Long-term safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis: results from the open-label extension study, INPULSIS-ON

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Summary

Background The efficacy and safety of nintedanib, an intracellular tyrosine kinase inhibitor, in patients with idiopathic pulmonary fibrosis were assessed in two phase 3, placebo-controlled INPULSIS trials. Patients who completed the 52-week treatment period in an INPULSIS trial could receive open-label nintedanib in the extension trial, INPULSIS-ON. We aimed to assess the long-term efficacy and safety of nintedanib in INPULSIS-ON.

Methods Patients who completed the 52-week treatment period of INPULSIS, and the follow-up visit 4 weeks later, were eligible for INPULSIS-ON. The off-treatment period between INPULSIS and INPULSIS-ON could be 4–12 weeks. Patients receiving nintedanib 150 mg twice daily or placebo at the end of an INPULSIS trial received nintedanib 150 mg twice daily in INPULSIS-ON. Patients receiving nintedanib 100 mg twice daily or placebo at the end of an INPULSIS trial could receive nintedanib 100 mg twice daily or 150 mg twice daily in INPULSIS-ON. Spirometric tests were done at baseline, at weeks 2, 4, 6, 12, 24, 36, 48, and then every 16 weeks. The primary outcome of INPULSIS-ON was to characterise the long-term safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis, and this was analysed in patients who received at least one dose of nintedanib in INPULSIS-ON. This study is registered with ClinicalTrials.gov, number NCT01619085, and with EudraCT, number 2011-002766-21.

Findings The first patient was enrolled into INPULSIS-ON in July 2, 2012. Of 807 patients who completed the INPULSIS trials, 734 (91%) were treated in INPULSIS-ON. 430 (59%) patients had received nintedanib in INPULSIS and continued nintedanib in INPULSIS-ON, and 304 (41%) had received placebo in INPULSIS and initiated nintedanib in INPULSIS-ON. Median exposure time for patients treated with nintedanib in both the INPULSIS and INPULSIS-ON trials was 44·7 months (range 11·9–68·3). The safety profile of nintedanib in INPULSIS-ON was consistent with that observed in INPULSIS. Diarrhoea was the most frequent adverse event in INPULSIS-ON (60·1 events per 100 patient exposure-years in patients who continued nintedanib, 71·2 events per 100 patient exposure-years in patients who initiated nintedanib). 20 (5%) of 430 patients who continued nintedanib and 31 (10%) of 304 patients who initiated nintedanib permanently discontinued nintedanib because of diarrhoea. The adverse event that most frequently led to permanent discontinuation of nintedanib was progression of idiopathic pulmonary fibrosis (51 [12%] patients continuing nintedanib and 43 [14%] patients initiating nintedanib). The event rate of bleeding was 8·4 events per 100 patient exposure-years in patients who continued nintedanib and 6·7 events per 100 patient exposure-years in patients who initiated nintedanib. The event rate of major adverse cardiovascular events was 3·6 events per 100 patient exposure-years in patients who continued nintedanib and 2·4 events per 100 patient exposure-years in patients who initiated nintedanib. The event rate of myocardial infarction using the broad scope (ie, all possible cases) was 1·3 events per 100 patient exposure-years in patients who continued nintedanib and 0·7 events per 100 patient exposure-years in patients who initiated nintedanib.

Interpretation These findings suggest that nintedanib has a manageable safety and tolerability profile over long-term use, with no new safety signals. Patients with idiopathic pulmonary fibrosis could use nintedanib over the long-term to slow disease progression.

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Introduction

Idiopathic pulmonary fibrosis is a chronic fibrosing interstitial lung disease characterised by progressive loss of lung function, dyspnoea, and impaired quality of life.[1,2] The prognosis for patients with idiopathic pulmonary fibrosis is poor; data collected in the USA, before the availability of antifibrotic therapy in 2014, suggested a median survival after diagnosis of 3–5 years.[3,4] Acute deteriorations in respiratory function, which are often of unknown cause, constitute a major

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Research in context

Evidence before this study

In the two phase 3 placebo-controlled INPULSIS trials, nintedanib 150 mg twice daily significantly reduced the annual rate of decline in forced vital capacity (FVC) versus placebo, with an adverse event profile that was acceptable for most patients. Results from the open-label extension of the phase 2 TOMORROW trial identified no new safety signals and suggested an effect of nintedanib on slowing the progression of idiopathic pulmonary fibrosis beyond 52 weeks; however, only 35 patients treated with nintedanib 150 mg twice daily entered the extension study. We searched PubMed for all English-language papers published between Jan 1, 1990, and July 20, 2018, using the search terms "nintedanib", "idiopathic pulmonary fibrosis", "efficacy", and "safety". We reviewed the articles identified for relevance. No other large clinical trials have investigated the long-term effects of nintedanib in patients with idiopathic pulmonary fibrosis.

Added value of this study

These results from INPULSIS-ON, the open-label extension of the INPULSIS trials, show that nintedanib had a manageable safety and tolerability profile over the long term. No new safety signals were identified over a treatment duration of up to 68 months. The findings also suggest that the effect of nintedanib on slowing the progression of idiopathic pulmonary fibrosis persists beyond 4 years. The rates of FVC decline in INPULSIS-ON were generally consistent between subgroups, irrespective of patient characteristics at baseline, including FVC.

