Adv Ther (2025) 42:1075–1093
https://doi.org/10.1007/s12325-024-03079-2

ORIGINAL RESEARCH

# Real-World Safety, Tolerability and Effectiveness of Nintedanib in Patients with Idiopathic Pulmonary Fibrosis: Final Report of Post-marketing Surveillance in Japan

Yoshikazu Inoue · Takashi Ogura · Arata Azuma · Yasuhiro Kondoh · Sakae Homma · Kenya Muraishi · Rie Ikeda · Kaori Ochiai · Yukihiko Sugiyama · Toshihiro Nukiwa

Received: September 2, 2024 / Accepted: November 22, 2024 / Published online: December 23, 2024


## ABSTRACT

***Introduction***: Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrotic interstitial pneumonia, which is characterised by progressive worsening of dyspnoea and lung function. Nintedanib treatment is recommended to slow IPF disease progression. The aim of this post-marketing surveillance (PMS) study was to evaluate the safety and effectiveness of nintedanib over 24 months in patients with IPF in a real-world setting in Japan.

***Methods***: This prospective, non-interventional, all-case PMS study of nintedanib included Japanese patients with IPF who started nintedanib between 7 October 2015 and 2 May 2023. The primary outcome was to determine the proportion of patients with adverse drug reactions (ADRs), and the secondary outcome was the adjusted absolute change from baseline in forced vital capacity (FVC) at 24 months.

***Results***: In total, 5717 patients from 1013 institutions were included in the safety analysis (mean ± standard deviation age 71.7 ± 8.1 years, 78.1% male, 70.8% current or former smokers). Most patients (83.9%) had initiated nintedanib at a dose of 150 mg capsules twice daily. At 24 months, 2841 patients (64.8%) had discontinued nintedanib, mainly due to adverse events (44.0%), ADRs (24.1%) or insufficient effectiveness (5.7%). The most common ADRs were

**Prior Presentation:** An interim analysis of this post-marketing surveillance study was previously published by Ogura and colleagues in 2023, titled 'Real-world safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis: Interim report of a post-marketing surveillance in Japan' (Adv Ther. 2023;40:1474-93). In addition, this manuscript is based on a previous presentation by Arata Azuma at the European Respiratory Society (ERS) International Congress in Milan, Italy (9–13 September 2023) in the session 'Inflammatory endotyping: the macrophage across disease areas', titled 'Real-World Safety and Effectiveness of Nintedanib in Patients with Idiopathic Pulmonary Fibrosis'.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s12325-024-03079-2.

Y. Inoue (✉)
Osaka Anti-Tuberculosis Association, Osaka Fukujuji Hospital, Osaka, Japan
e-mail: giichiyi@me.com

Y. Inoue
Clinical Research Center, NHO Kinki Chuo Chest Medical Center, 1180 Nagasone-Cho, Kita-Ku, Sakai, Osaka 591-8555, Japan

T. Ogura
Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, Kanagawa, Japan
e-mail: takaoguogu@gmail.com

diarrhoea (35.5%), hepatic function abnormal (14.4%), decreased appetite (9.9%), liver disorders (7.8%) and nausea (5.8%). The adjusted absolute mean change in FVC from baseline to 24 months was – 212.3 mL (95% confidence interval – 235.3, – 189.3).

***Conclusion***: This is the largest prospective study to investigate patients with IPF who were treated with nintedanib. The safety and effectiveness of nintedanib treatment in this real-world setting of Japanese patients with IPF was similar to that reported in previous studies. Nintedanib effectively slowed the progression of IPF. No new safety concerns were identified, and the need for appropriate management of hepatic disorders and diarrhoea (as per the approved product information) was confirmed.

***Study Registration***: ClinicalTrials.gov (NCT02607722)/European Union electronic register of Post-Authorisation Studies (EUPAS10891).

**Keywords:** Adverse drug reactions; Effectiveness; Idiopathic pulmonary fibrosis; Nintedanib; Post-marketing surveillance study; Real-world; Safety; Tolerability

## Key Summary Points

*Why carry out this study?*

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrotic interstitial pneumonia, which is characterised by progressive worsening of dyspnoea and lung function.

To slow the progression of IPF, treatment with nintedanib 150 mg capsules twice daily is recommended; the dose may be reduced to 100 mg twice daily if required to aid tolerability.

This prospective post-marketing surveillance (PMS) study was conducted in Japan to assess the safety and effectiveness of nintedanib in patients with IPF in a real-world setting.

*What was learned from the study?*

The most common adverse drug reactions reported during 24 months of nintedanib treatment were diarrhoea, hepatic function abnormal, decreased appetite, liver disorders and nausea.

Over 24 months, nintedanib suppressed the decline in forced vital capacity.

The safety and effectiveness of nintedanib treatment were similar to those reported in previous studies and no new safety concerns were identified in this real-world setting of Japanese patients with IPF; the need for appropriate management of hepatic disorders and diarrhoea was confirmed.

A. Azuma
Mihara General Hospital, Saitama, Japan
e-mail: azuma_arata@yahoo.co.jp

A. Azuma
Nippon Medical School, Tokyo, Japan

Y. Kondoh
Department of Respiratory Medicine and Allergy, Tosei General Hospital, Aichi, Japan
e-mail: yshr.kondoh@gmail.com

S. Homma
Department of Respiratory Medicine, School of Medicine, Toho University, Tokyo, Japan
e-mail: sahomma210@gmail.com

K. Muraishi · R. Ikeda
Nippon Boehringer Ingelheim Co., Ltd., Tokyo, Japan
e-mail: kenya.muraishi@boehringer-ingelheim.com

R. Ikeda
e-mail: rie.ikeda@boehringer-ingelheim.com

K. Ochiai
PMS Center, EPS Corporation, Tokyo, Japan
e-mail: kaori.ochiai.ext@boehringer-ingelheim.com

Y. Sugiyama
Division of Pulmonary Medicine, Department of Medicine, Nerima Hikarigaoka Hospital, Tokyo, Japan
e-mail: sugiyuki14@gmail.com

T. Nukiwa
Professor Emeritus, Tohoku University, Sendai, Japan
e-mail: toshinkw47@gmail.com

## INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrotic interstitial pneumonia of unknown cause [1]. It mainly occurs in older people, is characterised by progressive worsening of dyspnoea and lung function and is associated with a poor prognosis [1]. In Japan, the reported median survival time from initial diagnosis was 35 months in 2014 [2]. Japanese claims database analyses showed that the prevalence of IPF was 10 per 100,000 people in 2003–2007 in the Hokkaido prefecture, with those aged 60–69 years being most affected [2], and 27 per 100,000 people in 2017–2018 across Japan, with those aged 75–79 years being most affected [3].

International [4] and Japanese [5] treatment guidelines recommend treatment with the antifibrotic agents nintedanib or pirfenidone to slow disease progression in patients with IPF. In Japan, changes in IPF treatment reflect changes in guideline recommendations and the availability of drug therapies in Japan [6]. A claims-based study of IPF treatment trends in Japan from 2008 to 2019 found that, although the proportion of patients who did not receive any IPF treatment tended to decline over time, approximately 30% of patients still received no drug therapy in the most recent years of the study [6]. Over time, the proportion of patients who received antifibrotic drugs increased [6], following their recommendation as a first-line agent in 2015 [4], while the use of corticosteroids tended to decrease [6], following a change in recommendation for their use in 2011 [7]. Antifibrotic drugs were the most commonly prescribed IPF therapy from 2017 onwards (in approximately 50% of patients) [6], consistent with when these drugs became available in Japan (pirfenidone in 2008 [8] and nintedanib in 2015 [9]).

The approval of nintedanib for IPF was based on data from the phase III INPULSIS-1 and -2 trials, in which nintedanib significantly reduced the decline in forced vital capacity (FVC) over 52 weeks compared with placebo in patients with IPF, consistent with a slowing of disease progression [9]. In INPULSIS-2, time to first acute exacerbation was significantly increased with nintedanib versus placebo, whereas in INPULSIS-1, there was no significant between-group difference [9].

A prespecified sensitivity analysis of pooled data from INPULSIS-1 and –2 on time to first adjudicated acute exacerbation (assessed by an independent review committee) showed that nintedanib had a significant benefit compared with placebo [9]. The proportion of patients with an acute exacerbation that was assessed as "confirmed" or "suspected" was lower in the nintedanib group (1.9%) than in the placebo group (5.6%) [9]. The hazard ratio (HR) for time to first acute exacerbation was 0.64 [95% confidence interval (CI) 0.39, 1.05; $P = 0.08$], and the effect of nintedanib was inconsistent with the risk of acute exacerbations [9]. However, a subsequent pooled analysis of the INPULSIS and TOMORROW trials showed a significant reduction in the risk of first acute exacerbation with nintedanib (HR 0.53; 95% CI 0.34, 0.83; $P = 0.0047$) [10].

In the INPULSIS and TOMORROW trials, the most common adverse event (AE) with nintedanib was diarrhoea [9–11]. In the INPULSIS trials, elevated liver enzymes were also reported at a higher incidence with nintedanib than with placebo [9]. In a subgroup analysis of 126 Japanese patients enrolled in the INPULSIS trials, diarrhoea and hepatic function abnormal was reported by 75.0% and 18.4% of patients, respectively [12]. Although diarrhoea was of mild-to-moderate severity and reversible for most patients (94.7%), 25% of patients in the Japanese subgroup discontinued nintedanib because of AEs, including diarrhoea (3.5%) and increased hepatic enzyme levels (2.6%) [12]. Taken together, these findings indicate that nintedanib may be associated with AEs that can lead to discontinuation in patients with IPF, thereby reducing treatment effectiveness in slowing disease progression.

