Report on the Deliberation Results

May 22, 2020
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Ofev Capsules 100 mg, Ofev Capsules 150 mg
Non-proprietary Name	Nintedanib Ethanesulfonate (JAN*)
Applicant	Nippon Boehringer Ingelheim Co., Ltd.
Date of Application	October 24, 2019

Results of Deliberation

In its meetings held before and on May 20, 2020, the Second Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.
The re-examination period is 5 years and 10 months.

Approval Conditions

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

This English translation of this Japanese review report is intended to serve as reference material made available for the convenience of users. In the event of any inconsistency between the Japanese original and this English translation, the Japanese original shall take precedence. PMDA will not be responsible for any consequence resulting from the use of this reference English translation.

Review Report

April 13, 2020
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Ofev Capsules 100 mg, Ofev Capsules 150 mg
Non-proprietary Name	Nintedanib Ethanesulfonate
Applicant	Nippon Boehringer Ingelheim Co., Ltd.
Date of Application	October 24, 2019
Dosage Form/Strength	Soft capsules: Each capsule containing 120.4 mg of Nintedanib Ethanesulfonate (equivalent to 100 mg of nintedanib) or 180.6 mg of Nintedanib Ethanesulfonate (equivalent to 150 mg of nintedanib).
Application Classification	Prescription drug, (4) Drug with a new indication
Items Warranting Special Mention	Priority review (PSEHB/PED Notification No. 1204-5 dated December 4, 2019, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of progressive fibrosing interstitial lung disease, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below, with the following condition. The safety and other aspects of the product in clinical practice should be further evaluated in post-marketing surveillance, etc.

Indications	Idiopathic pulmonary fibrosis Systemic sclerosis-associated interstitial lung disease Progressive fibrosing interstitial lung disease

(Underline denotes additions.[1)])

[1)] Dashed line denotes additions made in accordance with the partial change approval dated December 20, 2019.

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Dosage and Administration The usual adult dosage is 150 mg of nintedanib administered orally twice daily, after breakfast and evening meal. The dose may be reduced to 100 mg of nintedanib twice daily according to the patient's condition.

(No change)

Approval Conditions

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

March 18, 2020

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval	
Brand Name	Ofev Capsules 100 mg, Ofev Capsules 150 mg
Non-proprietary Name	Nintedanib Ethanesulfonate
Applicant	Nippon Boehringer Ingelheim Co., Ltd.
Date of Application	October 24, 2019
Dosage Form/Strength	Soft capsules: Each capsule containing 120.4 mg of Nintedanib Ethanesulfonate (equivalent to 100 mg of nintedanib) or 180.6 mg of Nintedanib Ethanesulfonate (equivalent to 150 mg of nintedanib).
Proposed Indications	Idiopathic pulmonary fibrosis <u>Progressive fibrosing interstitial lung disease</u> (Underline denotes additions.)
Proposed Dosage and Administration	The usual adult dosage is 150 mg of nintedanib administered orally twice daily, after breakfast and evening meal. The dose may be reduced to 100 mg of nintedanib twice daily according to the patient's condition. (No change)

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List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Nintedanib ethanesulfonate (hereinafter referred to as "nintedanib") which is the active ingredient of Ofev Capsules 100 mg and Ofev Capsules 150 mg is a small molecule tyrosine kinase inhibitor discovered by Boehringer Ingelheim GmbH (Germany). It inhibits intracellular signaling at platelet-derived growth factor (PDGF) receptors, fibroblast growth factor (FGF) receptors, and vascular endothelial growth factor (VEGF) receptors. In Japan, nintedanib was approved for the treatment of idiopathic pulmonary fibrosis (IPF) in July 2015, and for the treatment of systemic sclerosis-associated interstitial lung disease (SSc-ILD) in December 2019.

Interstitial lung disease (ILD) refers to a large group of more than 200 pulmonary disorders that are characterized by scarring of the interstitium resulting from alveolar epithelial cell injuries due to various causes and subsequent aberrant injury repair (*Interstitial lung disease.* 5th ed. People's Medical Publishing House;2011; 3-12, 61-5). A proportion of patients with some types of ILDs develop a progressive pulmonary fibrosing phenotype. Such ILDs include IPF, idiopathic nonspecific interstitial pneumonia (iNSIP), unclassifiable idiopathic interstitial pneumonia, autoimmune ILDs (ILDs associated with collagen disorders including rheumatoid arthritis, systemic sclerosis [SSc], polymyositis/dermatomyositis, Sjogren's syndrome, systemic lupus erythematosus, and mixed connective tissue disease), chronic hypersensitivity pneumonitis, sarcoidosis, and occupational or environmental fibrosing lung diseases. Progressive fibrosing ILD (PF-ILD) is characterized by worsening of respiratory symptoms and a decline in lung function, eventually resulting in death (*Eur Respir Rev.* 2019;28:180100, *Respir Res.* 2019;20:57, etc.). The applicant attempted to estimate the total number of patients with PF-ILD in Japan. First, the estimated number of patients with each underlying ILD diagnosis was calculated from the number of specified intractable disease medical treatment recipient certificates issued for relevant diseases, the results of the survey of occupational diseases conducted by the Ministry of Health, Labour and Welfare, and other publications. Then, the estimated number of patients with PF-ILD was obtained based on the above estimated number of patients with underlying ILD diagnoses and the proportion of patients with each underlying ILD diagnosis who develop a progressive pulmonary fibrosing phenotype (*Curr Med Res Opin.* 2019;35:2015-24). According to the calculation above, an estimated 32,000 people in Japan are affected by PF-ILD.

The therapies approved in Japan for the treatment of ILDs include pirfenidone and nintedanib for IPF, nintedanib for SSc-ILD, and corticosteroids and immunosuppressive agents (e.g., tacrolimus) for polymyositis/dermatomyositis-associated ILDs. However, no approved drugs are available for patients with PF-ILD with other underlying ILD diagnoses, and the development of new drugs with the aim at slowing the progression of fibrosis in such patients has been desired.

Nintedanib inhibits PDGF-, FGF-, and VEGF-medicated signaling pathways, which are involved in the pathogenesis of pulmonary fibrosis (*Cytokine Growth Factor Rev.* 2004;15:255-73; *Am J Respir Crit Care Med.* 2002;166:765-73). As with the cases of the treatment of IPF and SSc-ILD, the development of nintedanib for the treatment of PF-ILD was undertaken, with the expectation that nintedanib would slow the progression of pulmonary fibrosis in patients with PF-ILD. Recently, the applicant has filed a partial change application

for nintedanib, based primarily on the results of a global clinical study in patients with PF-ILD, including Japanese participants.

The clinical development program of nintedanib for the treatment of PF-ILD was initiated in [redacted] 20[redacted]. Nintedanib was approved for the treatment of PF-ILD in the US in March 2020, whereas a marketing authorization application for the same indication is still under review in the EU, as of March 2020.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

Because the present application is intended for the addition of a new indication, no new data on quality aspects have been submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The applicant submitted data including results from a primary pharmacodynamic study that evaluated the effects of nintedanib on an animal model of chronic allergic lung inflammation and fibrotic lung remodeling (i.e., a mouse model with pathological characteristics resembling chronic hypersensitivity pneumonitis). Pharmacological parameters are expressed as mean values.