Implications of all the available evidence

Long-term use of nintedanib slows disease progression in patients with idiopathic pulmonary fibrosis and has a manageable safety and tolerability profile.

cause of morbidity and mortality in patients with idiopathic pulmonary fibrosis.[5]

Nintedanib, an intracellular inhibitor of tyrosine kinases, is an approved treatment for idiopathic pulmonary fibrosis. In the latest international clinical practice guidelines for idiopathic pulmonary fibrosis, nintedanib received a conditional recommendation for use, indicating that it is an appropriate choice for most patients, while recognising that individual patients' preferences play an important part in treatment decisions.[6]

See Online for appendix

The efficacy, safety, and tolerability of 52 weeks' treatment with nintedanib versus placebo were assessed in the phase 2 TOMORROW trial[7] and the two replicate phase 3 INPULSIS trials.[8] In the TOMORROW trial, nintedanib 150 mg twice daily was associated with a reduced annual rate of decline in forced vital capacity (FVC), and a lower incidence of investigator-reported acute exacerbations than with placebo.[7] In both INPULSIS trials, nintedanib significantly reduced the annual rate of decline in FVC versus placebo, with pooled data from the two trials indicating a between-group difference of 109·9 mL per year (95% CI 75·9–144·0), and a numerical reduction in the risk of an investigator-reported acute exacerbation (hazard ratio [HR] 0·64, 95% CI 0·39–1·05; p=0·08).[8] Nintedanib had a manageable safety and tolerability profile, predominantly characterised by gastrointestinal adverse events, of which mild diarrhoea was the most common.[9]

As a chronic disease, idiopathic pulmonary fibrosis might require long-term treatment. Therefore, data are needed about the efficacy, safety, and tolerability of nintedanib beyond the 52 weeks of treatment assessed in the TOMORROW and INPULSIS trials. Data from the open-label extension of the TOMORROW trial suggested an effect of nintedanib on slowing disease progression beyond 52 weeks and identified no new safety signals; however, only 35 patients treated with nintedanib 150 mg twice daily entered the extension study. Patients who completed the INPULSIS trials were eligible to receive nintedanib as part of an open-label extension trial known as INPULSIS-ON. Here, we present the final results of INPULSIS-ON.

Methods

Study design and participants

The design of the INPULSIS and INPULSIS-ON trials is summarised in the appendix. Briefly, to be eligible to enter the INPULSIS trials, patients had to be aged 40 years or older, with an FVC 50% predicted or higher, and a diffusing capacity of the lung for carbon monoxide 30–79% predicted. A full list of eligibility criteria is described in the original INPULSIS study.[8,10] Patients were randomly assigned (3:2) to receive nintedanib 150 mg twice daily or placebo twice daily for 52 weeks. Dose reductions to 100 mg twice a day and treatment interruptions were allowed to manage adverse events; dose re-escalation to 150 mg twice daily was permitted. Patients who completed the 52-week treatment period and follow-up visit (4 weeks later) in an INPULSIS trial were eligible to enter INPULSIS-ON. Per protocol, the off-treatment period between INPULSIS and INPULSIS-ON could be between 4 and 12 weeks.

Patients were enrolled from 24 countries (Australia, Belgium, Canada, Chile, China, Czech Republic, Finland, France, Germany, Greece, India, Ireland, Israel, Italy, Japan, South Korea, Mexico, Netherlands, Portugal, Russia, Spain, Turkey, UK, and USA).

Patients with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations more than 1·5 times the upper limit of normal or bilirubin more than 1·5 times the upper limit of normal were not eligible to participate in INPULSIS-ON (unless they had ALT and

AST >1·5 times and <3 times the upper limit of normal recorded at the end of INPULSIS). Patients with risk of bleeding (ie, requiring fibrinolysis, full-dose therapeutic anticoagulation, or high-dose antiplatelet therapy) were not eligible. Patients with major thromboembolic events (ie, stroke, deep-vein thrombosis, pulmonary embolism, or myocardial infarction) that developed after completion of the INPULSIS trial were not eligible to participate in INPULSIS-ON.

The trial was done in accordance with the protocol, the principles of the Declaration of Helsinki, the International Conference of Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice, and with applicable regulatory requirements. Patients re-provided written informed consent before entering INPULSIS-ON. The trial protocol was approved by the independent ethics committees or institutional review boards of the participating centres.

Procedures

Patients receiving nintedanib 150 mg twice daily or placebo at the end of an INPULSIS trial received nintedanib 150 mg twice daily in INPULSIS-ON. Patients receiving nintedanib 100 mg twice daily or placebo at the end of an INPULSIS trial could receive nintedanib 100 mg twice daily or 150 mg twice daily in INPULSIS-ON; the dose was based on discussion between the patient and investigator. Initially, the protocol did not allow dose escalation from 100 mg twice daily to 150 mg twice daily during INPULSIS-ON, but after a protocol amendment after unblinding of the INPULSIS trials, patients were allowed to increase their dose from 100 mg twice daily to 150 mg twice daily at any time. As in the INPULSIS trials, permanent or temporary dose reductions to 100 mg twice daily and treatment interruptions were allowed, to manage adverse events. Investigators were provided with recommendations for the management of diarrhoea and increases in liver enzyme concentrations, consistent with those given in the INPULSIS trials.[9] Spirometric tests were done at baseline, at weeks 2, 4, 6, 12, 24, 36, 48, and then every 16 weeks indefinitely (until the end of the trial), in accordance with American Thoracic Society/European Respiratory Society guidelines.[11] All spirometric measurements were done on machines provided by the sponsor and the results were centrally reviewed, with training and feedback provided to the investigators. The database was locked for final analysis on Sept 12, 2017.