This all-case, post-marketing surveillance (PMS) study, the largest to date, evaluated the safety and effectiveness of nintedanib in patients with IPF in a Japanese real-world setting. An interim analysis of this study using safety data up to 12 months previously showed that about 50% of patients discontinued nintedanib within the first year of treatment, with

poor baseline lung function being associated with an increased risk of early treatment discontinuation [13]. In this PMS study, we report the final analysis of data up to 24 months.

# METHODS

## Study Design

The design of this study has been previously described in detail [13]. Briefly, this was a prospective, non-interventional, all-case PMS study (NCT02607722, EUPAS10891) that assessed the safety and effectiveness of nintedanib in Japanese patients with IPF.

The study was conducted under the direction of the Ministry of Health, Labour and Welfare (MHLW) and the protocol was approved by the MHLW before its initiation. Participating institutes were contracted by Boehringer Ingelheim. As per the Japanese Pharmaceutical and Medical Device Act, this study was conducted in accordance with the Good Post-marketing Study Practice (GPSP) guidance. Under GPSP regulations, institutional review board approval and patient written informed consent were not required, unless such procedures were specifically required by the participating institutions.

## Outcomes

The primary outcome was the proportion of patients with any suspected adverse drug reaction (ADR), defined as an AE that was considered to be at least possibly drug-related by the investigator.

The secondary outcome was the adjusted absolute change from baseline in FVC at 24 months of nintedanib treatment, assessed in the total population and by nintedanib dose intensity (< 80% vs. ≥ 80%) using a compound symmetric matrix to model the within-patient errors. The model included fixed effects for visit, sex, baseline age, baseline height, baseline value, and baseline value-by-visit and random effect for all patients.

## Patients and Treatment

Patients initiating nintedanib were registered by their physician anonymously using case report forms (CRFs) through a central registration system managed by the study sponsor, Boehringer Ingelheim. CRFs were completed for all patients who initiated at least one dose of nintedanib by 15 October 2017. Thereafter (i.e. on or after 16 October 2017), CRFs were only completed as deemed necessary by the study sponsor. Patients were required to meet the diagnostic criteria for IPF, according to the most recent American Thoracic Society, European Respiratory Society, Japanese Respiratory Society or Latin American Thoracic Society guidelines.

Nintedanib 150 mg capsules were administered orally twice daily (bid) after meals in accordance with the package insert. Dose initiation at or reduction to 100 mg bid was permitted at the investigator's discretion in patients with underlying conditions that may have increased their risk for serious AEs; a subsequent dose increase to 150 mg bid was also permitted.

## Data Collection

Clinical data, including suspected ADRs, pulmonary function test results and actual nintedanib doses, were recorded at months 1, 3, 6, 9, 12, 15, 18, 21 and 24 after the initiation of nintedanib in patients who continued to receive treatment. The decline in FVC was evaluated up to 24 months. The incidence of investigator-reported acute exacerbations of IPF was evaluated over 24 months and was based on the Japanese Respiratory Society diagnostic criteria [14]. In Japan, the disease severity staging system for IPF, which uses a combination of arterial oxygen tension ($PaO_2$) at rest and oxygen saturation measured by pulse oximetry ($SpO_2$) during the 6-min walk test (6MWT), has been used to determine medical care subsidies. According to this system, the severity of IPF is classified into four stages: stage I (characterized

by resting $PaO_2$ ≥ 80 Torr), stage II (70–79 Torr), stage III (60–69 Torr), and stage IV (< 60 Torr). Among patients with stage II/III IPF, the severity is increased by one stage if the lowest $SpO_2$ is < 90% during a 6MWT [15].

An AE was defined as any untoward medical occurrence following the administration of nintedanib with or without a causal relationship with this treatment, i.e. any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with nintedanib. AEs and ADRs were classified by using system organ classes and preferred terms in the Japanese version of the Medical Dictionary for Regulatory Activities (MedDRA), version 24.1. A serious AE was defined as any AE that resulted in death, was life-threatening, required in-patient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity, or was a congenital anomaly/birth defect. A serious ADR was any serious AE that was judged by the attending physician as being related to nintedanib treatment.

### Statistical Analysis

The target sample size was 1000 patients, based on previous clinical trials with nintedanib [16], where a sample size of 1000 would have 95% power to detect any ADR in at least one patient occurring at a frequency of ≥ 0.3%.

Most analyses were descriptive, using mean and standard deviation (SD), median and quartiles 1 and 3 (Q1 and Q3, respectively) for continuous variables and frequency for categorical variables.

Safety outcomes were assessed in the safety analysis set (i.e. all patients who received at least one dose of nintedanib and had follow-up data) and the proportion of patients, rates per 100 patient exposure-years and 95% CIs were calculated. Effectiveness outcomes were evaluated in the effectiveness analysis set, which included all patients who received nintedanib according to the approved product label (i.e. not off-label), and had at least one post-baseline effectiveness evaluation. Change from baseline in effectiveness outcomes (continuous variables) were analysed using a mixed-effects model for repeated measures, with visit, sex, baseline age, baseline height, baseline FVC (or FVC% predicted) and FVC (or FVC% predicted)-by-visit being the fixed effects and the patient being the random effect. FVC outcomes were evaluated in the FVC effectiveness set, which included all patients with FVC or FVC% predicted values at baseline and after starting nintedanib treatment.

A logistic regression, including univariate and multivariate analysis, was used to determine potential risk factors associated with AEs and ADRs. Patients were divided into age subgroups based on the median age at enrolment of 73 years (i.e. < 73 and ≥ 73 years). In the univariate analysis, the independent variables were age (< 73 vs. ≥ 73 years), sex (male vs. female), body surface area (BSA; < 1.63 vs. ≥ 1.63 $m^2$), baseline FVC% predicted (< 70% vs. ≥ 70%), smoking history (never smoked vs. ex- or current smoker), IPF severity stage (I/II vs. III + IV), previous medication for IPF (yes vs. no), concomitant medication for IPF (yes vs. no) and the initial nintedanib dose (100 mg vs. 150 mg bid). The dependent variables were occurrence of overall ADRs, hepatic disorders and diarrhoea. Hepatic disorders included liver-related investigations, signs and symptoms [standardised MedDRA Queries (SMQ)], hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (sub-SMQ), cholestasis and jaundice of hepatic origin (sub-SMQ) and hepatitis, non-infectious (sub-SMQ). If an independent variable had an upper 95% CI < 1 or a lower 95% CI > 1 it was considered to be a risk factor for overall ADRs, hepatic disorders or diarrhoea. Variables in the multivariate analysis included age (< 73 vs. ≥ 73 years), sex (male vs. female), BSA (< 1.63 vs. ≥ 1.63 $m^2$) and baseline FVC% predicted (< 70% vs. ≥ 70%), regardless of the univariate analysis results and any other factors for which the 95% CI of odds ratio (OR) did not cross 1 during univariate analysis.

# RESULTS

## Patient Disposition and Characteristics

Between 7 October 2015 and 2 May 2023, 5737 patients from 1013 institutions had confirmed evaluable data (Supplementary Material Fig. S1). Of these, 20 patients were excluded from analysis because no data were recorded following the registration visit ($n = 18$), the data were not reliable ($n = 1$) or because treatment with nintedanib was not administered ($n = 1$). Therefore, 5717 patients were included in the safety analysis set. The effectiveness analysis set included 5660 patients; 57 patients were excluded because they received nintedanib as off-label treatment. Of these patients, 3124 had FVC or FVC% predicted values at baseline and after starting nintedanib treatment (i.e. the FVC effectiveness set).

The baseline characteristics of patients in the safety analysis set are shown in Table 1. The mean ± SD age of the cohort was 71.7 ± 8.1 years, 78.1% of the population were male and 70.8% were current or former smokers. Among 4384 patients whose IPF severity stage was evaluated, the proportion of patients classified as having stage I, II, III and IV disease was 25.1%, 5.0%, 23.6% and 34.4%, respectively. The mean ± SD FVC at baseline was 2122.4 ± 721.8 mL and 69.5 ± 37.8 FVC% predicted. Prior treatment for IPF was reported for 1328 patients (23.2%), while 1826 patients (31.9%) received concomitant drug therapy for IPF, including corticosteroids in 1362 patients (23.8%).

## Nintedanib Treatment

Overall, 5717 patients had baseline nintedanib dose information recorded; 4794 patients (83.9%) initiated nintedanib at 150 mg bid, 766 (13.4%) started at 100 mg bid and 129 (2.3%) received another dose (Table 1). During 24 months of follow-up, 1715 of 4794 patients (35.8%) who started nintedanib at 150 mg bid had a dose reduction to 100 mg bid; the median time to dose reduction was 145.2 days. The mean and median nintedanib exposure duration were 370.7 days and 336.0 days, respectively.

## Discontinuation

At 24 months, 2841 patients (64.8%) had discontinued nintedanib. The rate of AEs leading to discontinuation was 40.6 per 100 patient exposure-years. The main reasons for discontinuation of nintedanib were AEs (40.4% of the safety study population; Supplementary Material Table S1) and insufficient effectiveness (5.7%). The most common AEs leading to treatment discontinuation were progression of IPF (8.2%), diarrhoea (7.0%), decreased appetite (4.6%), hepatic function abnormal (3.9%) and liver disorder (1.8%). The other reasons for discontinuation were loss to follow-up (4.7%), improvement (0.4%), and other (9.8%; Fig. 1).