3.1 Primary pharmacodynamics

3.1.1 Effects on an animal model of chronic allergic lung inflammation and fibrotic lung remodeling (CTD 4.2.1.1-01)

In a mouse model of chronic allergic lung inflammation and fibrotic lung remodeling, an allergen challenge induced severe allergic lung inflammation accompanied by fibrotic lung remodeling, leading to the development of the pathological alterations seen in patients with PF-ILD, such as increased inflammatory cytokines, increased eosinophil and lymphocyte counts in the bronchoalveolar lavage fluid, and pulmonary fibrosis (*PLos ONE.* 2014;9:e91223).

Mice were first sensitized intraperitoneally with a mixture of ovalbumin, cockroach allergen, and house dust mite allergen, and then challenged with these 3 allergens via alternate inhalation. From 3 weeks after the start of the allergen challenges, the mice received an oral dose of nintedanib 0 (vehicle), 12.5, 25, or 50 mg/kg twice daily for 5 days per week. The effects of nintedanib on pulmonary fibrosis and inflammation were evaluated at 7 weeks after the start of the allergen challenges.

Nintedanib reduced the allergen challenge-induced increase in the collagen content in lung tissues in a dose-dependent manner, by 10.0%, 20.6%, and 45.1% at 12.5, 25, and 50 mg/kg, respectively. Nintedanib also dose-dependently reduced the allergen challenge-induced increases in eosinophil and lymphocyte counts in the bronchoalveolar lavage fluid. The reductions in eosinophil count by nintedanib versus vehicle were 24.5%, 23.4%, and 32.9%, respectively, at 12.5, 25, and 50 mg/kg. The reductions in lymphocyte count by nintedanib versus vehicle were 22.7%, 37.7%, and 44.6%, respectively, at 12.5, 25, and 50 mg/kg. Furthermore, nintedanib reduced the allergen challenge-induced increases in inflammatory mediators (IL-1β, IL-5, IL-12, and KC), at at least 1 of the tested doses.

3.R Outline of the review conducted by PMDA

The applicant's explanation about the effects of nintedanib on PF-ILD:

In a mouse model of lung inflammation and fibrotic lung remodeling induced by prolonged allergen challenge, nintedanib inhibited both the fibrosis and inflammation. Nintedanib has also been shown to exert inhibitory effects on lung fibrosis and inflammation in multiple animal models, including mouse and rat models of bleomycin-induced pulmonary fibrosis, as well as a mouse model of silica-induced pulmonary fibrosis and a mouse SSc-ILD model (see "Review Report for Ofev Capsules 100 mg and Ofev Capsule 150 mg," dated May 20, 2015 and November 14, 2019). These findings suggested that nintedanib slowed the progression of pulmonary fibrosis, regardless of the fibrotic triggers, in various animal models reflecting the pathology of PF-ILD.

PMDA's view:

The pharmacological effects of nintedanib have been demonstrated by the data submitted by the applicant, and nintedanib is expected to be effective in the treatment of PF-ILD.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Because the present application is intended for the addition of a new indication, no new data on non-clinical pharmacokinetics have been submitted. The non-clinical pharmacokinetics of nintedanib were evaluated during the review for the initial approval.

5. Toxicity and Outline of the Review Conducted by PMDA

Because the present application is intended for the addition of a new indication, no new toxicity data have been submitted. The toxicity of nintedanib was evaluated during the review for the initial approval.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Plasma nintedanib concentrations were measured by high performance liquid chromatography/tandem mass spectrometry (HPLC-MS/MS) (lower limit of quantitation, 0.500 ng/mL).

Unless otherwise specified, the dose and concentration of nintedanib are expressed as the salt-free equivalent, and pharmacokinetic parameters are expressed as the mean ± standard deviation (SD).

6.2 Clinical pharmacology

As evaluation data, the results of a global phase III study in patients with PF-ILD (Study 1199.247 [CTD 5.3.5.1]) were submitted.

6.2.1 Global phase III study (CTD 5.3.5.1; Study 1199.247 [February 2017 to August 2019])

Table 1 shows the trough plasma nintedanib concentrations in patients with PF-ILD who received multiple oral doses of nintedanib 150 mg[1)] twice daily (bid) in a global phase III study [see Section 7.1].

Table 1. Trough plasma nintedanib concentrations (ng/mL) following multiple oral doses of nintedanib in patients with PF-ILD

Population	Dose	N	Week 4	Week 24
Overall population	150 mg[a)]	221	14.0 ± 9.76 (205)	13.7 ± 9.83 (195)
	150 mg→100 mg[b)]	35	16.1 ± 8.33 (28)	8.30 ± 4.81 (31)
	150 mg→100 mg→150 mg[c)]	11	14.0 ± 7.73 (11)	9.67 ± 5.77 (10)
	100 mg[d)]	5	11.2 ± 3.62 (5)	14.4 ± 2.72 (4)
	100 mg→150 mg→100 mg[e)]	1	41.4 (1)	53.0 (1)
Japanese subpopulation	150 mg[a)]	30	20.2 ± 12.3 (30)	17.1 ± 9.03 (29)
	150 mg→100 m[b)]	8	17.8 ± 8.52 (7)	10.6 ± 7.62 (7)
	150 mg→100 mg→150 mg[c)]	2	15.8, 22.9 (2)	10.3, 21.8 (2)
	100 mg[d)]	4	10.7 ± 4.02 (4)	14.4 ± 2.72 (4)
	100 mg→150 mg→100 mg[e)]	1	41.4 (1)	53.0 (1)

Mean ± SD (number of evaluable patients), or individual values when ≤2 patients were evaluable.
(a) Nintedanib was administered at a dose of 150 mg bid from Week 4 through Week 24.
(b) Nintedanib was administered at a dose of 150 mg bid at Week 4, and was then reduced to 100 mg bid, which was continued through Week 24.
(c) Nintedanib was administered at a dose of 150 mg bid at Week 4, and was then reduced to 100 mg bid, followed thereafter by a re-escalation to 150 mg bid, which was continued through Week 24.
(d) Nintedanib was administered at a dose of 100 mg bid from Week 4 through Week 24.
(e) Nintedanib was administered at a dose of 100 mg bid at Week 4, and was then increased to 150 mg bid, followed thereafter by a reduction to 100 mg bid, which was continued through Week 24.

6.R Outline of the review conducted by PMDA

The applicant's explanation about ethnic differences in the pharmacokinetics of nintedanib in patients with PF-ILD:

In Study 1199.247 involving patients with PF-ILD, nintedanib exposure following multiple oral doses of nintedanib tended to be higher in the Japanese subpopulation than in the overall population (Table 1). However, the magnitude of this tendency was comparable to that seen in patients receiving nintedanib for the approved indications, IPF and SSc-ILD (see "Review Report for Ofev Capsules 100 mg and Ofev Capsule 150 mg," dated May 20, 2015 and November 14, 2019), and was therefore unlikely to be of clinical significance in the treatment of PF-ILD, as had been concluded for the approved indications.

PMDA accepted the applicant's explanation, and concluded that no particular pharmacokinetic problems had been identified with respect to evaluating the efficacy and safety of nintedanib in Japanese patients with PF-ILD based on the results of the global clinical study including Japanese participants.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The submitted efficacy and safety evaluation data, as shown in Table 2, are the results of a global phase III study.

[1)] Dose reduction to 100 mg bid was allowed, if needed to manage adverse events.