Outcomes

The primary objective of INPULSIS-ON was to characterise the long-term safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis. This was assessed with clinical and laboratory evaluation and the recording of adverse events reported during and until 28 days after discontinuation of treatment. Adverse events were coded with the Medical Dictionary for Regulatory Activities (version 20.1). Because of the mechanism of action of nintedanib, bleeding, major adverse cardiovascular events, and myocardial infarction were considered to be of particular interest.

Exploratory efficacy endpoints included the annual rate of decline in FVC during INPULSIS-ON calculated over 192 weeks, absolute change in FVC (mL and % predicted) from baseline to week 192, time to first acute exacerbation, and time to death. We chose a timepoint of 192 weeks because this was the timepoint reached by the last patient included in INPULSIS-ON who was still receiving nintedanib when the sponsor stopped the trial. We assessed the annual rate of decline in FVC over 192 weeks in subgroups defined by sex, age (<70 and ≥70 years), race (white or Asian), baseline FVC (≤50%, >50% to ≤70%, >70% to ≤90%, and >90% predicted), and concomitant medication use at the start of INPULSIS-ON (bronchodilators, proton pump or histamine H2 receptor inhibitors, corticosteroids, statins, and N-acetylcysteine). We also assessed subgroups by nintedanib dose during INPULSIS-ON (150 mg twice daily only, 100 mg twice daily only, or both doses), dose adjustments (at least one dose reduction and treatment interruption, at least one dose reduction only, at least one treatment interruption only, no dose reduction or treatment interruption), and dose intensity (≤90% and >90%) during INPULSIS-ON. We defined dose intensity as the amount of drug administered over the trial divided by the amount of drug that would have been received had the 150 mg twice daily dose been administered throughout the trial.

We defined exacerbations using criteria similar to the recommendations published in 2007.[12] Protocol-defined acute exacerbations met all of the following criteria: unexplained worsening or development of dyspnoea within the previous 30 days; new diffuse pulmonary infiltrates on chest radiography or new high-resolution CT parenchymal abnormalities with no pneumothorax or pleural effusion (no new ground-glass opacities), or both since the preceding visit; and exclusion of known causes of acute worsening, including infection, left-sided heart failure, pulmonary embolism, and any identifiable cause of acute lung injury, in accordance with routine clinical practice and microbiological studies. Acute exacerbations and deaths were reported as adverse events during and until 28 days after discontinuation of treatment. Acute exacerbations reported by the investigators in INPULSIS-ON were not adjudicated.

Patients who discontinued nintedanib treatment in INPULSIS-ON discontinued from the trial and no further data were collected about them. An end-of-trial visit was done for patients who discontinued nintedanib treatment, as well as a follow-up visit 28 days after drug discontinuation. No data were collected from patients who completed an INPULSIS trial but did not participate in INPULSIS-ON.

Statistical analysis

Efficacy and safety analyses were descriptive and based on patients who received at least one dose of nintedanib in INPULSIS-ON. To aid interpretation of the data, we divided patients who entered INPULSIS-ON into two groups: those who had already received nintedanib (masked) in INPULSIS and continued nintedanib (open-label) in INPULSIS-ON, and those who had received placebo in INPULSIS and initiated nintedanib in INPULSIS-ON.

For adverse events, we calculated event rates per 100 patient exposure-years. We calculated the annual rate of decline in FVC over 192 weeks using random coefficient regression (a mixed-effects model) with fixed effects for sex, age and height, and random effect of patient-specific intercept and time. To calculate the slope of FVC decline, we used all available FVC measurements collected at timepoints between baseline and week 192 in INPULSIS-ON; all patients with at least one post-baseline FVC measurement were included in the analysis. In the analysis of change from baseline in FVC over time, we included only data from patients with an FVC measurement at the respective timepoint. We calculated Kaplan-Meier estimates and confidence intervals (using the Greenwood variance formula) for time to first acute exacerbation and time to death. We calculated the incidence of acute exacerbations as the number of patients with at least one acute exacerbation divided by the total years at risk, multiplied by 100. Total years at risk was defined as the time from the start of treatment until the start of the first event (for patients with an event) or the end of the time at risk (for patients without events) plus 1 day.

This study is registered with ClinicalTrials.gov, number NCT01619085, and with EudraCT, number 2011-002766-21

