Safety and Tolerability of Nintedanib in Japanese Patients with Progressive Fibrosing Interstitial Lung Diseases

First Interim Report of a 2-Year Post-marketing Surveillance

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ABSTRACT

Objective: To assess the safety of nintedanib in the treatment of patients with progressive fibrosing interstitial lung diseases (PF-ILDs) in real-world clinical settings in Japan.

Methods: A non-interventional, prospective, observational 2-year post-marketing surveillance was undertaken of Japanese patients treated with nintedanib for PF-ILD (other than idiopathic pulmonary fibrosis) who were under routine clinical care between October 1, 2020 and October 15, 2022. Nintedanib 150 mg b.i.d. or 100 mg b.i.d. was administered; dose increase or decrease was allowed. Patients starting treatment with nintedanib were registered using case report forms (CRFs). An interim safety analysis was performed using the data snapshot taken on October 15, 2022. The primary outcome was the incidence of adverse drug reactions (ADRs). In general, the safety analyses were descriptive, focusing on hepatic function disorders, ADRs, serious adverse events (SAEs), and adverse events (AEs) leading to treatment discontinuation or death.

Results: As of October 15, 2022, 425 patients had been enrolled; 250 12-week CRFs had been collected and, of these, 207 CRFs were cleaned; 207 patients were included in the safety analysis. ADRs occurred in 108/207 patients (52.17%). The most common ADRs were diarrhea (n=49 [23.67%]) and hepatic function abnormal (n=19 [9.18%]). Treatment was discontinued in 52/207 (25.12%) patients, mainly for AEs. AEs leading to discontinuation occurred in 34/207 patients (16.43%). The most common was diarrhea (n=8 [3.86%]).

Conclusions: The safety profile of nintedanib in Japanese patients with PF-ILDs in clinical practice is consistent with previous reports. No new safety concerns were observed.

Key words: Adverse drug reactions, Nintedanib, Post-marketing surveillance, Progressive fibrosing interstitial lung disease (PF-ILD), Safety

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INTRODUCTION

Nintedanib (Ofev®) (a small molecule intracellular tyrosine kinase inhibitor)[1] is approved for the treatment of progressive fibrosing interstitial lung disease (PF-ILD) in Japan[2], and 45 other countries[3], including the United States[4], Canada[5], and the European Union[6]. Regulatory approval was based on findings from the INBUILD trial, a randomized, placebo-controlled Phase Ⅲ trial that evaluated the efficacy and safety of nintedanib in patients with PF-ILDs[7,8]. PF-ILD pertains to fibrotic interstitial lung diseases that become progressive, self-sustaining, and are independent of etiology[7,9]. PF-ILD is associated with worsening respiratory symptoms, declining lung function, decreased quality of life, and early death[10,11].

Prior to the INBUILD trial, nintedanib was already previously indicated for idiopathic pulmonary fibrosis (IPF)[7]. The INBUILD trial was designed to evaluate the efficacy and safety of nintedanib in PF-ILDs other than IPF[7]. Estimates for the proportion of patients with ILDs who develop PF-ILD range from 10.4 to 60.6%[12].

The INBUILD trial has shown that nintedanib slows the annual rate of decline in forced vital capacity (FVC), irrespective of the underlying diagnosis, and interstitial lung disease (ILD) progression[8,13,14]. The safety profile in the patient subgroups was consistent with observations in the overall study population. The risks of treatment with nintedanib are primarily related to the gastrointestinal tract (diarrhea, nausea, vomiting, abdominal pain) and increases in liver enzymes and bilirubin[8,15-18]. Results from subgroup and subset analyses of the INBUILD trial[19,20] showed that although the percentage of Japanese patients with AEs leading to permanent dose reduction in the nintedanib group was higher than in the overall study population, the safety profile of nintedanib in Japanese patients is consistent with the earlier findings[8,13]. However, as the number of Japanese patients treated with nintedanib in the INBUILD trial was small (52/332), post-marketing surveillance of the safety profile of nintedanib treatment for PF-ILD patients in Japanese clinical practice is needed. Hence, this interim safety analysis of a 2-year post-marketing surveillance was undertaken to assess the safety of nintedanib treatment in Japanese patients with PF-ILDs in real-world clinical settings.