Table 2. Summary of the clinical efficacy and safety study

Region	Study identifier	Phase	Subjects	Number of patients enrolled	Dosage regimen	Main endpoints
Global	1199.247	III	Patients with PF-ILD	663 (a) 332 (b) 331	Twice daily oral dose (a) Nintedanib 150 mg[a)] (b) Placebo	Efficacy Safety

a) Dose reduction to 100 mg bid or treatment interruption was allowed, if needed to manage adverse events.

7.1 Global phase III study (CTD 5.3.5.1; Study 1199.247 [February 2017 to August 2019])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in 15 countries/regions, including the US, Japan, and France, to evaluate the efficacy and safety of nintedanib in patients with PF-ILD[2)] (target sample size, 600 patients [300 per group]).

Nintedanib 150 mg or placebo was orally administered twice daily, until the study period of ≥52 weeks was completed or a withdrawal criterion was met. Dose reduction to 100 mg twice daily or treatment interruption was allowed if needed to manage adverse events.[3)]

All 663 randomized[4)] patients (332 in the nintedanib group and 331 in the placebo group) were included in the treated set (TS), and the TS was used for safety and efficacy analyses. Analyses were conducted for 2 different populations: (a) the overall population and (b) patients with a usual interstitial pneumonia (UIP)-like fibrotic pattern[5)] on high resolution computed tomography (HRCT). The proportions of patients who discontinued the study drug during the 52 weeks were 24.1% (80 of 332 patients) in the nintedanib group and 14.8% (49 of 331 patients) in the placebo group. The most common reason for discontinuation was "adverse events" (19.6% [65 of 332 patients] in the nintedanib group, 10.3% [34 of 331 patients] in the placebo group). The proportions of patients who discontinued the study drug during the whole study were 34.3% (114 of 332 patients) in the nintedanib group and 30.2% (100 of 331 patients) in the placebo group. The most common reason for discontinuation was "adverse events" (25.6% [85 of 332 patients] in the nintedanib group, 18.7% [62 of 331 patients] in the placebo group).

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2) Key inclusion criteria:
Adults aged ≥18 years (≥20 years in Japan) who met all the following criteria were enrolled in the study.
(a) Patients with a diagnosis of ILD
(b) Patients who met at least 1 of the following criteria (i) to (iv) within 24 months before screening, despite treatment with unapproved medications* that are used in clinical practice to treat ILD: (i) a decline in FVC percent predicted (%FVC) of ≥10%, (ii) a decline in %FVC of ≥5% to <10% combined with worsening of respiratory symptoms, (iii) a decline in %FVC of ≥5% to <10% combined with increasing extent of fibrotic changes on chest imaging, and (iv) worsening of respiratory symptoms and increasing extent of fibrotic changes on chest imaging
(c) Fibrosing lung disease on HRCT performed within 12 months before screening, with disease extent of >10%
(d) For patients with collagen disorder, stable collagen disorder
(e) Diffusing capacity for carbon monoxide (DLco) percent predicted (%DLco) of ≥30 to <80% at screening
(f) %FVC of ≥45% at screening
Patients who were diagnosed with IPF according to the 2011 ATS/ERS/JRS/ALAT guidelines (*Am J Respir Crit Care Med.* 2011;183:788-824) were excluded from the study.
* Unapproved medications that are used in clinical practice to treat ILD include, but are not limited to corticosteroids, azathioprine, mycophenolate mofetil, N-acetylcysteine, rituximab, cyclophosphamide, cyclosporine, and tacrolimus.

3) When an adverse event requiring treatment interruption was considered to be related to the study drug, treatment interruption of up to 4 weeks was allowed. After the treatment interruption, resuming treatment at a dose of 100 mg twice daily was recommended. If the reduced dose was tolerable, the dose was allowed to be re-escalated to 150 mg twice daily within 4 weeks. When an adverse event requiring treatment interruption was considered to be unrelated to the study drug, treatment interruption of up to 8 weeks was allowed. The study drug was resumed at the dose level used before the treatment interruption.

4) Randomization was stratified based on HRCT pattern (UIP-like fibrotic pattern only vs. other fibrotic patterns), as assessed centrally.

5) HRCT patterns which met criteria A, B, and C; criteria A and C; or criteria B and C below were classified as a UIP-like fibrotic pattern:
A. Definite honeycomb lung destruction with basal and peripheral predominance
B. Presence of reticular abnormality and traction bronchiectasis consistent with fibrosis with basal and peripheral predominance
C. Absence of atypical features. Ground glass opacity, if present, is less extensive than the reticular opacity pattern.

The treated set included a subpopulation of 108 Japanese patients (52 in the nintedanib group and 56 in the placebo group). In the Japanese subpopulation, the proportions of patients who discontinued the study drug during the 52 weeks were 21.2% (11 of 52 patients) in the nintedanib group and 19.6% (11 of 56 patients) in the placebo group. The most common reason for discontinuation was "adverse events" (13.5% [7 of 52 patients] in the nintedanib group, 12.5% [7 of 56 patients] in the placebo group. The proportions of patients who discontinued the study drug during the whole study in the Japanese subpopulation were 42.3% (22 of 52 patients) in the nintedanib group and 32.1% (18 of 56 patients) in the placebo group. The most common reason for discontinuation was "adverse event" (28.8% [15 of 52 patients] in the nintedanib group, 21.4% [12 of 56 patients] in the placebo group).

The primary efficacy endpoint was the annual rate of decline in forced vital capacity (FVC) over the first 52 weeks [see Section 10 for the definition). Table 3 shows the results of the primary efficacy endpoint. In both the overall population and the subgroup of patients with UIP-like fibrotic pattern only, a pairwise comparison showed a statistically significant difference between the nintedanib group and the placebo group, demonstrating the superiority of nintedanib to placebo. The annual rates of decline in FVC over the 52 weeks in the Japanese subpopulation are shown in Table 4.

Table 3. Annual rate of decline in FVC over 52 weeks (mL/year) (TS)

	Overall population		Patients with HRCT with UIP-like fibrotic pattern only	
	Nintedanib	Placebo	Nintedanib	Placebo
Baseline FVC (mL)	2,340.1 ± 740.2 (332)	2,321.2 ± 728.0 (331)	2,363.4 ± 762.9 (206)	2,373.6 ± 720.1 (206)
Week 52 FVC (mL)	2,271.8 ± 783.0 (265)	2,157.8 ± 733.0 (274)	2,301.4 ± 814.2 (160)	2,210.5 ± 713.7 (162)
Change from baseline (mL)	−75.1 ± 250.8 (265)	−181.1 ± 220.0 (274)	−68.7 ± 240.8 (160)	−197.9 ± 237.8 (162)
Annual rate of decline in FVC [95% CI][a)]	−80.8 [−110.4, −51.2]	−187.8 [−216.9, −158.6]	−82.9 [−123.7, −42.0]	−211.1 [−251.4, −170.8]
Compared with placebo [95% CI][a)] *P*-value[a)b)]	107.0 [65.4, 148.5] <0.0001		128.2 [70.8, 185.6] <0.0001	

Mean ± SD (N)

(a) A random coefficient regression model including treatment, HRCT pattern (for the overall population only), baseline FVC (mL), and treatment-by-time and baseline FVC-by-time interactions as fixed effects, and individual intercept and time as random effects

(b) A Hochberg procedure was used for multiplicity adjustment, to maintain a 2-sided significance level of 5% in hypothesis tests that compared the nintedanib group and the placebo group in the 2 co-primary populations, i.e., the overall population and the subpopulation of patients with HRCT with UIP-like fibrotic pattern only.

