IPF.

Executive summary

- Nintedanib has been approved as a treatment for idiopathic pulmonary fibrosis (IPF) by regulatory authorities in the USA and Europe.
- Nintedanib is an intracellular inhibitor of tyrosine kinases that interferes with processes active in fibrosis such as fibroblast activation, migration and differentiation and the secretion of extracellular matrix.
- Results from the Phase II TOMORROW trial and two Phase III INPULSIS® trials have shown that nintedanib reduces disease progression in patients with IPF by reducing the rate of decline in forced vital capacity by about 50%.
- Subgroup analyses of data from the INPULSIS® trials have demonstrated that nintedanib has a consistent effect on slowing disease progression across a broad population of patients defined by a variety of baseline characteristics.
- In the INPULSIS® trials, nintedanib reduced the risk of adjudicated confirmed or suspected acute exacerbations by 68%.
- Nintedanib has a manageable safety and tolerability profile in patients with IPF. Management of adverse events through treatment interruption, dose reduction and symptomatic treatment of diarrhea enables most patients to stay on treatment.

Disclaimer

The author was fully responsible for all content and editorial decisions, was involved at all stages of manuscript development and has approved the final version.

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