PATIENTS AND METHODS

1 Study design

This was a non-interventional, prospective, observational, post-marketing surveillance (NCT04559581) based on newly collected data of patients under routine care in Japan between October 1, 2020 and October 15, 2022. The study design is summarized in **Fig. 1**. At baseline and approximately week 4, 12, 24, 36, 52, 72, 84, 96, and 104 after the initiation of nintedanib, treatment states of nintedanib, previous/concomitant medications, pulmonary function test results, laboratory test results, and AEs were recorded, as long as the patients continued to receive treatment.

The aim of the surveillance was to confirm the safety of nintedanib in a real-world setting in Japanese patients with PF-ILDs. The study was conducted at 102 institutions in Japan with respiratory, rheumatology, or other specialists. The primary outcome was the incidence of adverse drug reactions (ADRs) for which a causal relationship between nintedanib and an AE could not be excluded by either the investigator or sponsor. The safety focus in this surveillance was hepatic function disorder among the important identified risks specified in the pharmaceutical

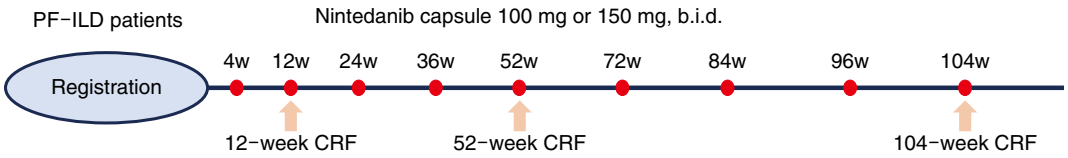

Fig. 1 Design of nintedanib post-marketing surveillance

risk management plan of this drug.

This post-marketing surveillance was conducted in accordance with the Ministry of Health, Labour, and Welfare (MHLW); the protocol was approved by the MHLW prior to surveillance initiation. In accordance with Good Post-Marketing Study Practice (GPSP) guidance, neither informed consent from patients nor ethics approval were required, as this was a non-interventional observational study using anonymized data.

2 Patients and treatment

Patients in Japan who were prescribed nintedanib and were not previously treated with the drug prior to enrolment were eligible for the surveillance. Those with a diagnosis of IPF or PF-ILD due to systemic scleroderma as an underlying disease were excluded.

Nintedanib 150 mg b.i.d.(300 mg/day) or 100 mg b.i.d.(200 mg/day) was administered after meals in accordance with the package insert, but a dose increase or decrease was also permitted at the investigator's discretion. Healthcare providers registered each patient starting treatment with nintedanib using a case report form (CRF) on an Electronic Data Capture system within 14 days whenever possible from the day of treatment initiation.

3 Data collection

The following were documented at enrolment: demographics (sex, age), baseline clinical characteristics (smoking history, height, body weight, underlying diagnosis, comorbidities, and baseline medications), Child-Pugh classification (with any hepatic concomitant disease), vital signs, and immunological test findings. Information pertinent to nintedanib treatment was gathered: time (years) since the first PF-ILD diagnosis, criteria for assessment of progression (images, symptoms, respiratory function examination), criteria for chest high-resolution computed tomography (HRCT) (usual interstitial pneumonia [UIP]-like pattern or others), ILD symptoms (dyspnea, cough), criteria for PF-ILD within 24 months (clinically significant decline in FVC % predicted based on ≧10% relative decline; marginal decline in FVC % predicted based on ≧5 to ≦10% relative decline in FVC combined with worsening of respiratory symptoms; marginal decline in FVC % predicted based on ≧5 to ≦10% relative decline in FVC combined with increasing extent of fibrotic changes on chest imaging; worsening of respiratory symptoms and increasing extent of fibrotic changes on chest imaging), reason for nintedanib prescription, treatment states of nintedanib (start date, reason for use, dosage and administration status), concomitant therapies, pulmonary function test, and laboratory tests (aspartate aminotransferase [AST]/alanine aminotransferase [ALT] collected from all cases as possible).

Enrolled patients were followed up to 104 weeks (2 years) after the initiation of nintedanib or until discontinuation of treatment.