Table 4. Annual rate of decline in FVC over 52 weeks (mL/year) (TS, Japanese subpopulation)

	Japanese subpopulation		Japanese patients with HRCT with UIP-like fibrotic pattern only	
	Nintedanib	Placebo	Nintedanib	Placebo
Baseline FVC (mL)	2123.6 ± 692.5 (52)	2249.0 ± 623.9 (56)	2190.7 ± 720.0 (39)	2242.6 ± 623.7 (45)
Week 52 FVC (mL)	2016.0 ± 695.2 (45)	2080.8 ± 590.8 (46)	2094.4 ± 728.8 (33)	2058.7 ± 585.2 (38)
Change from baseline (mL)	−136.8 ± 251.8 (45)	−204.0 ± 207.0 (46)	−142.4 ± 181.2 (33)	−221.2 ± 211.1 (38)
Annual rate of decline in FVC [95% CI]	−148.3 [−221.2, −75.4][a)]	−240.4 [−312.9, −167.9][a)]	−163.6 [−254.9, −72.2][b)]	−257.1 [−343.3, −171.0][b)]
Compared with placebo [95% CI]	92.1 [−10.7, 194.8][a)]		93.6 [−31.8, 219.0][b)]	
Annual rate of decline in FVC [95% CI]	−153.9 [−225.6, −82.2][c)]	−235.8 [−307.5, −164.2][c)]	−161.9 [−235.7, −88.1][d)]	−247.4 [−317.4, −177.4][d)]
Compared with placebo [95% CI]	81.9 [−19.8, 183.7][c)]		85.5 [−16.3, 187.2][d)]	

Mean ± SD (N)

a) A random coefficient regression model in the overall population, including HRCT pattern, baseline FVC (mL), and baseline FVC-by-time, treatment-by-subpopulation (Japanese vs. non-Japanese), and treatment-by-subpopulation (Japanese vs. non-Japanese)-by-time interactions as fixed effects, and individual intercept and time as random effects

b) A random coefficient regression model in patients with HRCT with UIP-like fibrotic pattern only, including baseline FVC (mL), and baseline FVC-by-time, treatment-by-subpopulation (Japanese vs. non-Japanese), and treatment-by-subpopulation (Japanese vs. non-Japanese)-by-time interactions as fixed effects, and individual intercept and time as covariates

c) A random coefficient regression model in the Japanese subpopulation, including treatment, HRCT pattern, baseline FVC (mL), and treatment-by-time and baseline FVC-by-time interactions as fixed effects, and individual intercept and time as random effects

d) A random coefficient regression model in the subpopulation of Japanese patients with HRCT with UIP-like fibrotic pattern only, including treatment, baseline FVC (mL), and treatment-by-time and baseline FVC-by-time interactions as fixed effects, and individual intercept and time as covariates

During the whole study, adverse events were reported in 98.2% (326 of 332) of patients in the nintedanib group and 93.1% (308 of 331) of patients in the placebo group. The common adverse events are shown in Table 5.

Adverse events led to death in 6.3% (21 of 332) of patients in the nintedanib group and 10.9% (36 of 331) of patients in the placebo group. The adverse events leading to death in the nintedanib group were acute respiratory failure in 4 patients; respiratory failure in 3 patients; pneumonia in 2 patients; and interstitial lung disease, pulmonary fibrosis, interstitial lung disease/respiratory failure, arteriosclerosis coronary artery, septic shock, lung infection/pulmonary fibrosis, pulmonary sepsis, bacterial sepsis/acute respiratory failure, cardiac failure congestive, cardiac arrest, cardiac failure, and death in 1 patient each. The adverse events leading to death in the placebo group were interstitial lung disease and respiratory failure in 5 patients each; pneumonia in 3 patients; respiratory distress and acute respiratory failure in 2 patients each; interstitial lung disease/connective tissue disorder, infectious pleural effusion, neoplasm malignant, lung neoplasm malignant, pneumothorax, aortic aneurysm rupture/shock haemorrhagic, sudden cardiac death, sudden death, dyspnoea, hypersensitivity pneumonitis, bronchitis, cerebral haemorrhage, myocardial infarction, cardiac death, lung squamous cell carcinoma metastatic, chronic respiratory failure, hepatic cirrhosis, pneumonia aspiration, and bronchitis/interstitial lung disease in 1 patient each. A causal relationship to the study drug could not be ruled out in 1 patient in the nintedanib group (pulmonary sepsis) and 3 patients in the placebo group (aortic aneurysm rupture/shock haemorrhagic, cerebral haemorrhage, and myocardial infarction in 1 patient each).

Serious adverse events were reported in 44.3% (147 of 332) of patients in the nintedanib group and 49.5% (164 of 331) of patients in the placebo group. The common adverse events are shown in Table 6.

Adverse events led to treatment discontinuation in 22.0% (73 of 332) of patients in the nintedanib group and 14.5% (48 of 331) of patients in the placebo group.

Adverse drug reactions were reported in 81.9% (272 of 332) of patients in the nintedanib group and 40.5% (134 of 331) of patients in the placebo group.

Table 5. Adverse events reported by ≥5.0% of patients in either treatment group (whole study, safety analysis set)

Events	Nintedanib N = 332	Placebo N = 331	Events	Nintedanib N = 332	Placebo N = 331
Diarrhoea	240 (72.3)	85 (25.7)	Back pain	28 (8.4)	27 (8.2)
Nausea	100 (30.1)	33 (10.0)	Constipation	26 (7.8)	32 (9.7)
Vomiting	64 (19.3)	16 (4.8)	Upper respiratory tract infection	26 (7.8)	25 (7.6)
Nasopharyngitis	54 (16.3)	48 (14.5)	Urinary tract infection	22 (6.6)	21 (6.3)
Decreased appetite	54 (16.3)	23 (6.9)	GGT increased	22 (6.6)	7 (2.1)
Dyspnoea	52 (15.7)	57 (17.2)	Respiratory tract infection	20 (6.0)	15 (4.5)
Weight decreased	49 (14.8)	18 (5.4)	Dizziness	19 (5.7)	15 (4.5)
ALT increased	49 (14.8)	13 (3.9)	Asthenia	19 (5.7)	14 (4.2)
Bronchitis	48 (14.5)	64 (19.3)	Hepatic function abnormal	19 (5.7)	3 (0.9)
AST increased	43 (13.0)	13 (3.9)	Oedema peripheral	18 (5.4)	22 (6.6)
Cough	40 (12.0)	51 (15.4)	Insomnia	18 (5.4)	18 (5.4)
Headache	37 (11.1)	27 (8.2)	Pyrexia	17 (5.1)	19 (5.7)
Pneumonia	36 (10.8)	30 (9.1)	Chest pain	17 (5.1)	15 (4.5)
Fatigue	34 (10.2)	21 (6.3)	Gastrooesophageal reflux disease	17 (5.1)	9 (2.7)
Abdominal pain	34 (10.2)	10 (3.0)	Arthralgia	13 (3.9)	24 (7.3)
Abdominal pain upper	33 (9.9)	7 (2.1)	Pruritus	12 (3.6)	18 (5.4)
Interstitial lung disease	28 (8.4)	56 (16.9)			

n (%)