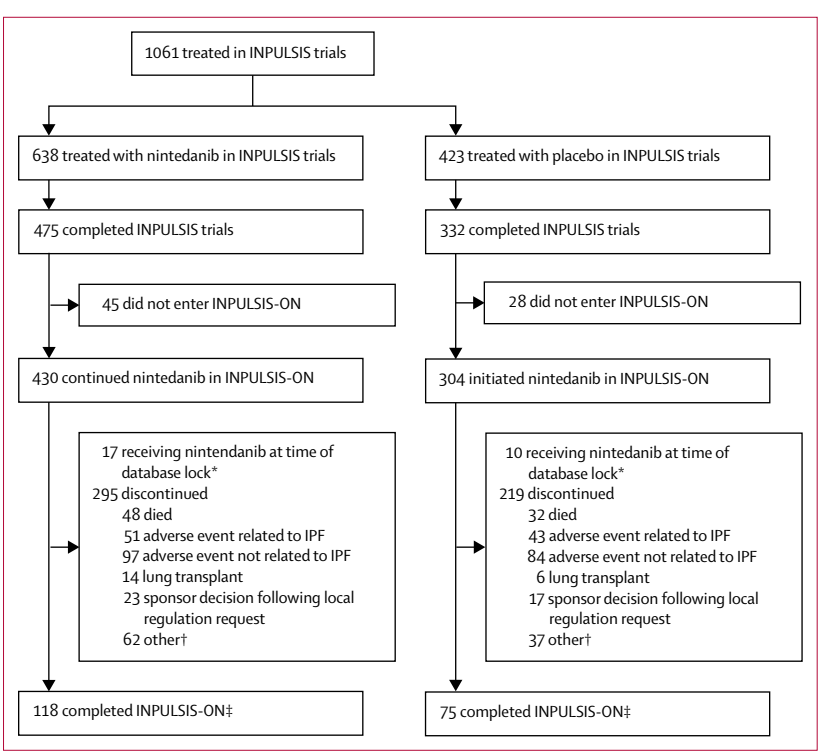


Figure 1: **Trial profile**

*Patients without access to commercial nintedanib outside the trial received nintedanib provided by the sponsor for as long as they wanted to do so. †Reasons included loss to follow-up, withdrawal of informed consent. ‡Patients who completed INPULSIS-ON were receiving commercially available nintedanib at the time of database lock.

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report. The funder had no role in data collection. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The first patient was enrolled into INPULSIS-ON on July 2, 2012. Of 807 patients who completed the INPULSIS trials, 734 (91%) were treated in INPULSIS-ON, of whom 430 (59%) were continuing nintedanib and 304 (41%) were initiating nintedanib (figure 1). Baseline characteristics at the start of INPULSIS-ON were similar between these groups and similar to those at the start of the INPULSIS trials, except that mean FVC % predicted was slightly lower at the start of INPULSIS-ON (table 1). Patients treated in INPULSIS-ON were mostly male (n=587; 80%) and white (n=431; 59%) and had a mean age of 67·2 years (SD 7·8) and mean FVC of 76·2% predicted (19·1).

The median exposure to nintedanib in all patients treated in INPULSIS-ON was 31·5 months (range 0·0–56·3). Median exposure in INPULSIS-ON was 32·8 months (0·1–56·3) in patients who continued nintedanib, and 29·4 months (0·0–55·0) in patients who initiated nintedanib (table 2). Median total exposure in patients treated with nintedanib in both INPULSIS and INPULSIS-ON was 44·7 months (11·9–68·3).

295 (69%) of 430 patients continuing nintedanib and 219 (72%) of 304 patients who initiated nintedanib in INPULSIS-ON discontinued nintedanib during the trial (figure 1). The most common reason for discontinuing nintedanib was adverse events not related to idiopathic pulmonary fibrosis (figure 1; appendix). These occurred most frequently in the first year of INPULSIS-ON. 40 patients from Japan discontinued nintedanib between October and November, 2015, after a local regulation request because the commercial drug became available through prescription.

132 (31%) of 430 patients who continued nintedanib and 131 (43%) of 304 who initiated nintedanib had at least one dose reduction; 152 (35%) and 130 (43%) had at least one treatment interruption; 200 (47%) and 177 (58%) had at least one dose reduction or at least one treatment interruption, or both; and 84 (20%) and 84 (28%) had at least one dose reduction and treatment interruption. 230 (53%) patients who continued nintedanib and

127 (42%) who initiated nintedanib had no dose reduction or treatment interruption. A total of 36 (8%) patients who continued nintedanib and 39 (13%) patients who initiated nintedanib had at least one dose increase from 100 mg twice daily to 150 mg twice daily. 473 (64%) patients had a dose intensity greater than 90%.

A summary of adverse events in INPULSIS-ON and the INPULSIS trials is presented in tables 3 and 4. Diarrhoea was the most frequent adverse event (table 4). In INPULSIS-ON, the event rate of diarrhoea was 60·1 events per 100 patient exposure-years in patients who continued nintedanib and 71·2 events per 100 patient exposure-years in patients who initiated nintedanib. 20 (5%) of 430 patients who continued nintedanib and 31 (10%) of 304 patients who initiated nintedanib permanently discontinued nintedanib because of diarrhoea (table 3).

In INPULSIS-ON, 15 (3%) patients continuing nintedanib and 20 (7%) patients initiating nintedanib had increased concentrations of ALT, AST, or both that were three times the upper limit of normal (appendix). The event rate of bleeding was 8·4 events per 100 patient exposure-years in patients who continued nintedanib and 6·7 events per 100 patient exposure-years in patients who initiated nintedanib (table 5). The event rate of major adverse cardiovascular events was 3·6 events per 100 patient exposure-years in patients who continued nintedanib and 2·4 events per 100 patient exposure-years in patients who initiated nintedanib (table 5). The event rate of myocardial infarction using the broad scope (ie, all possible cases) was 1·3 events per 100 patient exposure-years in patients who continued nintedanib and 0·7 events per 100 patient exposure-years in patients who initiated nintedanib (table 5).

The adverse event that most frequently led to permanent discontinuation of nintedanib was progression of idiopathic pulmonary fibrosis (51 [12%] patients continuing nintedanib and 43 [14%] patients initiating nintedanib; table 3). The proportion of patients who had at least one serious adverse event in INPULSIS-ON was similar between patients who continued and initiated nintedanib (n=300 [70%] and n=206 [68%]; table 3).