The proportion of patients who continued nintedanib and the reasons for treatment discontinuation were analysed every 6 months (Fig. 1). The proportion of patients who discontinued treatment due to AEs at 24 months included 5.4% of patients with acute exacerbations and 2.4% with disease progression. The proportion of patients who discontinued due to AEs (excluding disease progression) increased with disease severity, from 31.3% in patients with stage I IPF to 40.5% in those who had reached stage IV.

The total duration of nintedanib treatment was 5801.5 patient exposure-years.

## Adverse Events

In the safety analysis set, the incidence of AEs and ADRs was 84.0% and 67.2%, respectively (Fig. 2a). Serious AEs occurred in 2316 patients (40.5%) and serious ADRs occurred in 530 patients (9.3%). AEs led to a nintedanib dose reduction in 1309 patients (22.9%), discontinuation in 2312 patients (40.4%) and death in 1131 patients (19.8%). ADRs led to a dose reduction in 1259 patients (22.0%), nintedanib discontinuation in 1375 patients (24.1%) and death in 101 patients (1.8%).

The most common AEs (occurring in ≥ 4% of patients) were diarrhoea, progression of IPF, hepatic function abnormal, decreased appetite,

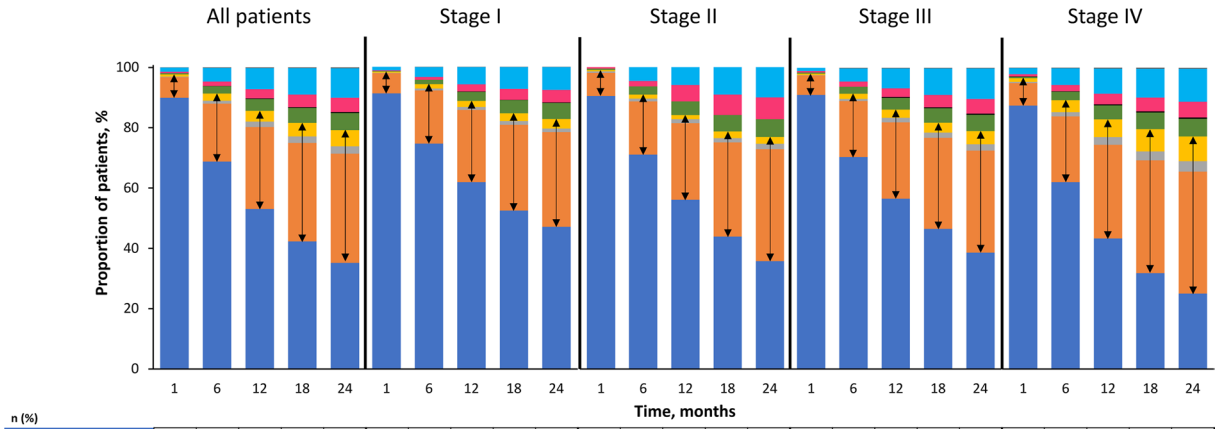
**Table 1** Baseline patient demographic and clinical characteristics and nintedanib treatment pattern

| Characteristic | All patients ($n$ = 5717[a]) |
|---|---|
| Age, years | |
| Mean ± SD | 71.7 ± 8.1 |
| Median | 73.0 |
| < 75 years, *n* (%) | 3476 (60.8) |
| ≥ 75 years, *n* (%) | 2241 (39.2) |
| Sex, *n* (%) | |
| Male | 4463 (78.1) |
| Female | 1254 (21.9) |
| Body weight, kg | (*n* = 5425) |
| Mean ± SD | 59.4 ± 12.5 |
| Median | 59.1 |
| BMI, kg/m$^2$ | (*n* = 5394) |
| Mean ± SD | 22.8 ± 3.9 |
| Median | 22.8 |
| BSA, m$^2$ | (*n* = 5394) |
| Mean ± SD | 1.62 ± 0.19 |
| Median | 1.63 |
| BSA category, *n* (%) | |
| < 1.73 m$^2$ | 3883 (67.9) |
| ≥ 1.73 m$^2$ | 1511 (26.4) |
| Data missing | 323 (5.7) |
| Current or previous smoking history, *n* (%) | 4047 (70.8) |
| IPF severity stage, *n* (%) | (*n* = 4384) |
| I | 1101 (25.1) |
| II | 221 (5.0) |
| III | 1033 (23.6) |
| IV | 1506 (34.4) |
| Unknown | 25 (0.6) |
| Data missing | 498 (11.4) |
| FVC, mL | (*n* = 4962) |
| Mean ± SD | 2122.4 ± 721.8 |
| FVC,% predicted | (*n* = 4524) |
| Mean ± SD | 69.5 ± 37.8 |
| Median | 67.2 |
| FVC% predicted category, *n* (%) | |
| < 70% | 2494 (43.6) |
| ≥ 70% | 2030 (35.5) |
| Data missing | 1193 (20.9) |
| Previous treatment for IPF, *n* (%) | 1328 (23.2) |
| Pirfenidone | 1044 (18.3) |
| Corticosteroids | 239 (4.2) |
| Immunosuppressants | 121 (2.1) |
| Baseline IPF medication,[b] *n* (%) | 1826 (31.9) |
| Corticosteroids | 1362 (23.8) |
| Pirfenidone | 208 (3.6) |
| Immunosuppressants | 313 (5.5) |
| Nintedanib treatment during observation period | |
| Exposure duration, days | |
| Mean ± SD | 370.7 ± 281.6 |
| Median | 336.0 |
| Initial starting dose, *n* (%) | |
| 100 mg bid | 766 (13.4) |
| 150 mg bid | 4794 (83.9) |
| Other | 129 (2.3) |
| Data missing | 28 (0.5) |
| Dose changes, *n* (%) | |
| Reduction from 150 to 100 mg bid | 1715/4794 (35.8) |
| Increase from 100 to 150 mg bid | 180/766 (23.5) |
| Time to first dose reduction, days | (*n* = 1715) |
| Mean ± SD | 145.2 ± 153.2 |
| Median | 86.0 |
| Time to treatment discontinuation, days | (*n* = 3818) |
| Mean ± SD | 241.0 ± 213.2 |
| Median | 182.0 |

*bid* twice daily, *BMI* body mass index, *BSA* body surface area, *IPF* idiopathic pulmonary fibrosis, *FVC* forced vital capacity, *SD* standard deviation

[a]*n* = 5717 unless otherwise indicated

[b]Including drugs for treatment of acute exacerbation, regardless of other treatment use




| n (%) | All patients | | | | | Stage I | | | | | Stage II | | | | | Stage III | | | | | Stage IV | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Continued | 3944 (90.0) | 3016 (68.8) | 2326 (53.1) | 1854 (42.3) | 1543 (35.2) | 1004 (91.2) | 821 (74.6) | 681 (61.9) | 577 (52.4) | 518 (47.1) | 200 (90.5) | 157 (71.0) | 124 (56.1) | 97 (43.9) | 79 (35.8) | 940 (91.0) | 727 (70.4) | 584 (56.5) | 481 (46.6) | 399 (38.6) | 1317 (87.5) | 934 (62.0) | 653 (43.4) | 479 (31.8) | 377 (25.0) |
| AEs (excluding disease progression) | 298 (6.8) | 841 (19.2) | 1192 (27.2) | 1434 (32.7) | 1587 (36.2) | 74 (6.7) | 194 (17.6) | 263 (23.9) | 313 (28.4) | 345 (31.3) | 17 (7.7) | 39 (17.7) | 56 (25.3) | 69 (31.2) | 82 (37.1) | 67 (6.5) | 192 (18.6) | 262 (25.4) | 312 (30.2) | 350 (33.9) | 113 (7.5) | 329 (21.9) | 468 (31.1) | 564 (37.5) | 610 (40.5) |
| Disease progression | 10 (0.2) | 43 (1.0) | 78 (1.8) | 92 (2.1) | 107 (2.4) | 1 (0.1) | 7 (0.6) | 11 (1.0) | 13 (1.2) | 13 (1.2) | 1 (0.5) | 2 (0.9) | 3 (1.4) | 3 (1.4) | 4 (1.8) | 1 (0.1) | 7 (0.7) | 16 (1.6) | 18 (1.7) | 22 (2.1) | 6 (0.4) | 21 (1.4) | 38 (2.5) | 45 (3.0) | 52 (3.5) |
| Acute exacerbation | 31 (0.7) | 105 (2.4) | 158 (3.6) | 200 (4.6) | 235 (5.4) | 5 (0.5) | 16 (1.5) | 22 (2.0) | 29 (2.6) | 35 (3.2) | 1 (0.5) | 3 (1.4) | 3 (1.4) | 5 (2.3) | 5 (2.3) | 5 (0.5) | 18 (1.7) | 28 (2.7) | 34 (3.3) | 45 (4.4) | 18 (1.2) | 60 (4.0) | 89 (5.9) | 111 (7.4) | 124 (8.2) |
| Insufficient effectiveness | 17 (0.4) | 105 (2.4) | 172 (3.9) | 217 (5.0) | 248 (5.7) | 2 (0.2) | 16 (1.5) | 33 (3.0) | 48 (4.4) | 58 (5.3) | 1 (0.5) | 6 (2.7) | 10 (4.5) | 12 (5.4) | 13 (5.9) | 4 (0.4) | 24 (2.3) | 40 (3.9) | 50 (4.8) | 56 (5.4) | 7 (0.5) | 43 (2.9) | 70 (4.7) | 83 (5.5) | 88 (5.8) |
| Improved | 2 (0.1) | 2 (0.1) | 9 (0.2) | 11 (0.3) | 16 (0.4) | 0 | 0 | 1 (0.1) | 1 (0.1) | 2 (0.2) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 (0.3) | 3 (0.3) | 4 (0.4) | 2 (0.1) | 2 (0.1) | 5 (0.3) | 6 (0.40) | 7 (0.5) |
| Lost to follow-up | 19 (0.4) | 67 (1.5) | 132 (3.0) | 182 (4.2) | 208 (4.7) | 2 (0.2) | 10 (0.9) | 26 (2.4) | 40 (3.6) | 46 (4.2) | 1 (0.5) | 4 (1.8) | 12 (5.4) | 15 (6.8) | 16 (7.2) | 5 (0.5) | 18 (1.7) | 30 (2.9) | 42 (4.1) | 50 (4.8) | 11 (0.7) | 31 (2.1) | 53 (3.5) | 69 (4.6) | 79 (5.3) |
| Other | 62 (1.4) | 198 (4.5) | 308 (7.0) | 384 (8.8) | 429 (9.8) | 13 (1.2) | 36 (3.3) | 63 (5.7) | 79 (7.2) | 83 (7.5) | 0 | 10 (4.5) | 13 (5.9) | 20 (9.1) | 22 (10.0) | 11 (1.1) | 45 (4.4) | 68 (6.6) | 91 (8.8) | 105 (10.2) | 31 (2.1) | 84 (5.6) | 126 (8.4) | 144 (9.6) | 164 (10.9) |
| Missing | 1 (0.0) | 7 (0.2) | 9 (0.2) | 10 (0.2) | 11 (0.3) | 0 | 1 (0.1) | 1 (0.1) | 1 (0.1) | 1 (0.1) | 0 | 0 | 0 | 0 | 0 | 0 | 2 (0.2) | 2 (0.2) | 2 (0.2) | 2 (0.2) | 1 (0.1) | 2 (0.1) | 4 (0.3) | 5 (0.3) | 5 (0.3) |