Table 6. Serious adverse events reported by ≥1.0% of patients in either treatment group (whole study, safety analysis set)

Events	Nintedanib N = 332	Placebo N = 331
Pneumonia	24 (7.2)	16 (4.8)
Interstitial lung disease	19 (5.7)	45 (13.6)
Acute respiratory failure	16 (4.8)	7 (2.1)
Respiratory failure	11 (3.3)	10 (3.0)
Pulmonary fibrosis	7 (2.1)	5 (1.5)
Dyspnoea	6 (1.8)	13 (3.9)
Pneumothorax	6 (1.8)	6 (1.8)
Drug-induced liver injury	6 (1.8)	0
Pulmonary hypertension	5 (1.5)	9 (2.7)
Atrial fibrillation	5 (1.5)	1 (0.3)
Bronchitis	4 (1.2)	5 (1.5)
Influenza	4 (1.2)	4 (1.2)
Fall	3 (0.9)	4 (1.2)
Hypersensitivity pneumonitis	2 (0.6)	4 (1.2)
Basal cell carcinoma	2 (0.6)	4 (1.2)
Chronic respiratory failure	1 (0.3)	6 (1.8)
Pulmonary embolism	1 (0.3)	5 (1.5)

n (%)

Adverse events reported in the Japanese subpopulation during the whole study were analyzed. Adverse events were reported in 100.0% (52 of 52) of patients in the nintedanib group and 100.0% (56 of 56) of patients in the placebo group. The common adverse events in the Japanese subpopulation are shown in Table 7.

Adverse events led to death in 14.3% (8 of 56) of patients in the placebo group. The adverse events leading to death were interstitial lung disease in 2 patients, and pneumothorax, respiratory failure, hepatic cirrhosis, cerebral haemorrhage, lung neoplasm malignant, and pneumonia aspiration in 1 patient each. A causal relationship to the study drug could not be ruled out in 1 patient (cerebral haemorrhage).

Serious adverse events were reported in 55.8% (29 of 52) of patients in the nintedanib group and 64.3% (36 of 56) of patients in the placebo group. The common serious adverse events in the Japanese subpopulation are shown in Table 8.

In the Japanese subpopulation, adverse events led to treatment discontinuation in 28.8% (15 of 52) of patients in the nintedanib group and 21.4% (12 of 56) of patients in the placebo group.

Adverse drug reactions were reported in 94.2% (49 of 52) of patients in the nintedanib group and 39.3% (22 of 56) of patients in the placebo group.

Table 7. Adverse events reported by ≥5.0% of patients in either treatment group (whole study, safety analysis set, Japanese subpopulation)

Events	Nintedanib N = 52	Placebo N = 56	Events	Nintedanib N = 52	Placebo N = 56
Diarrhoea	44 (84.6)	20 (35.7)	Abdominal pain upper	3 (5.8)	3 (5.4)
Nasopharyngitis	21 (40.4)	21 (37.5)	Pneumomediastinum	3 (5.8)	3 (5.4)
Nausea	15 (28.8)	1 (1.8)	Gastritis	3 (5.8)	2 (3.6)
Hepatic function abnormal	13 (25.0)	2 (3.6)	Hypertension	3 (5.8)	1 (1.8)
Interstitial lung disease	12 (23.1)	26 (46.4)	Oedema peripheral	3 (5.8)	1 (1.8)
AST increased	9 (17.3)	1 (1.8)	Malaise	3 (5.8)	0
Bronchitis	8 (15.4)	7 (12.5)	Drug-induced liver injury	3 (5.8)	0
Pneumonia	8 (15.4)	6 (10.7)	Eczema	2 (3.8)	6 (10.7)
ALT increased	8 (15.4)	1 (1.8)	Pneumonia bacterial	2 (3.8)	4 (7.1)
Vomiting	8 (15.4)	0	Epistaxis	2 (3.8)	3 (5.4)
Constipation	7 (13.5)	12 (21.4)	Pruritus	2 (3.8)	3 (5.4)
Weight decreased	7 (13.5)	3 (5.4)	Abdominal distension	1 (1.9)	3 (5.4)
Decreased appetite	6 (11.5)	6 (10.7)	Herpes zoster	1 (1.9)	3 (5.4)
Insomnia	5 (9.6)	8 (14.3)	Glucose urine present	1 (1.9)	3 (5.4)
Pyrexia	5 (9.6)	6 (10.7)	Upper respiratory tract inflammation	1 (1.9)	3 (5.4)
Hypokalaemia	5 (9.6)	0	Headache	1 (1.9)	3 (5.4)
Back pain	4 (7.7)	9 (16.1)	Contusion	1 (1.9)	3 (5.4)
Influenza	4 (7.7)	4 (7.1)	Rhinitis allergic	0	5 (8.9)
Haemorrhoids	4 (7.7)	2 (3.6)	Hyperglycaemia	0	5 (8.9)
Stomatitis	4 (7.7)	2 (3.6)	Hyperkalaemia	0	4 (7.1)
Pharyngitis	4 (7.7)	2 (3.6)	Hyponatraemia	0	4 (7.1)
Dry skin	4 (7.7)	2 (3.6)	Spinal compression fracture	0	4 (7.1)
Pneumothorax	3 (5.8)	4 (7.1)			

n (%)

Table 8. Serious adverse events reported by ≥2 patients in either treatment group (whole study, safety analysis set, Japanese subpopulation)

Events	Nintedanib N = 52	Placebo N = 56
Interstitial lung disease	10 (19.2)	25 (44.6)
Pneumonia	5 (9.6)	2 (3.6)
Pneumothorax	3 (5.8)	4 (7.1)
Influenza	3 (5.8)	0
Drug-induced liver injury	3 (5.8)	0
Pneumomediastinum	2 (3.8)	1 (1.8)
Bronchopulmonary aspergillosis	2 (3.8)	1 (1.8)
Condition aggravated	2 (3.8)	1 (1.8)
Hypoxia	2 (3.8)	0
Idiopathic interstitial pneumonia	2 (3.8)	0
Bronchitis	2 (3.8)	0
Pneumonia bacterial	1 (1.9)	2 (3.6)
Respiratory failure	0	2 (3.6)
Pneumonia pneumococcal	0	2 (3.6)
Pneumonia aspiration	0	2 (3.6)
Spinal compression fracture	0	2 (3.6)

n (%)

7.R Outline of the review conducted by PMDA

7.R.1 Development plan

The applicant's explanation about the development plan for nintedanib:

Interstitial lung disease (ILD) is an umbrella term encompassing various lung disorders, including IPF, iNSIP, IIPs (e.g., undifferentiated IIPs), autoimmune ILDs, and chronic hypersensitivity pneumonitis. Progressive fibrosing ILD (PF-ILD) has a poor prognosis, and is characterized by progressive clinical features such as worsening of respiratory symptoms, declines in lung function and physical function, and deterioration in quality of life (QOL), resulting in death (*Respir Res.* 2019;20:57, etc). PF-ILD is not a single disease, but refers to a group of ILD diagnoses that share a common pathological feature of "progressive fibrosis." PF-ILD has been diagnosed and treated according to the following guidelines and other treatment procedures.