Changes in FVC over time in INPULSIS-ON are shown in figure 2. Mean change in FVC from baseline to week 192 was −327·2 mL (SD 385·3) in all patients treated in INPULSIS-ON, −348·8 mL (392·9) in patients who continued nintedanib, and −293·4 mL (372·7) in patients who initiated nintedanib. Mean change in FVC % predicted from baseline to week 192 of INPULSIS-ON was −7·0% predicted (11·1) in all patients treated, −7·5% predicted (11·4) in patients who continued nintedanib, and −6·3% predicted (10·6) in patients who initiated nintedanib. The adjusted annual rate of decline in FVC calculated over 192 weeks was −135·1 mL per year (SE 5·8) in all patients treated, −145·0 mL per year (7·4) in patients who continued nintedanib, and −119·7 mL per year (9·2) in patients who initiated nintedanib (figure 3).

	INPULSIS		INPULSIS-ON	
	Nintedanib (n=638)	Placebo (n=423)	Continued nintedanib (n=430)	Initiated nintedanib (n=304)
Mean age, years	66·6 (8·1)	67·0 (7·9)	66·8 (7·8)	67·7 (7·8)
Sex				
Male	507 (79%)	334 (79%)	350 (81%)	237 (78%)
Female	131 (21%)	89 (21%)	80 (19%)	67 (22%)
Race				
White	360 (56%)	248 (59%)	252 (59%)	179 (59%)
Asian	194 (30%)	128 (30%)	121 (28%)	94 (31%)
Black	2 (<1%)	0	2 (<1%)	0
Missing*	82 (13%)	47 (11%)	55 (13%)	31 (10%)
Ex-smoker or current smoker	464 (73%)	301 (71%)	313 (73%)	217 (71%)
Mean weight, kg	79·2 (16·6)	78·6 (16·5)	78·5 (16·3)	77·8 (16·1)
Mean body-mass index, kg/m²	28·1 (4·6)	27·6 (4·6)	27·6 (4·4)	27·3 (4·5)
Mean FVC, % predicted	79·7 (17·6)	79·3 (18·2)	75·9 (18·3)	76·7 (20·1)

Data are mean (SD) or n (%). Data collected at baseline of INPULSIS and INPULSIS-ON. *In France, regulation did not permit the collection of data about race.

Table 1: **Baseline characteristics of patients in INPULSIS and INPULSIS-ON**

	INPULSIS		INPULSIS-ON	
	Nintedanib (n=638)	Placebo (n=423)	Continued nintedanib (n=430)	Initiated nintedanib (n=304)
Mean (SD)	10·3 months (3·4)	10·8 months (2·8)	30·2 months (16·0)	27·4 months (17·0)
Median	11·9 months	11·9 months	32·8 months	29·4 months
Range	0·0–12·7	0·0–13·1	0·1–56·3	0·0–55·0
Total exposure, patient-years	548	383	1083	696

Table 2: **Exposure in INPULSIS and INPULSIS-ON**

In the subgroup analysis of the adjusted annual rate of decline in FVC (over 192 weeks), findings were generally consistent across subgroups by age, race, and FVC % predicted at the start of INPULSIS-ON (appendix). However, there was a numerically greater rate of decline in FVC in male patients than in female patients (baseline FVC 2825 mL *vs* 1816 mL; adjusted annual rate −146·4 mL per year *vs* −86·2 mL per year). The rate of decline in FVC was higher in patients who were treated with N-acetylcysteine at baseline (n=32) than in patients who were not (n=702; appendix). The annual rate of decline in FVC was similar, irrespective of dose adjustments and dose intensity (appendix).

The incidence of acute exacerbations was 5·8 per 100 patient-years in patients who continued nintedanib in INPULSIS-ON and 5·2 per 100 patient-years in patients who initiated nintedanib in INPULSIS-ON (table 6; appendix).

105 (24%) patients who continued nintedanib and 83 (27%) patients who initiated nintedanib died over approximately 5 years' follow-up in INPULSIS-ON.

	INPULSIS		INPULSIS-ON	
	Nintedanib (n=638)	Placebo (n=423)	Continued nintedanib (n=430)	Initiated nintedanib (n=304)
≥1 adverse event(s)	609 (95%)	379 (90%)	422 (98%)	301 (99%)
≥1 severe adverse event(s)*	174 (27%)	99 (23%)	240 (56%)	172 (57%)
≥1 serious adverse event(s)†	194 (30%)	127 (30%)	300 (70%)	206 (68%)
≥1 adverse event(s) leading to permanent drug discontinuation‡§	123 (19%)	55 (13%)	172 (40%)	141 (46%)
Progression of IPF¶	13 (2%)	21 (5%)	51 (12%)	43 (14%)
Diarrhoea	28 (4%)	1 (<1%)	20 (5%)	31 (10%)
Nausea	13 (2%)	0	2 (<1%)	6 (2%)
Respiratory failure	0	1 (<1%)	8 (2%)	2 (1%)

Data are n (%) of patients. IPF=idiopathic pulmonary fibrosis. *An event that was incapacitating or that caused an inability to work or to perform usual activities. †An event that resulted in death, was immediately life-threatening, resulted in persistent or clinically significant disability or incapacity, required or prolonged hospitalisation, was related to a congenital anomaly or birth defect, or was deemed serious for any other reason. ‡Adverse events leading to permanent drug discontinuation in more than 1·5% of patients in any of the groups shown. §Includes patients who died after permanent drug discontinuation. ¶Corresponds to Medical Dictionary for Regulatory Activities term "IPF", which included disease worsening and acute exacerbations.