4 Outcomes and safety analysis

Primary outcome was the incidence of ADRs. Based on previous experience with ninte-

danib, special attention was paid to the occurrence of hepatic function disorders including liver enzyme elevation defined by abnormalities in any liver function parameter (i.e., AST, ALT, alkaline phosphatase [ALP], gamma glutamyl transferase [γ-GT], and total blood bilirubin level). Liver enzyme elevation was defined as AST and/or ALT ≧3x to <5x upper limit of normal [ULN], and ≧5x ULN. Other safety outcomes noted included the incidence of serious AEs (SAEs), AEs leading to death, AEs leading to treatment discontinuation, liver enzyme elevations, and acute ILD exacerbations related to nintedanib ADRs. Characteristics associated with ADRs were gathered (e. g., demographics, baseline characteristics). AEs/ADRs were classified by using preferred terms in the Japanese version of the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 and were based on the concept of treatment-emergent AEs.

For the safety analysis, the sample size of 354 was required to have 90% power for rejecting the null hypothesis of incidence=3.8% by using one sample chi-square test with a 0.05 two-sided significance level. The null hypothesis of incidence was based on the proportion of overall patients with maximum ALT and/or AST ≧5 ULN (3.8% [2/52]) in the Japanese nintedanib group of the INBUILD[19] trial. Safety data of patients with 12-week CRFs cleaned by October 15, 2022 were analyzed.

In general, the safety analyses were descriptive, focusing on any liver enzyme elevations, ADRs, SAEs, and AEs leading to treatment discontinuation or death. The frequency and incidence of AEs/ADRs were noted by system organ class and preferred term. All AEs occurring between the first intake of nintedanib prescribed at baseline and within 28 days (inclusive) after the last intake were considered 'treatment emergent'. No imputation of missing AE data was performed.

RESULTS

1 Patient disposition and characteristics

As of October 15, 2022, 425 patients had been enrolled in this nintedanib post-marketing surveillance. At the end of this period, 250 12-week CRFs had been collected; of these, 207 were cleaned. All 207 patients were included in the safety analysis (**Fig. 2**).

Patient demographics and baseline disease characteristics are shown in **Table 1**. The proportion of males and females were similar (about 50% each). Approximately 2% were current smokers; the rest either never smoked (94/207 [45.4%]) or were former smokers (97/207 [46.9%]). The mean (SD) age was 72.2 (10.0) years. The mean (SD) weight was 58.46 (13.69) kg, and the mean (SD) body mass index was 23.01 (4.13) kg/m^2.

The mean (SD) baseline FVC in 185 patients was 2039.6 (731.5) mL. The mean (SD) %FVC at baseline was 71.2% (19.7%). Of the diverse group of fibrosing ILDs with a progressive phenotype included in this interim analysis, the proportion of rheumatoid arthritis-associated ILD (23.19% [48/207 patients]) was the highest, followed by idiopathic nonspecific interstitial pneumonia (18.36% [38/207 patients]), unclassifiable idiopathic interstitial pneumonia (17.39% [36/207 patients]), hypersensitivity pneumonitis (9.18% [19/207 patients]), mixed connective tissue disease ILD (2.90% [6/207 patients]), and pneumoconiosis (0.48% [1/207 patients]). The mean (SD) duration of ILD was 4.8 (5.4) years.

Complications were reported for 169 patients (81.64%). Common ILD-related complications by MedDRA Preferred Terms observed in ≧4 patients (redundancy included) were "gastro-esophageal reflux disease" (n=38 [18.36%]), "diabetes mellitus" (n=30 [14.49%]),