- IIPs are classified based on the American Thoracic Society (ATS)/European Respiratory Society (ERS) statement on the international multidisciplinary classification of IIPs (*Am J Respir Crit Care Med.* 2013;40:640-6). In Japan, the "Guidelines for the Diagnosis and Management of Idiopathic Interstitial Pneumonitis (in Japanese)" (3rd rev ed. Nankodo; 2016), which presents a classification of IIPs based on the ATS/ERS statement, has been used for the diagnosis and management of IIPs. A multidisciplinary approach is taken for the diagnosis of IIPs by specialists in various areas in accordance with the classification and procedures presented in the above-mentioned guidelines, and a treatment strategy (e.g., steroids, immunosuppressive agents, smoking cessation) is established to manage the diagnosed disease. In this regard, there are no substantial differences in the diagnosis or management of IIPs between Japan and other countries.
- In contrast, no established guidelines that systematically describe the diagnosis or management of autoimmune ILDs are available in or outside of Japan, although several medications, including corticosteroids and immunosuppressive agents, are used for the treatment of collagen disorders, which are the underlying etiologies of the ILDs. Thus, despite differences in the approved drugs, the diagnosis

of and treatment strategies for autoimmune ILDs do not differ substantially between Japan and other countries.

- The diagnosis of and treatment strategies for other ILDs, including chronic hypersensitivity pneumonitis and sarcoidosis, do not differ substantially between Japan and other countries, though established clinical practice guidelines are available in some countries, but not in other countries.

As above, the diagnosis of and treatment algorithms for ILDs do not differ substantially between Japan and other countries; and the efficacy, safety, and pharmacokinetics of nintedanib in patients with IPF, the approved indication, were similar in Japanese and non-Japanese patients (see "Review Report for Ofev Capsules 100 mg, Ofev Capsule 150 mg," dated May 20, 2015). The applicant therefore considered it possible to conduct a global clinical study involving multiple countries including Japan, and prepare a clinical data package based on the results of the study.

● The target patient population of the phase III study:

Due to the small number of patients with each underlying etiology of PF-ILD, conducting a confirmatory study for each etiology seemed to be difficult. Therefore, in Study 1199.247 as a global phase III study, patients with ILDs who shared a pathological feature, "progressive fibrosis" were to be grouped together as patients with PF-ILD and enrolled in the study. Because no established definition of the term "progressive fibrosing" was available, patients with PF-ILD were defined as patients with ILDs who had the extent of lung fibrosis ≥10% on HRCT, decline in lung function, and worsening of respiratory symptoms and/or increasing fibrotic extent on chest imaging. Furthermore, the lung injury pattern seen on HRCT has a major impact on prognosis in patients with PF-ILD. In particular, PF-ILD with HRCT with UIP-like fibrotic pattern only has a rapidly progressive course, as compared with PF-ILD with other fibrotic patterns (*Thorax.* 2014;69:216-22, etc.) Therefore, patients with PF-ILD with "UIP-like fibrotic pattern only" and those with "other fibrotic patterns" were included at a 2:1 ratio to evaluate the efficacy of nintedanib in patients with UIP-like fibrotic pattern only, as well as the overall population. Patients with IPF were excluded from Study 1199.247, because nintedanib is already approved for the treatment of IPF, whereas patients with SSc-ILD were included in the study, although a global phase III study evaluating the efficacy and safety of nintedanib in patients with SSc-ILD (Study 1199.214) was still ongoing separately.

● Rationale for the dosage regimen used in the phase III study:

The basic dosage regimen used in Study 1199.247 was to be 150 mg twice daily, which is the same as the approved dosage and administration for the treatment of IPF, based on the pathophysiological resemblance between PF-ILD and IPF (shown below), and data including the results of clinical studies in patients with IPF. Dose reduction to 100 mg twice daily or treatment interruption was allowed, if needed to manage adverse events.

- IPF and PF-ILD share a common pathophysiologic cascade of fibrosis which is composed of the activation, migration, and proliferation of fibroblasts, the accumulation of myofibroblasts, and the deposition of an extracellular matrix. This cascade occurs downstream from the PDGF-, FGF-, and VEGF-medicated signaling pathways, which are inhibited by nintedanib.

- The efficacy and safety of nintedanib 150 mg twice daily was demonstrated in clinical studies in patients with IPF (see "Review Report for Ofev Capsules 100 mg, Ofev Capsule 150 mg," dated May 20, 2015).

● Primary efficacy endpoint selected for the phase III study:

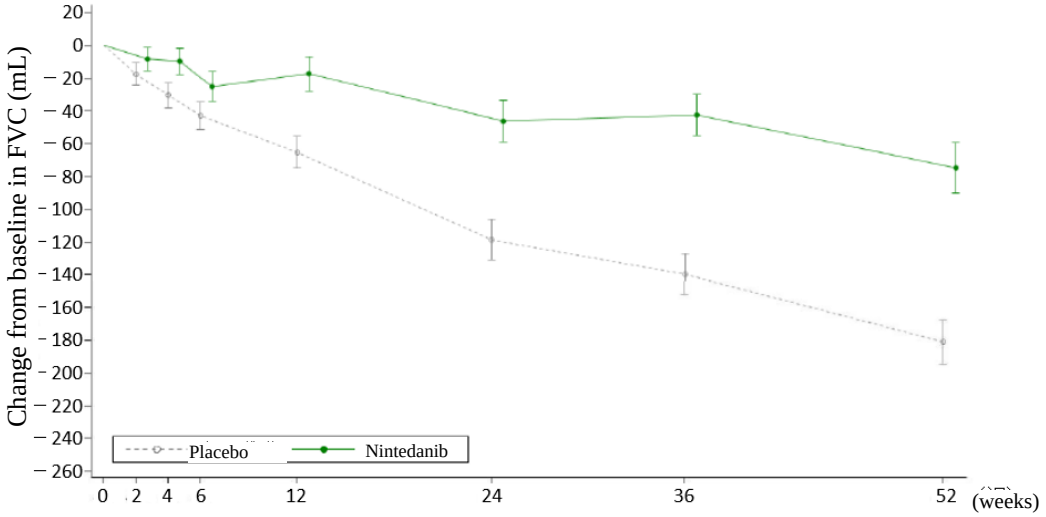
FVC has been accepted as an endpoint for evaluating ILD progression. At the same time, FVC has been used as a standard endpoint for assessing the pathology and treatment of IPF, which shares pathophysiological characteristics with PF-ILD (*Am J Respir Crit Care Med.* 2012;186:712-5), and has been shown to be associated with mortality (*Chest.* 2014;145:579-85, *EurRespir J.* 2011;38:176-83, etc). Furthermore, FVC has served as an efficacy endpoint in clinical studies involving patients with IPF (*N Engl J Med.* 2015;372:1189-91). Based on the above, the annual rate of decline in FVC over 52 weeks (mL/year) was selected as the primary endpoint of Study 1199.247.

PMDA accepted the applicant's explanations, and concluded that it would be possible to evaluate the efficacy and safety of nintedanib in Japanese patients with PF-ILD, based on the results of a global phase III study in which Japanese patients participated (Study 1199.247).