**Fig. 1** Nintedanib treatment continuation and discontinuations rates over time, according to idiopathic pulmonary fibrosis severity stage. *Arrows* indicate the three reasons for treatment discontinuation related to adverse events (AEs), i.e. "AEs (excluding disease progression)", "disease progression" and "acute exacerbation"

liver disorder, nausea, pneumonia and cough (Fig. 2b).

Neoplastic AEs (benign, malignant and unspecified) occurred in < 1.5% of patients, the most common (occurring in ≥ 0.2% of patients) being malignant neoplasm progression (1.4%), lung neoplasm malignant (1.0%), gastric cancer (0.3%) and recurrent lung carcinoma, cell-type unspecified (0.2%). ADRs occurring in ≥ 2% of patients were diarrhoea, hepatic function abnormal, decreased appetite, liver disorder and nausea (Fig. 2b).

The ADR event rates for gastrointestinal events were 50.5, 7.2 and 2.4 events per 100 patient exposure-years for diarrhoea, nausea and vomiting, respectively, and the ADR event rates for hepatic function abnormal and liver disorder were 16.9 and 8.9 events per 100 patient exposure-years, respectively (Table 2). The ADRs of hepatic disorders and diarrhoea had a median time to onset of 22.0 and 92.0 days, respectively (Supplementary Material Fig. S2). Hepatic disorders were mainly managed by treatment discontinuation (349 events), interruption (351 events) or dose reduction (305 events), while diarrhoea was mainly managed by dose reduction (501 events), with treatment being continued unchanged for 948 events, discontinued for 321 events and interrupted for 157 events.

The univariate logistic regression analysis identified several variables as possibly having an association with an increased risk of ADRs overall and ADRs of hepatic disorders or diarrhoea (Fig. 3a). The risk of ADRs overall was increased in female patients and in patients with stage I/II IPF, no concomitant IPF medication at baseline and an initial nintedanib dose of 150 mg bid. The analysis indicated that the risk of hepatic disorder ADRs was increased in female patients, and in patients with BSA < 1.63 $m^2$, no smoking history, baseline FVC < 70% predicted and an initial nintedanib dose of 150 mg bid. The risk of diarrhoea ADRs was increased in patients aged < 73 years, ex- or current smokers and in patients with BSA ≥ 1.63 $m^2$, baseline FVC ≥ 70% predicted, stage I/II IPF, no concomitant IPF medication and an initial nintedanib dose of 150 mg bid.

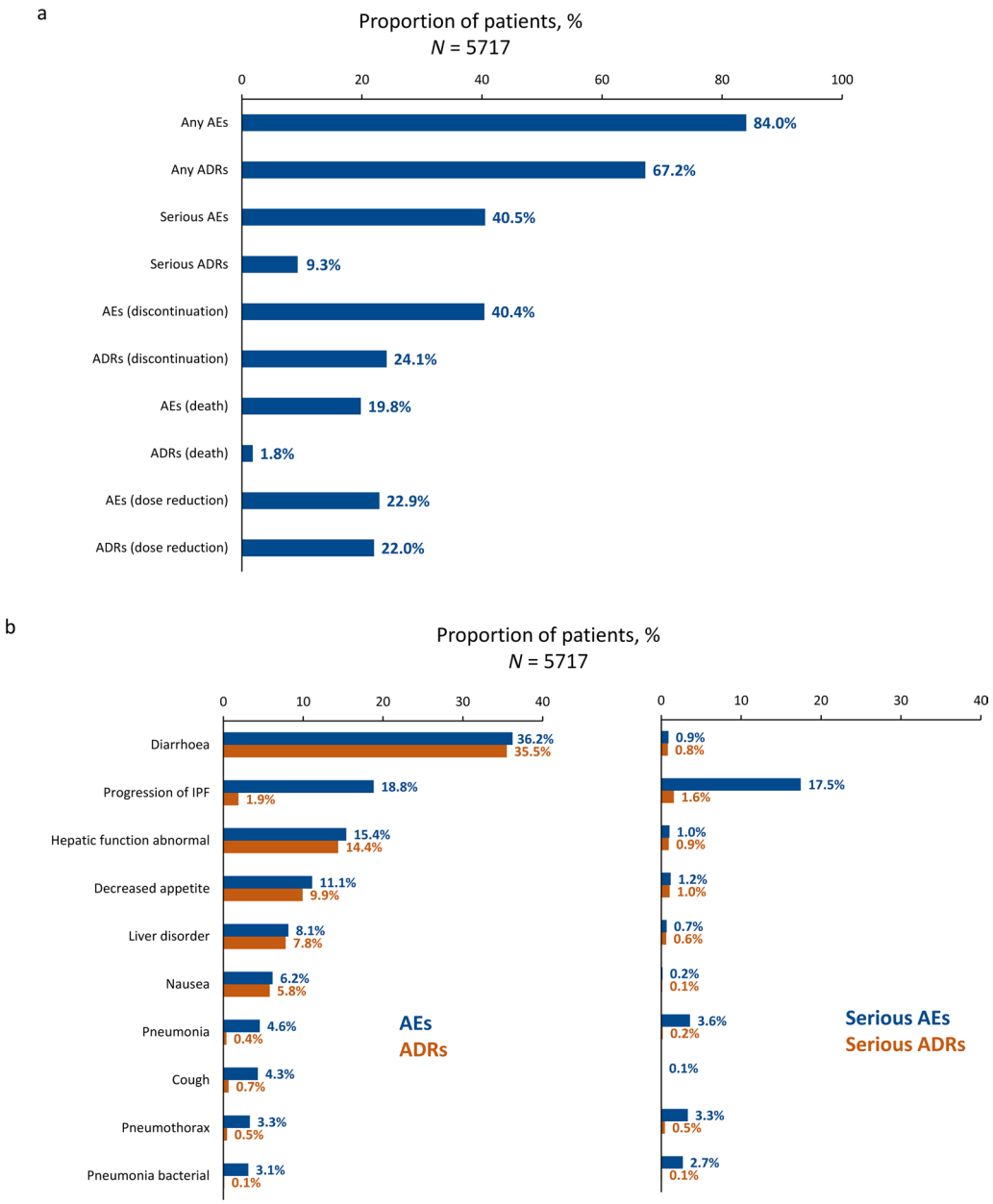



**Fig. 2** Incidence of adverse events (AEs) and adverse drug reactions (ADRs) with nintedanib as **a** overall summary and **b** the most common AEs and ADRs. *IPF* idiopathic pulmonary fibrosis

The multivariate analysis identified several potential risk factors for ADRs overall, hepatic disorder ADRs and diarrhoea ADRs (Fig. 3b). The risk of ADRs overall was increased in female patients and in patients aged ≥ 73 years, with no concomitant IPF medication and an initial nintedanib dose of 150 mg bid. The risk of hepatic disorder ADRs was increased in female patients and in patients with baseline FVC < 70% predicted and an initial nintedanib dose of 150 mg bid, while the risk of diarrhoea ADRs was increased in ex- or current smokers and in patients with BSA ≥ 1.63 $m^2$, baseline FVC ≥ 70% predicted, stage I/II IPF,

**Table 2** Adverse event rates of common AEs and ADRs

| Type of AE | Safety analysis set (*n* = 5717) | | | |
|---|---|---|---|---|
| | AEs | | ADRs | |
| | Events, *n* | Event rate, per 100 patient exposure-years[a] | Events, *n* | Event rate, per 100 patient exposure-years[a] |
| Diarrhoea | 3049 | 51.6 | 2985 | 50.5 |
| Progression of IPF | 1267 | 21.4 | 112 | 1.9 |
| Hepatic function abnormal | 1078 | 18.2 | 1001 | 16.9 |
| Liver disorder | 559 | 9.5 | 528 | 8.9 |
| Nausea | 457 | 7.7 | 424 | 7.2 |
| Constipation | 204 | 3.5 | 59 | 1.0 |
| Vomiting | 164 | 2.8 | 139 | 2.4 |
| Faeces soft | 119 | 2.0 | 112 | 1.9 |
| Bronchitis | 118 | 2.0 | 4 | 0.1 |

*ADRs* adverse drug reactions, *AEs* adverse events, *IPF* idiopathic pulmonary fibrosis

[a]Rate ≥ 2 per 100 patient exposure-years

no concomitant IPF medications and an initial nintedanib dose of 150 mg bid.