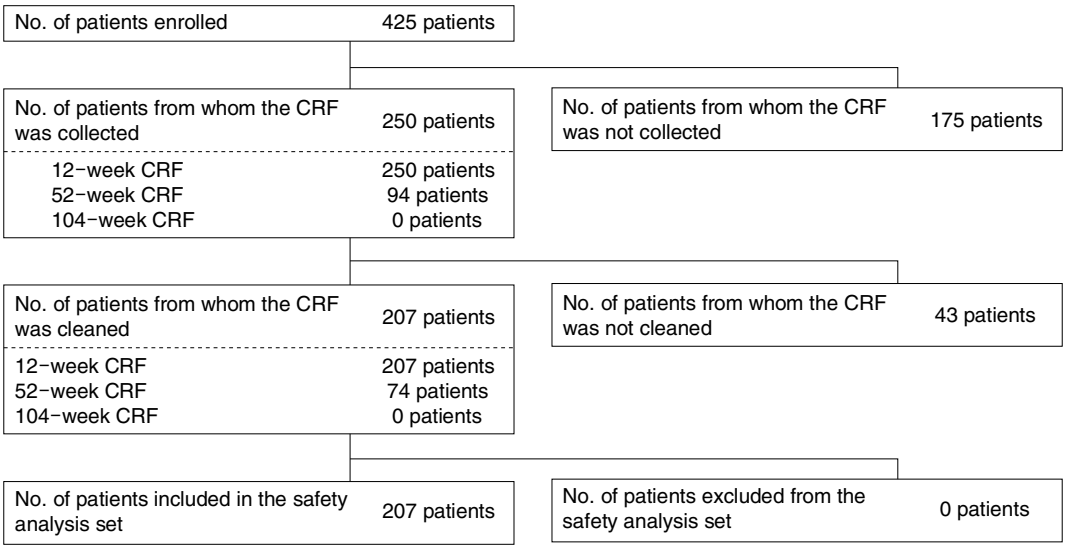

Fig. 2 Patient disposition
CRF: case report form

chronic obstructive pulmonary disease (*n*=9 [4.35%]), angina pectoris (*n*=8 [3.86%]), "pulmonary hypertension" (*n*=5 [2.42%]), and emphysema (*n*=4 [1.93%]) (**Table 1**).

There were 177 patients (85.51%) on concomitant drugs. Therapeutic categories of common concomitant drugs (redundancy included) were non-biologic disease-modifying antirheumatic drugs (DMARDs) in 80 patients (38.65%), and immunomodulators in 64 patients (30.92%). Common drugs were corticosteroids in 105 patients (50.72%), and tacrolimus in 43 patients (20.77%).

2 Nintedanib treatment

A total of 105 patients (50.7%) started nintedanib at a dose of 150 mg b.i.d., 80 patients (38.7%) initiated nintedanib at a dose of 100 mg b.i.d., and 22 patients (10.6%) received 100 mg or 150 mg once daily. One-third of patients (35/105 [33.3%]) who started nintedanib at 150 mg b.i.d. had a dose reduction to 100 mg b.i.d.; conversely, 18/80 (22.5%) of patients who started nintedanib at 100 mg b.i.d. had a dose increase to 150 mg b.i.d. The mean (SD) treatment duration of nintedanib was 182.4 (139.5) days (**Table 1**). Treatment was discontinued in 52/207 (25.12%) patients, mainly for "adverse event" in 35/207 (16.91%), and "patient's wish" in 13/207 (6.28%) (**Table 1**).

3 Frequency and incidence of adverse drug reactions

ADRs occurred in 108/207 patients (52.17%) in the safety analysis set (**Table 2**). The most common ADR was diarrhea (*n*=49 [23.67%]). Other ADRs occurring in >3 patients (1.45%) (mainly gastrointestinal) included abnormal hepatic function (*n*=19 [9.18%]), nausea (*n*=18 [8.70%]) and decreased appetite (*n*=10 [4.83%]).

Important identified risks were specified in the pharmaceutical risk management plan for nintedanib. Hepatic function disorders were a safety focus of the risk management plan. ADRs falling under "hepatic function disorders" were observed in 40 patients (19.32%); i.e., abnormal hepatic function (*n*=19 [9.18%]), liver disorder (*n*=9 [4.35%]), hepatic enzyme increased (*n*=

Table 1 Baseline demographic, clinical characteristics and nintedanib treatment exposure/pattern (1)