7.R.2 Efficacy

The applicant's explanation about the efficacy of nintedanib in the treatment of PF-ILD:

In both the overall population and the population of patients with UIP-like fibrotic pattern only, a pairwise comparison showed a statistically significant difference in the annual rate of decline in FVC (mL/year) over 52 weeks, the primary endpoint of Study 1199.247, between the nintedanib group and the placebo group, demonstrating the superiority of nintedanib to placebo (Table 3). To confirm the robustness of the primary analysis, sensitivity analyses were conducted. The same random coefficient regression model as used for the primary analysis, except for the manner in which missing data were handled, was used. An analysis using only on-treatment data yielded a least squares mean difference [95% confidence interval (CI)] between the nintedanib group and the placebo group being 117.76 [77.53, 157.99]. The result of the sensitivity analysis did not differ substantially from the result of the primary analysis. In addition, sensitivity analyses using various multiple imputation procedures which differed in the handling of missing data were conducted. The least squares mean differences in the primary endpoint between the nintedanib group and the placebo group ranged from 92.23 to 97.19, with no considerable difference from the result of the primary analysis. Figure 1 shows the changes from baseline in FVC over 52 weeks. The changes from baseline in FVC tended to be greater in the nintedanib group than in the placebo group throughout the 52 weeks, and this tendency continued beyond Week 52 despite alterations in study requirements, such as the elimination of concomitant medication restrictions.



N	Week 2	Week 4	Week 6	Week 12	Week 24	Week 36	Week 52
Placebo	325	326	325	320	311	296	274
Nintedanib	326	320	322	314	298	285	265

Figure 1. Changes from baseline in FVC over the whole study (mL) (mean ± SD)
(Study 1199.247, TS, overall population)

Since the efficacy of nintedanib had been demonstrated in patients with SSc-ILD in a separate study (Study 1199.214), a sensitivity analysis for the primary endpoint was conducted on the population after excluding patients with SSc-ILD (23 in the nintedanib group and 16 in the placebo group). Table 9 shows the results of the sensitivity analysis. The annual rate of decline in FVC over 52 weeks showed a similar tendency before and after excluding patients with SSc-ILD from the overall population of Study 1199.247.

Table 9. Annual rates of decline in FVC over 52 weeks (mL/year)
(TS, the population excluding patients with SSc-ILD)

	Nintedanib	Placebo	Compared with placebo [95% CI]
Annual rate of decline in FVC over 52 weeks (mL/year)[a)]	−83.9 ± 15.9 (309)	−188.8 ± 15.4 (315)	104.9 [61.5, 148.3]

Least squares mean ± standard error (N)
(a) A random coefficient regression model including treatment, HRCT pattern, baseline FVC (mL), and treatment-by-time and baseline FVC-by-time interactions as fixed effects, and individual intercept and time as random effects

Table 10 shows the results of subgroup analyses for the primary endpoint of Study 1199.247 by patient characteristics. Although the results should be interpreted carefully due to the small numbers of patients in some subgroups, the annual rate of decline in FVC over 52 weeks tended to be higher in the nintedanib group than in the placebo group in all subgroups, identifying no patient characteristics that clearly affected the efficacy of nintedanib.

Table 10. Annual rates of decline in FVC over 52 weeks (mL/year) by patient characteristics (Study 1199.247, TS, overall population)

Patient characteristics		Nintedanib[a)]	Placebo[a)]	Compared with placebo[a)] [95% CI]
Age	<65 years old	−58.9 [−103.6, −14.2] (139)	−145.8 [−193.6, −98.0] (121)	86.9 [21.5, 152.2]
	≥65 years old	−97.5 [−136.7, −58.2] (193)	−212.6 [−249.3, −175.9] (210)	115.1 [61.4, 168.8]
Sex	Male	−88.9 [−131.4, −46.4] (179)	−234.1 [−276.5, −191.7] (177)	145.2 [88.5, 201.9]
	Female	−72.6 [−118.2, −27.0] (153)	−136.8 [−181.5, −92.1] (154)	64.2 [3.9, 124.6]
Body weight	≤65 kg	−101.8 [−160.5, −43.1] (91)	−184.8 [−243.5, −126.1] (89)	83.0 [1.7, 164.3]
	>65 kg	−73.2 [−108.1, −38.3] (241)	−188.8 [−223.1, −154.6] (242)	115.6 [67.2, 164.0]
Race	Asian	−115.5 [−173.7, −57.3] (84)	−208.5 [−268.8, −148.2] (80)	93.0 [9.3, 176.7]
	White	−69.9 [−104.9, −34.9] (242)	−180.5 [−214.3, −146.7] (246)	110.6 [62.0, 159.2]
	Black/African American	−1.8 [−289.8, 286.3] (5)	−224.3 [−449.7, 1.2] (5)	222.5 [−143.1, 588.1]
ILD type	Hypersensitivity pneumonitis	−104.4 [−164.0, −44.9] (84)	−177.5 [−233.4, −121.7] (89)	73.1 [−8.6, 154.8]
	iNSIP	−51.4 [−117.7, 15.0] (64)	−193.0 [−261.8, −124.2] (61)	141.6 [46.0, 237.2]
	Unclassifiable IIPs	−125.9 [−192.6, −59.1] (64)	−194.2 [−268.3, −120.1] (50)	68.3 [−31.4, 168.1]
	Autoimmune ILDs	−74.5 [−134.9, −14.0] (82)	−178.5 [−235.2, −121.7] (88)	104.0 [21.1, 186.9]
	Other ILDs	−17.7 [−104.9, 69.6] (38)	−214.8 [−297.0, −132.6] (43)	197.1 [77.6, 316.7]
%FVC	≤70%	−115.4 [−155.6, −75.2] (196)	−207.1 [−246.8, −167.3] (193)	91.7 [37.4, 146.0]
	>70%	−31.3 [−80.0, 17.4] (136)	−161.3 [−208.3, −114.2] (138)	130.0 [66.2, 193.7]
HRCT	UIP-like fibrotic pattern	−81.5 [−119.5, −43.4] (206)	−209.2 [−246.8, −171.6] (206)	127.8 [74.3, 181.2]
	Other fibrotic patterns	−79.9 [−127.0, −32.9] (126)	−155.4 [−201.6, −109.1] (125)	75.4 [9.5, 141.4]
Criteria for progression of ILD	Decline in %FVC of ≥10%	−72.5 [−115.4, −29.7] (160)	−235.0 [−275.9, −194.1] (172)	162.5 [103.5, 221.4]
	Decline in %FVC of ≥5% to <10%, combined with worsening of symptoms or increasing extent of fibrotic changes on chest imaging	−109.5 [−160.6, −58.4] (110)	−145.3 [−199.4, −91.2] (97)	35.8 [−38.4, 109.9]
	Worsening of symptoms or increasing extent of fibrotic changes on chest imaging	−49.7 [−117.0, 17.6] (62)	−127.5 [−193.9, −61.1] (61)	77.8 [−16.5, 172.0]
%DLco	≤35%	−81.7 [−144.3, −19.1] (80)	−171.8 [−240.9, −102.7] (61)	90.1 [−2.8, 183.0]
	>35% to <50%	−112.8 [−155.3, −70.4] (158)	−210.0 [−255.3, −164.8] (141)	97.2 [35.4, 159.1]
	>50%	−28.8 [−86.6, 29.1] (88)	−174.2 [−221.3, −127.0] (126)	145.4 [71.8, 219.0]
KL-6	≤1000 U/mL	−67.9 [−105.6, −30.2] (203)	−179.3 [−217.6, −140.9] (187)	111.4 [57.7, 165.1]
	>1000 U/mL	−104.3 [−153.2, −55.3] (118)	−207.5 [−255.0, −160.0] (125)	103.2 [35.2, 171.3]
Smoking history	Yes	−75.3 [−117.5, −33.1] (169)	−218.4 [−259.3, −177.5] (169)	143.1 [84.8, 201.4]
	No	−86.5 [−128.5, −44.5] (163)	−155.6 [−197.6, −113.6] (162)	69.1 [10.1, 128.1]