Table 3: **Summary of adverse events in INPULSIS and INPULSIS-ON**

	INPULSIS				INPULSIS-ON			
	Nintedanib (n=638)		Placebo (n=423)		Continued nintedanib (n=430)		Initiated nintedanib (n=304)	
	Number of events	Event rate (per 100 patient exposure-years)	Number of events	Event rate (per 100 patient exposure-years)	Number of events	Event rate (per 100 patient exposure-years)	Number of events	Event rate (per 100 patient exposure-years)
Diarrhoea	671	112·6	106	25·6	667	60·1	509	71·2
Bronchitis	92	15·5	62	15·0	166	15·0	101	14·1
Nasopharyngitis	117	19·6	91	22·0	139	12·5	125	17·5
Progression of IPF*	70	11·8	73	17·7	152	13·7	103	14·4
Cough	96	16·1	67	16·2	133	12·0	94	13·2
Nausea	208	34·9	29	7·0	95	8·6	113	15·8
Upper respiratory tract infection	72	12·1	55	13·3	125	11·3	55	7·7
Dyspnoea	50	8·4	51	12·3	108	9·7	72	10·1
Vomiting	102	17·1	11	2·7	80	7·2	77	10·8
Weight decreased†	64	10·7	15	3·6	67	6·0	66	9·2
Decreased appetite	75	12·6	26	6·3	53	4·8	67	9·4
Abdominal pain	68	11·4	10	2·4	34	3·1	49	6·9

Adverse events reported by investigators were coded according to preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 (INPULSIS) or 20.1 (INPULSIS-ON). Adverse events with an event rate >10 per 100 patient exposure–years in any of the groups shown are listed. IPF=idiopathic pulmonary fibrosis. *Corresponds to MedDRA preferred term "IPF", which included disease worsening and acute exacerbations. †Corresponds to MedDRA preferred term "weight decreased", which represents any loss of weight according to investigator's judgment.

Table 4: **Most frequent adverse events in INPULSIS and INPULSIS-ON**

Discussion

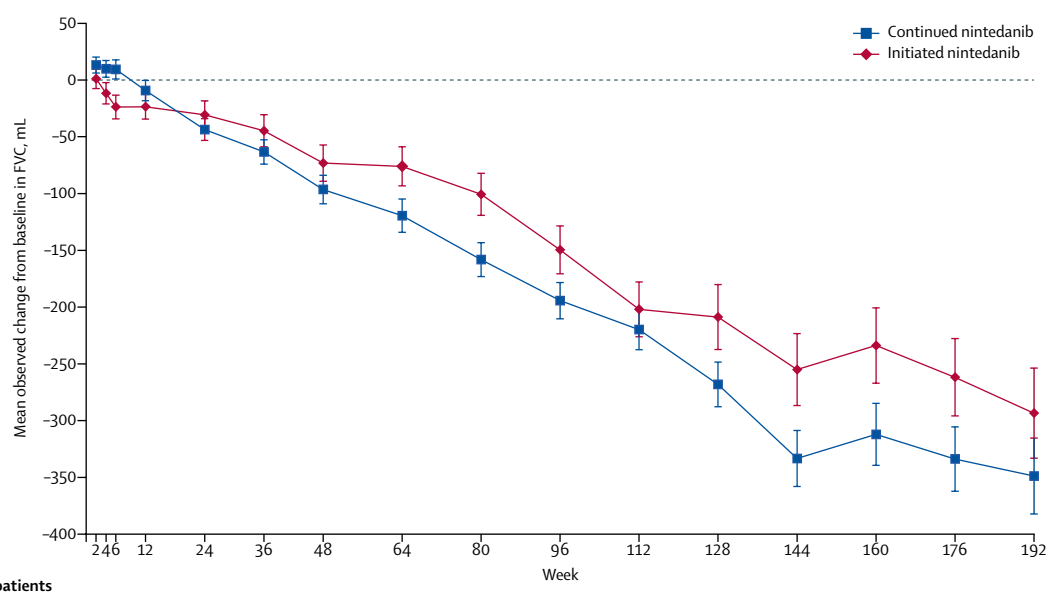
These analyses of data from the open-label INPULSIS-ON trial suggest that the safety, tolerability, and efficacy of nintedanib in patients with idiopathic pulmonary fibrosis are maintained in the long term and are consistent with findings from the INPULSIS trials. Continued treatment with nintedanib, for up to 68 months, had a manageable safety and tolerability profile, with no new safety signals identified. Similar to the TOMORROW and INPULSIS trials, the most common adverse event in INPULSIS-ON was diarrhoea, which led to treatment discontinuation in 5% of patients continuing nintedanib and 10% of patients who initiated nintedanib in INPULSIS-ON.