Characteristic	Safety population (n=207)
Age (years), mean±SD	72.2±10.0
Sex, n (%)	
Male	103 (49.76)
Female	104 (50.24)
Body weight (kg), mean±SD (n=198)	58.46±13.69
BMI (kg/m^2), mean±SD (n=195)	23.01±4.13
BSA (m^2), mean±SD (n=195)	1.59±0.21
Smoking history, n (%)	
Former smoker	97 (46.86)
Non-smoker	94 (45.41)
Current smoker	4 (1.93)
Clinical ILD diagnosis, n (%)	
Rheumatoid arthritis-associated ILD	48 (23.19)
Idiopathic nonspecific interstitial pneumonia	38 (18.36)
Unclassifiable idiopathic interstitial pneumonia	36 (17.39)
Hypersensitivity pneumonitis	19 (9.18)
Mixed connective tissue disease ILD	6 (2.90)
Pneumoconiosis	1 (0.48)
Other fibrosing ILDs	59 (28.50)
Duration of ILD (years), mean±SD/median (n=191)	4.83±5.42/3.69
Chest HRCT pattern, n (%)	
UIP pattern	96 (46.38)
Others	95 (45.89)
Rationale of assessment of ILD progression (progression within 2 years before initiating nintedanib) (duplicate count), n (%)	
Worsened respiratory symptoms and increased extent of fibrotic changes on chest imaging	146 (70.53)
Relative decline in FVC percent predicted ≧10%	68 (32.85)
Relative decline in FVC percent predicted ≧5 to <10% combined with worsening of respiratory symptoms	33 (15.94)
Relative decline in FVC percent predicted ≧5 to <10% combined with increased extent of fibrotic changes on chest imaging	30 (14.49)
FVC (mL) at baseline, mean±SD (n=185)	2039.6±731.5
%FVC (%) at baseline, mean±SD (n=184)	71.185±19.674
%DLco (%) at baseline, mean±SD (n=115)	56.435±18.735

BMI: body mass index, BSA: body surface area, DLco: diffusing capacity of lungs for carbon monoxide, FVC: forced vital capacity, HRCT: high-resolution computed tomography, ILD: interstitial lung disease, SD: standard deviation, UIP: usual interstitial pneumonia

3 [1.45%]), γ-GT increased (n=2 [0.97%]), ALT increased, blood bilirubin increased, hepatic encephalopathy, transaminases increased, abnormal hepatic enzyme, drug-induced liver injury, and liver function test increased (n=1 [0.48%] each, respectively) (**Table 3**). Hepatic encephalopathy and drug-induced liver injury (n=1 [0.48%] each, respectively) were

Table 1 Baseline demographic, clinical characteristics and nintedanib treatment exposure/pattern (2)

Characteristic	Safety population (n=207)
The common ILD-related complications present in at least 4 patients*, n(%)	
Gastroesophageal reflux disease	38 (18.36)
Diabetes mellitus	30 (14.49)
Chronic obstructive pulmonary disease	9 (4.35)
Angina pectoris	8 (3.86)
Pulmonary hypertension	5 (2.42)
Emphysema	4 (1.93)
Concomitant drugs, n (%)	
Corticosteroids	105 (50.72)
Tacrolimus	43 (20.77)
Ciclosporin	13 (6.28)
Azathioprine	7 (3.38)
Mycophenolate mofetil	5 (2.42)
Nintedanib treatment during observation period	
Initial starting dose, n (%)	
150 mg b.i.d.	105 (50.72)
100 mg b.i.d.	80 (38.65)
Other	22 (10.63)
Dose changes, n (%)	
Change from 150→100 mg b.i.d.	35 (33.33)
Change from 100→150 mg b.i.d.	18 (22.50)
Duration of treatment (days), mean±SD/median	182.4±139.5/115.0
Discontinuation of nintedanib[a]	
Discontinued nintedanib, n (%)	52 (25.12)
Reasons for discontinuation of nintedanib[b], n (%)	
AE	35 (16.91)
Patient's wish	13 (6.28)
Other personal reasons	6 (2.90)
No visit after last visit	3 (1.45)

[a]As of October 15, 2022; [b]Duplicate count. The CRF form of "Reasons for discontinuation" and "Adverse events leading to discontinuation" were different and analyzed separately.
*Complications were categorized in preferred terms of MedDRA Ver 25.0.
AE: adverse event, b.i.d.: twice-a-day administration, CRF: case report form, ILD: interstitial lung disease, MedDRA: Medical Dictionary for Regulatory Activities, SD: standard deviation

serious ADRs that were transient; the patients recovered.