## Effectiveness

At 24 months, the incidence rate of investigator-reported acute exacerbations of IPF in the overall effectiveness set was 13.1 per 100 patient exposure-years (744 events; Table 3) or 13.1% (Supplementary Material Table S2). The incidence of acute exacerbations increased numerically with increasing IPF severity from stages II to IV (Fig. 4). Higher rates of acute exacerbations were observed in patients with baseline FVC% predicted < 70% and in patients who were receiving corticosteroids at baseline.

In the FVC effectiveness set (*n* = 3124), the adjusted absolute mean change in FVC from baseline to 12 and 24 months was – 129.8 mL (95% CI – 148.3, – 111.3) and – 212.3 mL (95% CI – 235.3, – 189.3), respectively (Fig. 5). By 12 months, the adjusted annual rate of decline in FVC was greater in patients with a nintedanib dose intensity of < 80% than in those with a dose intensity of ≥ 80% (Fig. 6), representing a difference of 113.4 mL/year. Compared with patients who had a nintedanib dose intensity of < 80%, those with a dose intensity of ≥ 80% included a numerically higher proportion of male patients and patients aged < 75 years and had a numerically higher mean BMI (23.9 vs. 22.9 kg/m$^2$; Supplementary Material Table S3). At Month 12, 566 patients had a decline in FVC% predicted from baseline of ≤ 5%, 148 had a > 5% to ≤ 10% decline and 260 had a > 10% decline (Supplementary Material Table S4). Compared with patients who had a decline in FVC% predicted from baseline of ≤ 5% or > 5% to ≤ 10% at Month 12, patients with a > 10% decline in FVC% predicted included numerically lower proportions of patients who were male patients, current or ex-smokers and had received nintedanib at a dose intensity of ≥ 80%. Patients with a > 10% decline in FVC% predicted also had a numerically lower mean BMI and baseline FVC% predicted than the other comparator groups. Compared with patients who had a decline in FVC% predicted from baseline of ≤ 5% or > 5% to ≤ 10% at Month 12, a higher proportion of patients with a > 10% decline in FVC% predicted tended to have

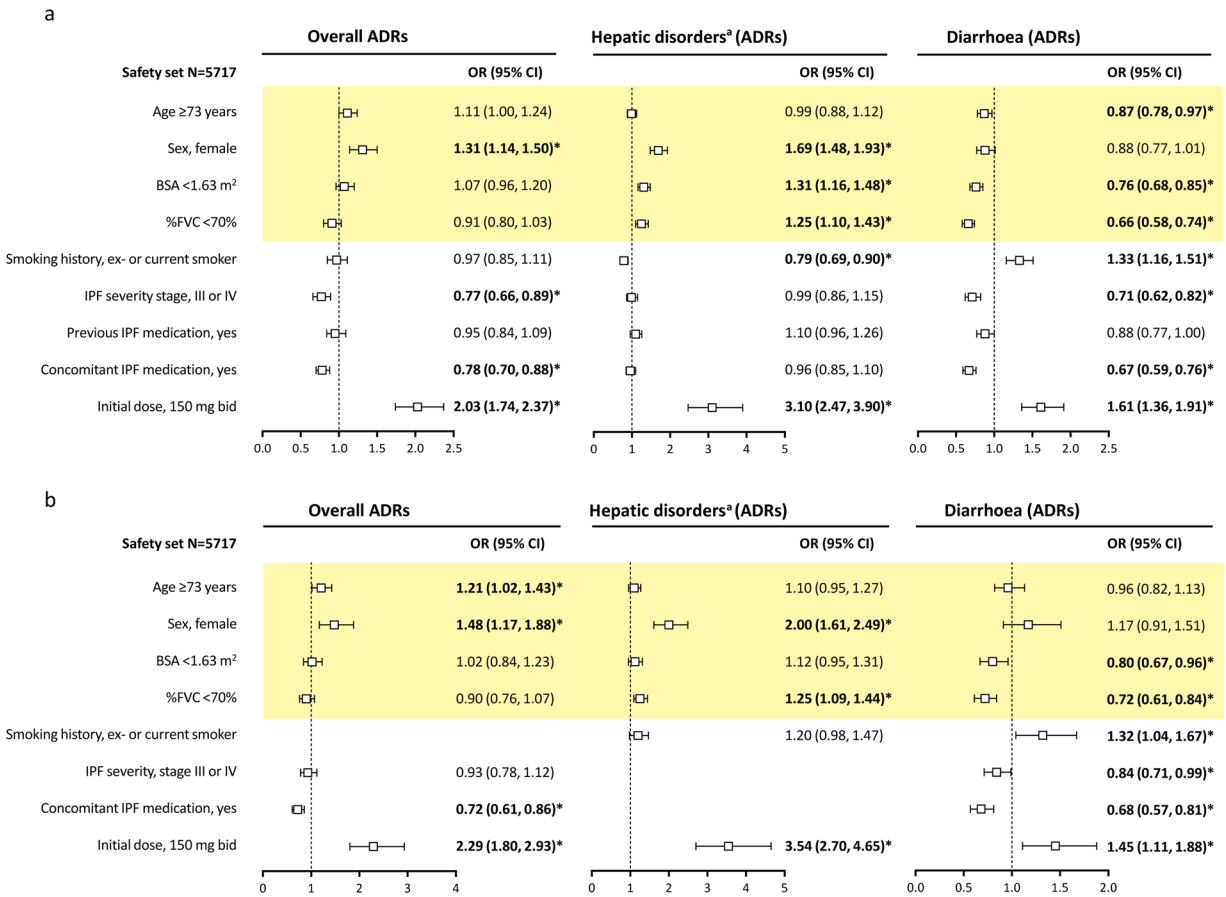



**Fig. 3** Logistic regression by **a** univariate and **b** multivariate analysis investigating risk factors associated with adverse drug reactions during nintedanib treatment. Variables in the multivariate analysis included age (< 73 vs. ≥ 73 years), sex (male vs. female), BSA (< 1.63 vs. ≥ 1.63 $m^2$) and FVC% (< 70 vs. ≥ 70%) regardless of the univariate analysis results and any other factors for which the 95% CI of ORs did not cross 1 during univariate analysis. [a]Liver-related investigations, signs and symptoms (standardised MedDRA Queries: SMQ), hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (sub-SMQ), cholestasis and jaundice of hepatic origin (sub-SMQ) and hepatitis, non-infectious (sub-SMQ). *Upper 95% CI < 1 or lower 95% CI > 1 (indicated in bold text). *ADRs* adverse drug reactions, *bid* twice daily, *BSA* body surface area, *CI* confidence interval, *FVC* forced vital capacity, *IPF* idiopathic pulmonary fibrosis, *MedDRA* Medical Dictionary for Regulatory Activities, *OR* odds ratio

received a nintedanib dose intensity of < 80% than a dose intensity of ≥ 80%.

## DISCUSSION

This PMS study of patients who initiated nintedanib therapy for IPF revealed that the incidence of AEs and ADRs at 24 months was 84.0% and 62.7%, respectively. Treatment discontinuations were mainly caused by AEs (in 44.0% of patients), ADRs (24.1%) and insufficient effectiveness (5.7%). Overall, AEs related to diarrhoea, progression of IPF, decreased appetite and hepatic function were the main reasons for discontinuation. At 24 months, the proportion of patients with acute exacerbations was 13.1%, and the adjusted absolute mean change in FVC from baseline was – 212.3 mL.

Approximately 65% of patients discontinued nintedanib treatment within 24 months, mainly

**Table 3** Incidence rate of acute exacerbations over 24 months

| Category | Events, *n* | Event rate, per 100 patient exposure-years |
|---|---|---|
| Total population | 744 | 13.1 |
| IPF severity stage[a] | | |
| I | 97 | 7.4 |
| II | 17 | 7.0 |
| III | 135 | 11.8 |
| IV | 273 | 21.2 |
| FVC% predicted at baseline class[b] | | |
| < 70% | 357 | 16.0 |
| ≥ 70% | 226 | 9.2 |
| OCS use at baseline[c] | | |
| Yes | 268 | 22.8 |
| No | 281 | 6.9 |

*FVC* forced vital capacity, *IPF* idiopathic pulmonary fibrosis, *OCS* oral corticosteroid

[a]Unknown 17.3 per 100 patient exposure-years, missing 13.0 per 100 patient exposure-years

[b]Missing 16.3 per 100 patient exposure-years

[c]Unknown 44.5 per 100 patient exposure-years

due to AEs and insufficient effectiveness. This was similar to that seen in the INPULSIS-ON trial (69–72%) [11]. As INPULSIS-ON patients were exposed to nintedanib for a longer period (median 31.5 months) [11], it may be possible that the incidence of discontinuation over time was higher in this study. The proportion of patients with AEs leading to discontinuation in this study was 40.4%, corresponding to an event rate of 40.6 per 100 patient exposure-years. This was similar to the INPULSIS-ON trial (40–46%) [11], but higher than reported in the INPULSIS-1 and –2 trials (17.6 and 21.0%, respectively) [9] and in Japanese patients enrolled in INPULSIS trials (25.0%) [12].