Exposure-adjusted event rates of major adverse cardiovascular events, myocardial infarction, and bleeding in patients who continued or initiated nintedanib in INPULSIS-ON were similar to those observed in placebo-treated patients in the INPULSIS trials.[8] These findings are supported by post-marketing surveillance data collected in the USA over a year, after the launch of nintedanib as a treatment for idiopathic pulmonary fibrosis.[13] In light of the high frequency of coronary artery disease and cardiovascular risk factors in patients with

	INPULSIS				INPULSIS-ON			
	Nintedanib (n=638)		Placebo (n=423)		Continued nintedanib (n=430)		Initiated nintedanib (n=304)	
	Number of events	Event rate (per 100 patient exposure-years)	Number of events	Event rate (per 100 patient exposure-years)	Number of events	Event rate (per 100 patient exposure-years)	Number of events	Event rate (per 100 patient exposure-years)
Major adverse cardiovascular events	26	4·4	11	2·7	40	3·6	17	2·4
Myocardial infarction (broad scope)	18	3·0	5	1·2	14	1·3	5	0·7
Myocardial infarction (narrow scope)	11	1·8	2	0·5	13	1·2	4	0·6
Bleeding	94	15·8	42	10·2	93	8·4	48	6·7

Major adverse cardiovascular events were based on fatal adverse events included in the Medical Dictionary for Regulatory Activities (MedDRA) system organ classes "cardiac disorders" and "vascular disorders"; fatal and non-fatal events in the subordinate standardised MedDRA query (SMQ) "myocardial infarction"; stroke based on selected preferred terms from the subordinate SMQs "haemorrhagic cerebrovascular conditions" and "ischemic cerebrovascular conditions"; and the MedDRA preferred terms "sudden death", "cardiac death", and "sudden cardiac death". Myocardial infarction was based on events in the subordinate SMQ "myocardial infarction". SMQs include narrow and broad terms; narrow terms are those that are highly likely to represent the condition of interest whereas broad terms are all possible cases, including some that may prove to be of little or no interest on closer inspection. Bleeding was based on the SMQ "haemorrhage terms [excluding laboratory terms]".

Table 5: **Major adverse cardiovascular events, myocardial infarction, and bleeding in INPULSIS and INPULSIS-ON**



Number of patients															
Continued nintedanib	416	410	408	408	392	375	352	331	306	289	265	239	217	171	154	138
Initiated nintedanib	296	291	287	284	266	250	233	210	195	177	159	149	133	112	99	88

Figure 2: **Change from baseline in FVC in INPULSIS-ON**
Error bars show SE. Data are from patients who had FVC data at each timepoint. FVC=forced vital capacity.

idiopathic pulmonary fibrosis,[14–16] these data are reassuring with regard to the cardiovascular safety of nintedanib and suggest that the risk of these events does not increase with continued nintedanib treatment.

The annual rates of decline in FVC calculated over 192 weeks in patients who continued or initiated nintedanib in INPULSIS-ON (–145·0 and –119·7 mL per year, respectively) were consistent with the annual rate of FVC decline in patients treated with nintedanib in INPULSIS (–113·6 mL per year). We do not consider the differences in FVC decline in INPULSIS-ON, between patients who received nintedanib and placebo in the preceding INPULSIS trial, to be clinically meaningful, particularly when put into perspective with the FVC decline observed in placebo-treated patients in INPULSIS (–223·5 mL per year) and the minimal clinically important difference in FVC, which is believed to be 2–6% predicted[17] (a difference of at least 75–80 mL). However, we acknowledge that selection biases might have contributed to the small difference observed between these subgroups. In a pooled analysis of data from the TOMORROW and INPULSIS trials, comprising data from 1231 patients, the annual rate

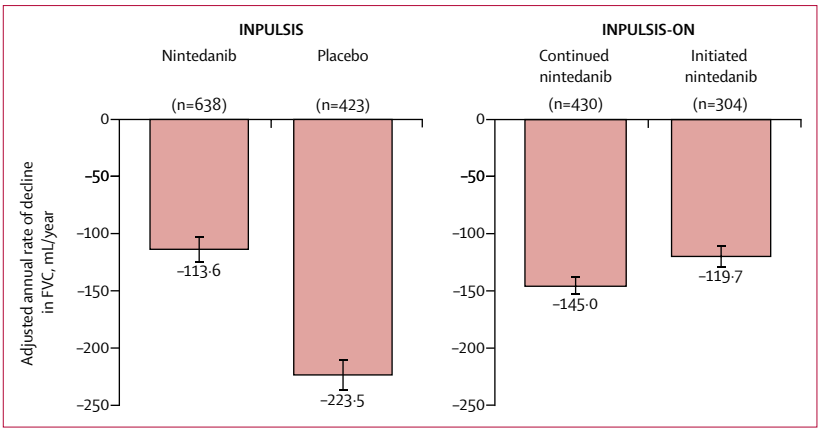


Figure 3: **Annual rate of decline in FVC over 52 weeks in INPULSIS and over 192 weeks in INPULSIS-ON**
Error bars show SE. FVC=forced vital capacity.

	INPULSIS		INPULSIS-ON	
	Nintedanib (n=638)	Placebo (n=423)	Continued nintedanib (n=430)	Initiated nintedanib (n=304)
Patients with ≥1 acute exacerbation, n (%)	31 (5%)	32 (8%)	63 (15%)	37 (12%)
Total years at risk	601	401	1084	709
Adjusted incidence rate of acute exacerbations, per 100 patient-years	5·2	8·0	5·8	5·2

Table 6: **Acute exacerbations in INPULSIS and INPULSIS-ON**

of decline in FVC over 52 weeks in patients treated with nintedanib 150 mg twice daily was –112·4 mL per year.[18] Similarly, in patients treated with nintedanib 150 mg twice daily for a mean total duration of 28 months across the TOMORROW trial and its open-label extension, the annual rate of FVC decline was –125·4 mL per year.[19] Data from contemporary clinical trials suggest that FVC decline in placebo-treated patients with idiopathic pulmonary fibrosis and mild or moderate lung function impairment at baseline is approximately 200 mL over 1 year.[20]