Besides "hepatic function disorders," ADRs falling under "gastrointestinal symptoms" (diarrhea, nausea, etc.) were also important identified risks specified in the pharmaceutical risk management plan of nintedanib. Gastrointestinal symptoms were observed in 69 patients (33.33%). The commonly observed gastrointestinal symptoms (≧ 2 patients) were diarrhea (n

Table 2 Incidence of ADRs

MedDRA PT, *n* (%)	Safety population (*n*=207)
Any ADR, *n* (%)	108 (52.17)
ADRs reported in ≧1% of patients, *n* (%)	
Diarrhea	49 (23.67)
Abnormal hepatic function	19 (9.18)
Nausea	18 (8.70)
Decreased appetite	10 (4.83)
Liver disorder	9 (4.35)
Hypertension	5 (2.42)
Hepatic enzyme increased	3 (1.45)
Vomiting	3 (1.45)
Stomatitis	3 (1.45)

ADR: adverse drug reaction, MedDRA: Medical Dictionary for Regulatory Activities, PT: preferred term

=49 [23.67%]), nausea (*n*=18 [8.70%]), stomatitis and vomiting (*n*=3 [1.45%] each, respectively), gastritis, and feces soft (*n*=2 [0.97%] each, respectively) (**Table 3**). Diarrhea (*n*=2 [0.97%]), diverticulum intestinal hemorrhagic, and pancreatitis (*n*=1 [0.48%] each, respectively) were serious ADRs that were transient; the patients recovered. Platelet count decreased (*n*=1 [0.48%]) which was a serious ADR falling under platelets decreased (one of important identified risks), was also transient; the patients recovered.

Important potential risks of nintedanib were specified in the pharmaceutical risk management plan, including bleeding and interstitial pneumonia. ADRs falling under "bleeding" were observed in 5 patients (2.42%), specifically, contusion (*n*=2 [0.97%]), diverticulum intestinal hemorrhagic, epistaxis, and upper gastrointestinal hemorrhage (*n*=1 [0.48%] each, respectively). Of these, diverticulum intestinal hemorrhagic was a serious ADR and the patient recovered. An ADR falling under "interstitial pneumonia" was interstitial lung disease (*n*=2 [0.97%]), a serious ADR that 1 patient did not recover from and one patient did.

4 Frequency and incidence of adverse events

1) Serious adverse events

Of 207 patients in the safety analysis set, SAEs were observed in 40 patients (19.32%). Common SAEs (≧2 patients) included ILD (*n*=12 [5.80%]), pneumonia and pneumonia bacterial (*n*=5 [2.42%] each, respectively), pneumothorax (*n*=4 [1.93%]), pneumomediastinum (*n*=3 [1.45%]), diarrhea, COVID-19, and cardiac failure (*n*=2 [0.97%] each, respectively).

2) Adverse events leading to discontinuation

AEs leading to discontinuation (≧2 patients) occurred in 34/207 patients (16.43%). They were diarrhea (*n*=8 [3.86%]), nausea (*n*=5 [2.42%]), decreased appetite (*n*=4 [1.93%]), abnormal hepatic function and ILD (*n*=3 [1.45%] each, respectively), pneumonia, pneumomediastinum, and pneumothorax (*n*=2 [0.97%] each, respectively).

3) Adverse events leading to death

Adverse events leading to death occurred in 9/207 patients (4.35%) and included interstitial lung disease (*n*=4 [1.93%]), pneumonia (concomitant with acute exacerbation of ILD), pneumonia aspiration, small-cell lung cancer, completed suicide, cardiac failure, and respiratory failure (*n*=1 [0.48%] each, respectively). In all cases, a causal relationship with nintedanib was ruled out.

DISCUSSION

In this interim analysis of post-marketing surveillance of Japanese patients with PF-ILDs other than IPF who were treated with nintedanib in clinical practice, the frequency of any ADRs was 52.17%, with diarrhea (23.67%) and abnormal liver function (9.18%) as two of the most common ADRs. Consistent with other studies[8,15,21], AEs were the most common reason for

Table 3 The incidence of ADRs considered important identified and potential risks[a]