Consideration should be given to differences in patient background characteristics between this study, the INPULSIS trial and INPULSIS Japanese data. When comparing patients in this PMS study with the INPULSIS total and Japanese populations [12], patients were older (mean age 71.7 vs. 66.6 and 68.4 years, respectively), had lower BMI (mean 22.8 vs. 28.1 and 24.4 kg/m$^2$, respectively) and poorer lung function (baseline FVC% predicted 69.5% vs. 79.7% and 80.9%, respectively). These differences may explain the higher rates of treatment discontinuation observed in this PMS study. In the interim analysis of this study, multivariate analysis showed that patients aged ≥ 75 years, those with BSA of < 1.58 m$^2$, those with baseline FVC < 70% predicted, stage III/IV IPF and male patients were more likely to discontinue nintedanib treatment within 3 and 12 months [13].

The incidence of AEs in this PMS study (84.0%) was numerically lower than that reported in previous phase III trials (94.5–99%) and Japanese subset data (98.7%) [9, 11, 12]; of note, under-reporting of AEs is a challenge in real-world studies [17], which could explain this difference. The most common AEs in this study were diarrhoea, progression of IPF, hepatic function abnormal, decreased appetite, liver disorder and nausea. The event rates of gastrointestinal AEs of diarrhoea, nausea and vomiting (51.6, 7.7 and 2.8 per 100 patient exposure-years, respectively) were lower than that reported in the group of patients who continued nintedanib treatment in an open-label extension of the INPULSIS trials (INPULSIS-ON; 60.1, 8.6 and 7.2 per 100 patient exposure-years, respectively) [11]. However, the rate of progression of IPF was higher in this analysis than in the INPULSIS-ON nintedanib continued group (21.4 vs. 13.7 per 100 patient exposure-years) [11].

The multivariate analysis identified that possible risk factors for developing ADRs overall included older age (≥ 73 years), no concomitant IPF medications at baseline and an initial nintedanib dose of 150 mg bid, as well as being female. Notably, multivariate analysis of ADRs indicated an OR > 1 in patients with a median age of ≥ 73 years compared with those aged < 73 years. There was no tendency for the OR to be high for frequently occurring liver disorders or diarrhoea. The analysis identified baseline FVC < 70% predicted and an initial nintedanib dose of 150 mg bid, as well as being

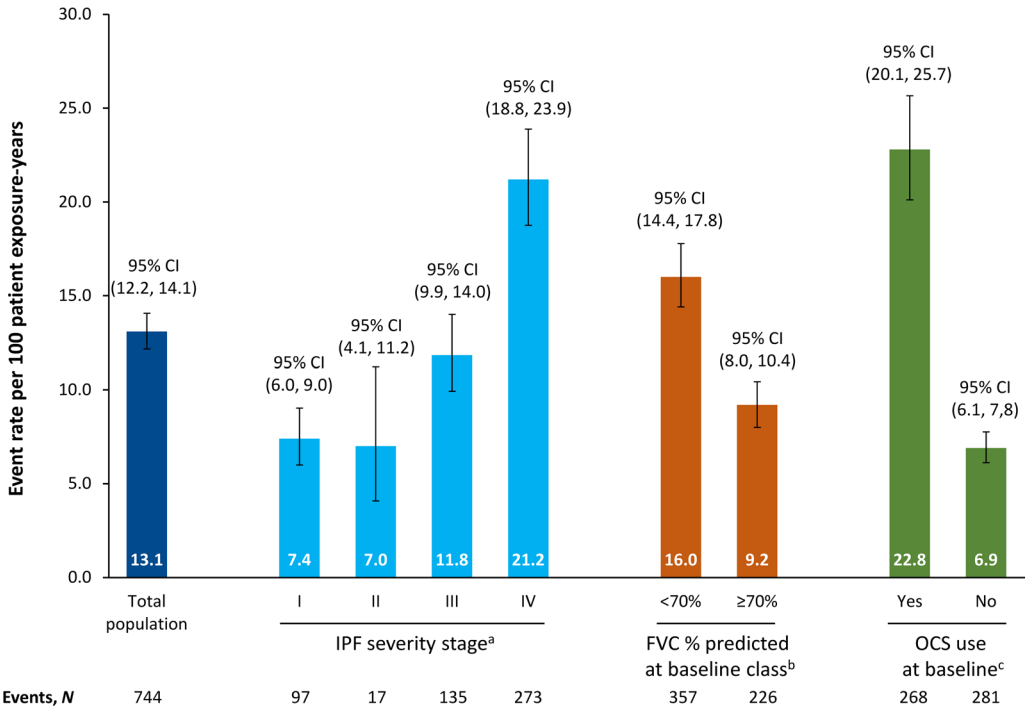



**Fig. 4** Incidence rate of acute exacerbations over 24 months. [a]Unknown ($n$ = 25) 17.3 (95% CI 3.6, 50.6) per 100 patient exposure-years, missing ($n$ = 498) 13.0 (95% CI 10.1, 16.4) per 100 patient exposure-years. [b]Missing ($n$ = 1193) 16.3 (95% CI 13.9, 19.0) per 100 patient exposure-years. [c]Unknown ($n$ = 420) 44.5 (95% CI 38.5, 51.2) per 100 patient exposure-years. *CI* confidence interval, *FVC* forced vital capacity, *IPF* idiopathic pulmonary fibrosis, *OCS* oral corticosteroid

female, to be possible risk factors for developing hepatic disorder ADRs, while possible risk factors for developing diarrhoea ADRs were being an ex- or current smoker, having a BSA ≥ 1.63 $m^2$, baseline FVC% ≥ 70% predicted, stage I/II IPF, no concomitant IPF medications and an initial nintedanib dose of 150 mg bid. Schmid and colleagues also showed that the risk of liver enzyme elevations was positively correlated with plasma nintedanib concentrations and female sex in patients with IPF and those with other fibrosing interstitial lung diseases [18]. The actual dose of nintedanib administered was a better predictor of the risk of developing diarrhoea than drug plasma concentrations, suggesting that gastrointestinal tract concentrations may be more relevant than plasma exposure [18]. We did not examine nintedanib plasma concentrations and their relationship to ADRs in this PMS study. Nevertheless, for case groups with a potentially higher risk of developing ADRs (older patients, female patients) that may necessitate treatment discontinuation, we would advise monitoring ADRs frequently and managing them appropriately in order to avoid treatment discontinuation. This is particularly important given the possible relationship between dose intensity and therapeutic benefit (discussed below).

The rate of acute exacerbations in this study was 13.1 per 100 patient exposure-years, corresponding to a proportion of 13.1%. The incidence of acute exacerbations in this PMS study is similar to that observed in INPULSIS-ON (12% in patients who initiated nintedanib and 15% in those who continued nintedanib) [11]. As the IPF severity stage increased, the incidence rate of acute exacerbations also increased.

Lower incidences of AEs together with higher FVC% are commonly reported in PMS studies with nintedanib. However, the incidence of AEs in this study was numerically lower than in INPULSIS-ON (84% vs. 98–99%) [11]. The rate

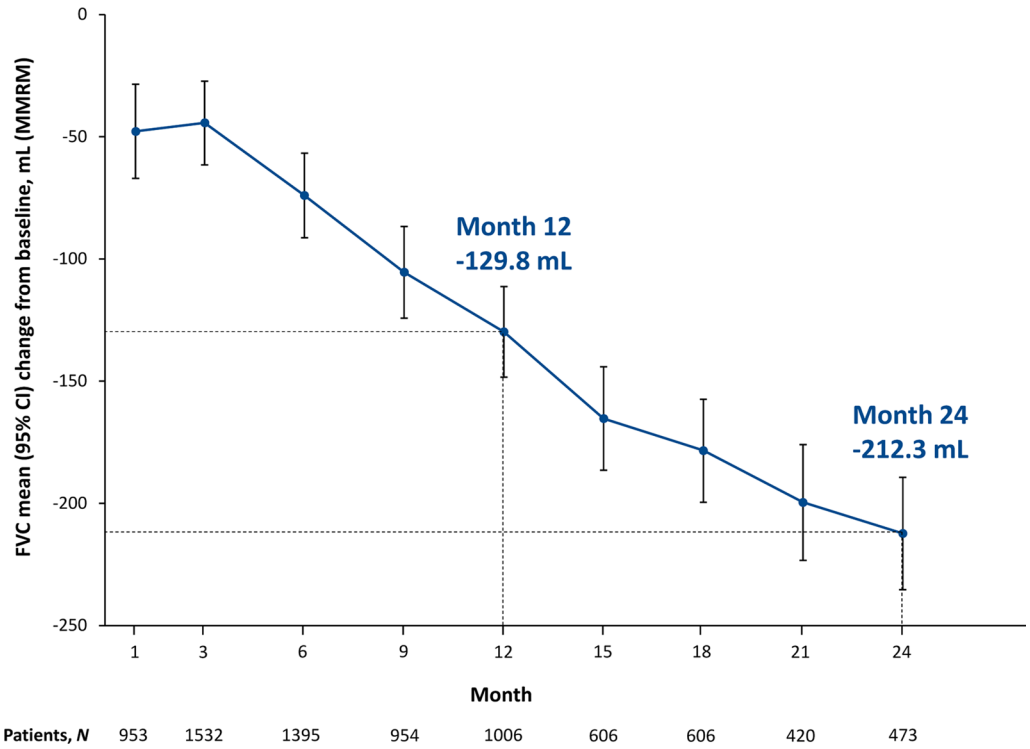



**Fig. 5** Adjusted absolute change from baseline in FVC during nintedanib treatment. *CI* confidence interval, *FVC* forced vital capacity, *MMRM* mixed model for repeated measure

of acute exacerbations in this study was 22.8 per 100 patient exposure-years in patients on corticosteroids at baseline, compared with 6.9 per 100 patient exposure-years in patients who were not. The proportion of patients on corticosteroids in this study when compared with the INPULSIS-1 and –2 studies was 23.8% vs. 22.0% and 20.7%, respectively [9, 11]. As previously reported in the interim analysis of this PMS study [13], and by others [19], baseline corticosteroid use is a risk factor for acute exacerbation of IPF.