Subgroup analyses showed that the annual rate of decline in FVC in INPULSIS-ON generally seemed to be consistent across groups, irrespective of demographic characteristics or FVC at baseline. A previous interim analysis of data from INPULSIS-ON[21] showed that the decline in FVC over 48 weeks was similar in patients with FVC up to 50% predicted and more than 50% predicted at the start of INPULSIS-ON, suggesting that patients with severely impaired lung volume, who were excluded from the INPULSIS trials, might receive the same benefit from nintedanib as might patients with less severe impairment, although it should be noted that only 41 patients had FVC ≤50% predicted.[21] The findings of INPULSIS-ON also support the prespecified subgroup analyses of data from the INPULSIS trials, which showed a consistent effect of nintedanib across patients defined by baseline characteristics including age, sex, race, and FVC.[22] Although there were some small differences in the annual rate of decline in FVC between subgroups by use of concomitant medications at the start of INPULSIS-ON, we do not regard the differences between these subgroups as clinically meaningful for the reasons previously described. Additionally, the difference in the annual rate of decline in FVC between subgroups defined by use of N-acetylcysteine at baseline should be interpreted with caution, because only 32 patients were receiving N-acetylcysteine at baseline. Subgroup analyses of data from the INPULSIS trials have also shown a consistent effect of nintedanib across subgroups defined by use of concomitant medications at baseline including corticosteroids,[22] statins,[23] and antiacid therapy.[24]

Dose reductions and treatment interruptions during INPULSIS-ON, as recommended for the management of adverse events, had no effect on the annual rate of FVC decline, suggesting that the long-term efficacy of nintedanib in reducing disease progression is sustained in patients who require dose adjustments. However, these data should not be interpreted as suggesting that 100 mg twice daily should be the starting dose of nintedanib in patients with idiopathic pulmonary fibrosis.

The incidence of acute exacerbations in INPULSIS-ON seemed to be similar to that in patients treated with nintedanib in INPULSIS,[8] supporting the results of the INPULSIS trials, which suggested that treatment with nintedanib might reduce the risk of acute exacerbations in patients with idiopathic pulmonary fibrosis.[25]

As with all open-label extension trials, these data have limitations, particularly the absence of a comparator group and the decreasing patient numbers over time, which were partly due to patients switching to prescribed nintedanib in clinical practice once it became available. There was a selection bias in the patients who entered INPULSIS-ON: patients in the INPULSIS trials who had a more favourable course of disease or were better able to tolerate nintedanib would have been more likely to complete the INPULSIS trial and so be eligible to enter INPULSIS-ON. Patients with less disease progression might also have been more likely to remain on treatment in INPULSIS-ON, potentially reducing the observed decline in FVC and mortality in INPULSIS-ON. The fact that data about FVC were collected after premature treatment discontinuation in the INPULSIS trials, but not in INPULSIS-ON, probably also affected the mean declines in FVC observed in these trials.

Interpretation of data on mortality in INPULSIS-ON is limited by an absence of data about patients' vital status after discontinuation from the trial. Similar to most clinical trials, the patient population in the INPULSIS and INPULSIS-ON trials was a selected population based on specific eligibility criteria. As such, patients with advanced functional impairment, who had certain comorbidities, or who were receiving certain medications were excluded from the INPULSIS trials, which could have influenced mortality. Nevertheless, these data, from the largest known

cohort of patients with idiopathic pulmonary fibrosis who have received an antifibrotic drug and regular FVC assessments over the long term, add to a growing body of evidence suggesting that nintedanib can provide long-term benefits to patients with the disease. Although an important goal of extension studies is to provide continued access to a potentially beneficial treatment from the end of a clinical trial to the time of its commercial availability, they also help to characterise the benefit-risk profile of a new drug. This is particularly important in the case of rare diseases, for which exposure in the target population tends to be short at the time of marketing authorisation.

Findings from the INPULSIS-ON trial suggest that the effect of nintedanib on slowing the progression of idiopathic pulmonary fibrosis persists beyond 4 years. Continued treatment with nintedanib had a manageable safety and tolerability profile, with no new safety signals identified.

Contributors

All authors (BC, JTH, MKa, UC, IG, TO, JWS, WS, MQ, SS, and MKr) were involved in the interpretation of the data and in the writing and critical review of the manuscript.

Declaration of interests

BC has received grants from Apellis and MedImmune, grants and personal fees from Boehringer Ingelheim and Roche, and personal fees from AstraZeneca and Sanofi. JTH has received grants and personal fees from Roche/Genentech and Boehringer Ingelheim. UC has received grants, personal fees, and non-financial support from Boehringer Ingelheim and Roche, and personal fees from Bayer, GlaxoSmithKline, UCB Celltech, Biogen, FibroGen, and AstraZeneca. IG has received personal fees from Boehringer Ingelheim, Roche, and Avalyn. TO has received grants and personal fees from Boehringer Ingelheim Japan, grants from the Ministry of Health, Labour and Welfare, personal fees from Astellas Pharma Inc, Shionogi & Co Ltd, Toray Industries Inc, AstraZeneca KK, AMCO Inc, and Kyorin Inc. WS, MQ, and SS are employees of Boehringer Ingelheim. MKr has received grants and personal fees from Boehringer Ingelheim and Roche. MKa and JWS declare no competing interests.

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