MedDRA PT, *n* (%)	Safety population (*n*=207)
Hepatic function disorders	40 (19.32)
Abnormal hepatic function	19 (9.18)
Liver disorder	9 (4.35)
Hepatic enzyme increased	3 (1.45)
γ-GT increased	2 (0.97)
ALT increased	1 (0.48)
Blood bilirubin increased	1 (0.48)
Hepatic encephalopathy[b]	1 (0.48)
Transaminases increased	1 (0.48)
Abnormal hepatic enzyme	1 (0.48)
Drug-induced liver injury[b]	1 (0.48)
Liver function test increased	1 (0.48)
Gastrointestinal symptoms	69 (33.33)
Diarrhea	49 (23.67)
Nausea	18 (8.70)
Stomatitis	3 (1.45)
Vomiting	3 (1.45)
Gastritis	2 (0.97)
Feces soft	2 (0.97)
Abdominal discomfort	1 (0.48)
Abdominal distension	1 (0.48)
Abdominal pain	1 (0.48)
Upper abdominal pain	1 (0.48)
Constipation	1 (0.48)
Diverticulum intestinal hemorrhagic[b]	1 (0.48)
Enterocolitis	1 (0.48)
Lip swelling	1 (0.48)
Pancreatitis[b]	1 (0.48)
Upper gastrointestinal hemorrhage	1 (0.48)
Platelets decreased	1 (0.48)
Platelet count decreased	1 (0.48)
Bleeding[c]	5 (2.42)
Contusion[c]	2 (0.97)
Diverticulum intestinal hemorrhagic[b,c]	1 (0.48)
Epistaxis[c]	1 (0.48)
Upper gastrointestinal hemorrhage[c]	1 (0.48)
Interstitial pneumonia[c]	2 (0.97)
Interstitial lung disease[b,c]	2 (0.97)

[a]In the Risk Management plan of nintedanib, [b]Serious ADR, [c]Important potential risk

γ-GT: gamma glutamyl transferase, ADR: adverse drug reaction, ALT: alanine aminotransferase, MedDRA: Medical Dictionary for Regulatory Activities, PT: preferred term

discontinuation. Most serious ADRs were transient. AEs leading to death occurred in 4.35% of the 207 patients. In all cases, a causal relationship with nintedanib was ruled out.

Japanese patients with PF-ILDs in this surveillance had a higher age, were more often female, had a lower proportion of UIP-like pattern on HRCT, had a higher proportion of rheumatoid arthritis-associated ILD and idiopathic non-specific interstitial pneumonia, and had a lower proportion of unclassifiable idiopathic interstitial pneumonias, than those in the INBUILD trial[19]. In addition, more patients in this surveillance were prescribed nintedanib concomitantly with tacrolimus, compared with those in the INBUILD trial, where tacrolimus was restricted within 4 weeks of randomization. About half of the patients started nintedanib at doses other than 150 mg b.i.d. in this surveillance. This may be partly because low body weight has been shown to be a predictor of AEs associated with nintedanib in patients with IPF, and Japanese patients are generally smaller than non-Japanese patients[15,22]. Indeed, an exposure-safety analysis of nintedanib in patients with chronic fibrosing ILDs showed a weak-to-moderate correlation between liver enzyme elevations and nintedanib plasma exposure, and a population pharmacokinetic analysis in patients with IPF suggested an association between patients with low body weight, and those of Asian race, and a small-to-moderate increase in nintedanib plasma exposure[23,24]. However, these findings do not warrant a priori dose adjustment because each of these covariates had a lesser effect on nintedanib plasma exposure than interpatient variability, and dose administered was a better predictor for risk of diarrhea than exposure.

Despite these differences in patient characteristics between patients in this surveillance and those in the INBUILD trial, the safety profile of nintedanib in this interim analysis of the surveillance was consistent with previous real-world and clinical reports[8,14,15,18,19,21,25]. In our analysis, the most common ADRs and AEs leading to discontinuation were gastrointestinal symptoms, including diarrhea and nausea, and hepatic function disorders, including abnormal hepatic function and liver disorder, and no new safety concerns were observed until the end of this observation period (October 15, 2022).

By virtue of the surveillance design, a limitation of the study is the lack of a control group. Another limitation is the potential underreporting of ADRs and AEs, because they were reported at the discretion of the site investigators, and patients in the real-world setting might not disclose all ADRs and AEs to the investigators. In addition, regional differences in the diagnosis and management of PF-ILD and variability in the types of physicians who manage patients with ILD (e.g., rheumatologists vs pulmonologists)[26] may have introduced a level of heterogeneity in clinical assessments and patient management.

CONCLUSION

In Japanese patients with PF-ILDs other than IPF, the safety profile of nintedanib in clinical practice is consistent with previous reports. No new safety concerns were observed at the end of the latest observation period.

CONFLICTS OF INTERESTS

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