The adjusted absolute mean change in FVC from baseline to Months 12 and 24 [– 129.8 mL (– 129.8 mL/year) and – 212.3 mL (– 106.2 mL/year), respectively] was slightly lower than the adjusted annual rate of FVC decline reported over 52 weeks in INPULSIS-1 and –2 (– 114.7 mL/year and – 113.6 mL/year, respectively) [9] and over 192 weeks in INPULSIS-ON (– 135.1 mL in all patients, – 145.0 mL/year in those who continued nintedanib, and – 119.7 mL/year in those who initiated nintedanib) [11]. However, this difference was not considered to be clinically relevant. Further, patients with a nintedanib dose intensity of ≥ 80% had a lower adjusted annual rate of decline in FVC by Month 12 than those with a dose intensity of < 80%, representing a difference in FVC of 113.4 mL/year. This finding contrasts with that of INPULSIS-ON, in which the annual rate of decline in FVC was similar, irrespective of nintedanib dose intensity (≤ 90% or > 90%) [11]. This could be explained by the differing background characteristics of patients in this study who had a nintedanib dose intensity < 80% versus ≥ 80%; the < 80% group included a numerically higher proportion of female patients and patients aged ≥ 75 years, and had a lower BMI and BSA than those in the ≥ 80% group. As shown in multivariate analysis of this PMS study, patients aged ≥ 73 years may have a higher risk of overall ADRs, which may lead to a higher risk of nintedanib discontinuation. This highlights the importance of careful management of AEs in this patient population. Compared with patients

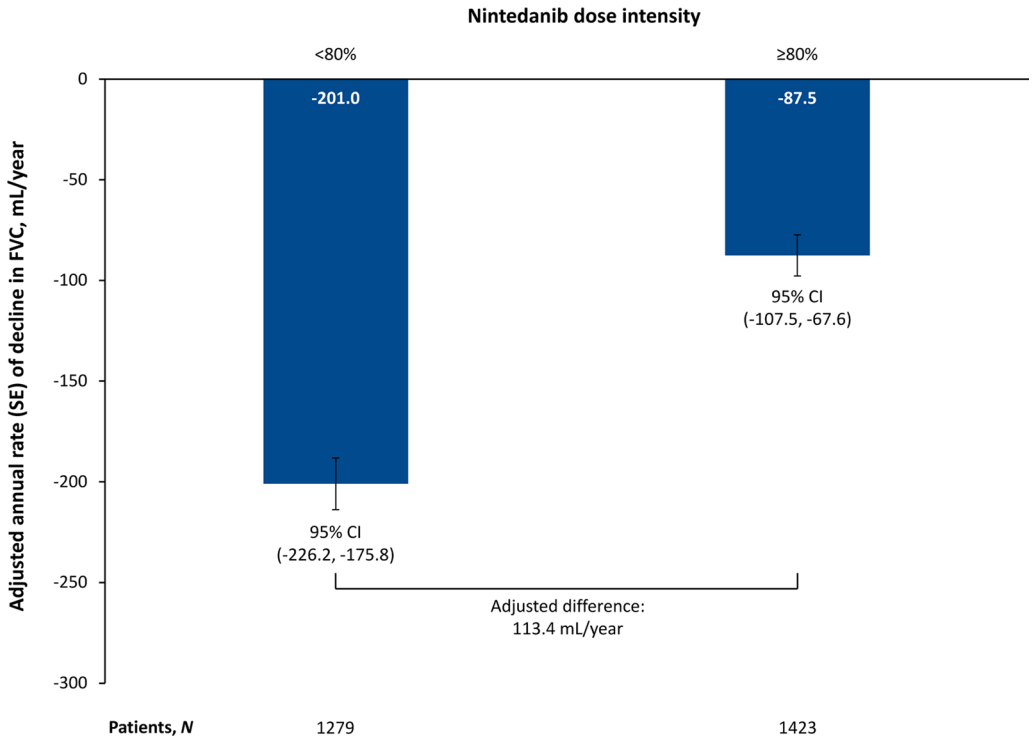



**Fig. 6** Adjusted annual rate of decline in FVC at 12 months according to nintedanib dose intensity. Dose intensity of 100%: 109,200 mg in total (300 mg × 364 days). Dose intensity is defined as the ratio of the actual dose of nintedanib (including cases of dose modification) to the estimated dose administered without cases of dose reduction and withdrawal over 12 months (364 days). This analysis included the patients who discontinued nintedanib before 12 months. *CI* confidence interval, *FVC* forced vital capacity, *SE* standard error

with a decline in FVC% predicted from baseline of ≤ 10% at Month 12, patients with a > 10% decline comprised a numerically lower proportion of male patients, current or ex-smokers and patients who received a nintedanib dose intensity ≥ 80%, and a higher proportion of female patients and patients who received a nintedanib dose intensity < 80%. Patients with a > 10% decline in FVC% predicted also had a numerically lower mean BMI and baseline FVC% predicted than those who had a smaller decline in FVC% predicted.

Factors that influence nintedanib dosage are highly complex. It is recommended that the initial dose of nintedanib should be 150 mg bid and continued at ≥ 80% exposure for clinical effectiveness. However, the dose may be reduced to 100 mg bid if the higher dose is poorly tolerated based on the patient's condition (e.g. the presence of nausea, vomiting, diarrhoea and/or aspartate transaminase or alanine aminotransferase levels > 3 times the upper limit of normal). Since this analysis did not reveal the risk factors that influence dose intensity, further studies are recommended to ascertain these factors.

Lung cancer is an important comorbidity of IPF, being reported in up to 31% of patients with IPF [20–24]. In contrast, the incidence of lung neoplasm malignant in patients treated with nintedanib was lower in this PMS study, although the observation period was shorter than in previous studies. Lung cancer has multifactorial causes, including carcinoma-associated fibroblasts (CAFs), which are thought to promote and regulate the development and progression of tumours [25]. Nintedanib appears to suppress CAFs, as shown in an in vitro study of the effects of the drug on profibrotic activation markers in lung adenocarcinoma tissue samples [26]. Encouragingly,

a retrospective study found that the incidence and prevalence of lung cancer and related mortality were significantly lower in patients with IPF who had received antifibrotic drugs (pirfenidone or nintedanib; $n = 189$) compared with patients who did not receive this treatment ($n = 156$) [27]. Further large-scale studies are necessary to verify the effects of antifibrotic drugs, including nintedanib, in the prevention of lung cancer in patients with IPF.

One of the major strengths of this PMS study was that it included the largest patient cohort treated with nintedanib to date. Only two observational studies of nintedanib in > 1000 patients have previously been conducted, both of which were in the US [28, 29]. Since there were no restrictions (e.g. age, lung function) on the data collected in this study, this dataset can be considered to be original and reflective of real-world nintedanib use in the Japanese population. Other strengths include the prospective data collection, external validity and overall generalisability of the findings from this real-world population of patients with IPF.

The limitations of this study include the lack of a control group, and the fact that it included patients solely from Japan. Further, since AE data were reported at the discretion of the investigator, only those AEs that were recorded by the physician were assessed. Therefore, some AE data may not have been collected and may be reflected in the lower rate of AEs reported in this analysis compared with INPULSIS-ON [11]. Similarly, not all physicians provided data on treatment discontinuation or the reason for discontinuation. Another limitation is that the diagnosis of IPF and of acute exacerbation in this study were assessed by the attending physician rather than being centrally evaluated, which could have introduced bias. Furthermore, the diagnosis of IPF was based on institutional judgement at each study site, which may have introduced variability in diagnosis, and this study did not investigate whether the multidisciplinary team (MDT) approach to IPF diagnosis was used (i.e. clinical–radiological or clinical–radiological–pathological multidisciplinary discussion); therefore, the rate of MDT diagnosis could not be assessed.

## CONCLUSION

This PMS study demonstrated that the safety and effectiveness of nintedanib in a real-world setting of Japanese patients with IPF is similar to that reported in previous studies. To ensure the continuation of nintedanib therapy to slow the progression of IPF, appropriate management of ADRs, such as hepatic disorders and diarrhoea, is crucial.

## ACKNOWLEDGEMENTS

We thank all the physicians, healthcare professionals and patients who collaborated in this study.

***Medical Writing, Editorial and Other Assistance.*** We would like to thank Carmen Innes, BSc, and Nireshnee Ramchundar, PhD, of inScience Communications, Springer Healthcare, who wrote the outline and first draft of the manuscript, respectively, and Sarah Greig, PhD, CMPP, of inScience Communications, Springer Healthcare, who assisted with post-submission revisions. Support for this editorial assistance was funded by Nippon Boehringer Ingelheim Co., Ltd.

***Authorship.*** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. The authors did not receive payment related to the development of the manuscript.

***Author Contributions.*** Yoshikazu Inoue, Takashi Ogura, Arata Azuma, Yasuhiro Kondoh, Sakae Homma, Kenya Muraishi, Rie Ikeda, Kaori Ochiai, Yukihiko Sugiyama, and Toshihiro Nukiwa contributed to the study design, data interpretation and manuscript preparation. Rie

Ikeda prepared the materials and collected the data, and Kaori Ochiai and Rie Ikeda analysed the data. All authors read and approved the final manuscript as submitted and are accountable for all aspects of the work.

***Funding.*** Sponsorship for this study, and the journal's Rapid Service Fee and the Open Access Fee were funded by Nippon Boehringer Ingelheim Co., Ltd. Boehringer Ingelheim was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations.

***Data Availability.*** To ensure independent interpretation of clinical results and enable authors to fulfil their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to relevant clinical data. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical data after publication of the primary manuscript in a peer-reviewed journal, regulatory activities are complete and other criteria are met. Researchers should use the https://vivli.org/ link to request access to data and visit https://www.mystudywindow.com/msw/datasharing for further information.

## *Declarations*

***Conflict of Interest.*** Yoshikazu Inoue has received grants from the Japanese Ministry of Health, Labour and Welfare, from the Japan Agency for Medical Research and Development, and from the NHO Respiratory Network; and lecture fees and/or consulting fees from Boehringer Ingelheim, Shionogi and Co., Ltd., Taiho Pharmaceutical Co., Kyorin Pharmaceutical, Galapagos, Roche, Tanabe Mitsubishi, AsahiKasei, Mochida, Chugai, AMGEN, Savara Co., Ltd., CSL Behring, Vicore Pharma AB, Horizon Therapeutics, GSK, AstraZeneca, and Novartis Pharma K.K. Takashi Ogura has received consulting fees from Boehringer Ingelheim, Bristol-Myers Squibb and Taiho Pharmaceutical Co.; and lecture fees or honoraria from Boehringer Ingelheim, Eisai Inc., Kyorin Pharmaceutical Co., Ltd., Shionogi and Co., Ltd. and Teijin Pharma. Arata Azuma has received consulting fees from Toray Co., Ltd.; lecture fees and participation on an advisory board from Boehringer Ingelheim and Taiho Pharmaceutical Co.; and support for travel from Boehringer Ingelheim. Yasuhiro Kondoh has received consulting fees from Boehringer Ingelheim, Chugai Pharmaceutical Co., Ltd., Healios K.K., Janssen Pharmaceutical K.K., Shionogi and Co., Ltd. and Taiho Pharmaceutical Co.; and payments or honoraria from Boehringer Ingelheim, Bristol-Myers Squibb, Eisai Inc., Janssen Pharmaceutical K.K., Kyorin Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma, Novartis Pharma K.K., Shionogi and Co., Ltd. and Teijin Pharma. Sakae Homma has received consulting fees from Boehringer Ingelheim. Kenya Muraishi and Rie Ikeda are employees of Nippon Boehringer Ingelheim Co., Ltd. Kaori Ochiai is an employee of EPS Corporation and is in charge of analysis work on behalf of Nippon Boehringer Ingelheim Co., Ltd. Yukihiko Sugiyama was on a data safety advisory board from Boehringer Ingelheim. Toshihiro Nukiwa has received consulting fees from Boehringer Ingelheim and payments or honoraria from Grifols.

***Ethical Approval.*** The study was conducted under the direction of the Ministry of Health, Labour and Welfare (MHLW) and the protocol was approved by the MHLW before its initiation. Participating institutes were contracted by Boehringer Ingelheim. As per the Japanese Pharmaceutical and Medical Device Act, this study was conducted in accordance with the Good Post-marketing Study Practice (GPSP) guidance. Under GPSP regulations, institutional review board approval and patient written informed consent were not required, unless such procedures were specifically required by the participating institutions.

## REFERENCES

1. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med. 2022;205:e18–47.

2. Natsuizaka M, Chiba H, Kuronuma K, et al. Epidemiologic survey of Japanese patients with idiopathic pulmonary fibrosis and investigation of ethnic differences. Am J Respir Crit Care Med. 2014;190:773–9.

3. Kondoh Y, Suda T, Hongo Y, et al. Prevalence of idiopathic pulmonary fibrosis in Japan based on a claims database analysis. Respir Res. 2022;23:24.

4. Raghu G, Rochwerg B, Zhang Y, et al. An official ATS/ERS/JRS/ALAT clinical practice guideline: Treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. Am J Respir Crit Care Med. 2015;192:e3–19.

5. Homma S, Bando M, Azuma A, et al. Japanese guideline for the treatment of idiopathic pulmonary fibrosis. Respir Investig. 2018;56:268–91.

6. Suda T, Kondoh Y, Hongo Y, et al. Current treatment status of patients with idiopathic pulmonary fibrosis in Japan based on a claims database analysis. Respir Investig. 2022;60:806–14.

7. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788–824.

8. Taniguchi H, Ebina M, Kondoh Y, et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J. 2010;35:821–9.

9. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2071–82.

10. Richeldi L, Cottin V, du Bois RM, et al. Nintedanib in patients with idiopathic pulmonary fibrosis: combined evidence from the TOMORROW and INPULSIS® trials. Respir Med. 2016;113:74–9.

11. Crestani B, Huggins JT, Kaye M, et al. Long-term safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis: results from the open-label extension study, INPULSIS-ON. Lancet Respir Med. 2019;7:60–8.

12. Azuma A, Taniguchi H, Inoue Y, et al. Nintedanib in Japanese patients with idiopathic pulmonary fibrosis: a subgroup analysis of the INPULSIS® randomized trials. Respirology. 2017;22:750–7.

13. Ogura T, Inoue Y, Azuma A, et al. Real-world safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis: interim report of a post-marketing surveillance in Japan. Adv Ther. 2023;40:1474–93.

14. Taniguchi H, Kondoh Y. Revised criteria for acute exacerbation of idiopathic pulmonary fibrosis. The Annual Report by Study Group of Ministry of Health and Welfare for Diffuse Lung Disease. Diffuse Lung Diseases Research Group from the Ministry of Health, Labor and Welfare of Japanese Government. 2004. pp. 114–9.

15. Takei R, Yamano Y, Kataoka K, et al. Pulse oximetry saturation can predict prognosis of idiopathic pulmonary fibrosis. Respir Investig. 2020;58:190–5.

16. Lancaster L, Crestani B, Hernandez P, et al. Safety and survival data in patients with idiopathic pulmonary fibrosis treated with nintedanib: pooled data from six clinical trials. BMJ Open Respir Res. 2019;6: e000397.

17. Alomar M, Tawfiq AM, Hassan N, Palaian S. Post marketing surveillance of suspected adverse drug reactions through spontaneous reporting: current status, challenges and the future. Ther Adv Drug Saf. 2020;11:2042098620938595.

18. Schmid U, Weber B, Sarr C, Freiwald M. Exposure-safety analyses of nintedanib in patients with chronic fibrosing interstitial lung disease. BMC Pulm Med. 2021;21:244.

19. Brereton CJ, Jo HE. Acute exacerbations of idiopathic pulmonary fibrosis and the role of corticosteroids. Breathe (Sheff). 2020;16: 200086.

20. Nagai A, Chiyotani A, Nakadate T, Konno K. Lung cancer in patients with idiopathic pulmonary fibrosis. Tohoku J Exp Med. 1992;167:231–7.

21. Miura Y, Saito T, Tanaka T, et al. Reduced incidence of lung cancer in patients with idiopathic pulmonary fibrosis treated with pirfenidone. Respir Investig. 2018;56:72–9.

22. Ozawa Y, Suda T, Naito T, et al. Cumulative incidence of and predictive factors for lung cancer in IPF. Respirology. 2009;14:723–8.

23. Tomassetti S, Gurioli C, Ryu JH, et al. The impact of lung cancer on survival of idiopathic pulmonary fibrosis. Chest. 2015;147:157–64.

24. Kato E, Takayanagi N, Takaku Y, et al. Incidence and predictive factors of lung cancer in patients with idiopathic pulmonary fibrosis. ERJ Open Res. 2018;4:00111–2016.

25. Yoshida GJ, Azuma A, Miura Y, Orimo A. Activated fibroblast program orchestrates tumor initiation and progression; molecular mechanisms and the associated therapeutic strategies. Int J Mol Sci. 2019;20:2256.

26. Gabasa M, Ikemori R, Hilberg F, Reguart N, Alcaraz J. Nintedanib selectively inhibits the activation and tumour-promoting effects of fibroblasts from lung adenocarcinoma patients. Br J Cancer. 2017;117:1128–38.

27. Naoi H, Suzuki Y, Mori K, et al. Impact of antifibrotic therapy on lung cancer development in idiopathic pulmonary fibrosis. Thorax. 2022;77:727–30.

28. Mooney J, Reddy SR, Chang E, Broder MS, Gokhale S, Corral M. Antifibrotic therapies reduce mortality and hospitalization among Medicare beneficiaries with idiopathic pulmonary fibrosis. J Manag Care Spec Pharm. 2021;27:1724–33.

29. Noth I, Oelberg D, Kaul M, Conoscenti CS, Raghu G. Safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis in the USA. Eur Respir J. 2018;52:1702106.