Least squares mean [95% CI] (N)

a) A random coefficient regression model including treatment, HRCT pattern (except for patient characteristic, "HRCT"), baseline FVC (mL), and baseline FVC-by-time, treatment-by-subpopulation, and treatment-by-subpopulation-time interactions as fixed effects, and individual intercept and time as random effects

Table 11 shows the results of the secondary endpoints. The nintedanib group tended to have a greater improvement than the placebo group in lung function-related endpoints that are associated with mortality in patients with chronic fibrosing ILDs (*Ann Rheum Dis.* 2019;78:122-30) (i.e., the proportions of patients with a relative decline from baseline in %FVC of >5% or >10% at Week 52), as well as respiratory symptom-related endpoints (changes from baseline in King's Brief Interstitial Lung Disease [K-BILD] total score and individual domain scores of Living with Pulmonary Fibrosis [L-PF] symptoms). Furthermore, the proportions of patients experiencing the first acute ILD exacerbation during the 52 weeks were 4.8% (16 of 332 patients) in the nintedanib group and 6.6% (22 of 331 patients) in the placebo group. The proportions of patients who died during the 52 weeks were 4.8% (16 of 332 patients) in the nintedanib group and 5.1% (17 of 331 patients) in the placebo group.

Table 11. Secondary endpoints at Week 52 (Study 1199.247, the treated set, the overall population)

	Nintedanib	Placebo	Comparison with placebo [95% CI]
Proportion of patients with a relative decline from baseline in %FVC of >5%	52.4 (174/332)	68.6 (227/331)	0.50 [0.36, 0.68] [b)]
Proportion of patients with a relative decline from baseline in %FVC of >10%	40.7 (135/332)	48.9 (162/331)	0.70 [0.52, 0.96] [b)]
Change from baseline in K-BILD total score[a)]	0.55 [−0.62, 1.72] (332)	−0.79 [−1.94, 0.37] (330)	1.34 [−0.31, 2.98]
Change from baseline in L-PF dyspnea symptom score[a)]	4.28 [2.43, 6.14] (329)	7.81 [5.97, 9.66] (323)	−3.53 [−6.14, −0.92]
Change from baseline in L-PF cough symptom score[a)]	−1.84 [−4.36, 0.69] (327)	4.25 [1.74, 6.76] (320)	−6.09 [−9.65, −2.53]

% (n/N) or least squares mean [95% CI] (N)

a) Mixed model repeated measures (MMRM) model including treatment, baseline value, HRCT pattern, visit, and treatment-by-visit and baseline value-by-visit interactions as fixed effects, and assuming an unstructured variance-covariance matrix for intrapatient errors

b) Adjusted odds ratios based on a logistic regression model including baseline %FVC, HRCT pattern, and treatment as covariates. Patients with missing data were considered as non-responders.

As above, the efficacy of nintedanib versus placebo was demonstrated as measured by the primary endpoint of FVC, which is an indicator deemed to be helpful for the assessment of ILD progression. Furthermore, the results of secondary endpoints tended to be better in the nintedanib group than in the placebo group. These results indicated that nintedanib was effective in slowing ILD progression in patients with PF-ILD.

According to efficacy analysis for Japanese patients with PF-ILD, the result for the primary endpoint (the annual rate of decline in FVC over 52 weeks) in the Japanese subpopulation was similar to that in the overall population (Table 4). In Study 1199.247, the patient characteristics that tended to clearly differ between the overall population and the Japanese subpopulation were body weight (mean body weight, 76.9 kg in the overall population vs. 61.6 kg in the Japanese subpopulation), HRCT pattern (the proportion of patients with UIP-like fibrotic pattern only, 62.1% in the overall population vs. 77.8% in the Japanese subpopulation), and clinical ILD diagnosis groups (unclassifiable IIPs, 17.2% in the overall population vs. 36.1% in the Japanese subpopulation; hypersensitivity pneumonitis, 26.1% in the overall population vs. 13.0% in the Japanese subpopulation). The mean age in the Japanese subpopulation was slightly higher than that in the overall population (65.8 years old in the overall population vs. 68.1 years old in the Japanese subpopulation). Subgroup analyses by these patient characteristics showed no clear differences in the efficacy of nintedanib among the subgroups (Table 10). These results suggest that the efficacy of nintedanib in Japanese patients with PF-ILD can be evaluated based on the results of Study 1199.247.

PMDA's view:

Study 1199.247 involving patients with PF-ILD demonstrated the superiority of nintedanib to placebo in the annual rate of decline in FVC over 52 weeks (mL/year), which was the primary endpoint. In the study, the efficacy of nintedanib was supported by the results for the ILD-related secondary endpoints. Furthermore, subgroup analyses by underlying ILD diagnosis showed no clear differences in the efficacy of nintedanib. Accordingly, nintedanib is expected to be effective in the treatment of PF-ILD. However, the effects of nintedanib on prognosis in patients with PF-ILD cannot be concluded based solely on the results of Study

1199.247. Therefore, prognostic information should continue to be collected from patients with PF-ILD during treatment with nintedanib.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.3 Safety

The applicant's explanation about the safety of nintedanib in patients with PF-ILD:

Table 12 presents a summary of the safety data from Study 1199.247 involving patients with PF-ILD, Study 1199.214 involving patients with SSc-ILD, and global phase III studies involving patients with IPF (pooled data from Studies 1199.32 and 1199.34). Despite limitations to comparisons among studies with different designs, such as patient characteristics and concomitant medications, the safety profile of nintedanib in patients with PF-ILD was comparable to that in patients treated for the approved indications, IPF and SSc-ILD, except for the incidence of "hepatic disorders combined," which was defined by the applicant as a group of adverse events related to hepatic disorders. The incidence of hepatic disorder-related adverse events tended to be higher in patients with PF-ILD than in patients with IPF or SSc-ILD. This is possibly because in Study 1199.247, the central laboratory used lower upper limits of normal (ULNs) for transaminases than those used in clinical studies for the approved indications,[6)] resulting in a more conservative assessment of adverse events mainly represented by elevated liver enzyme levels, i.e., AST increased/ALT increased, hepatic function abnormal, and GGT increased. In patients with PF-ILD, the proportion of patients with the elevation of AST or ALT ≥3 × ULN in the nintedanib group was 7.2-fold higher than that in the placebo group (13.0% in the nintedanib group vs. 1.8% in the placebo group); this between-group ratio did not differ substantially from the ratio in patients with IPF (7.1 [5.0% in the nintedanib group vs. 0.7% in the placebo group]) or that in patients with SSc-ILD (7.0 [4.9% in the nintedanib group vs. 0.7% in the placebo group]). Furthermore, all of the hepatic disorder-related adverse events reported in Study 1199.247, except for hepatic cirrhosis in 1 patient who had concurrent chronic hepatitis B at baseline, resolved after dose reduction, discontinuation of nintedanib therapy, or other measures. Therefore, the risk of hepatic disorders in patients with PF-ILD during treatment with nintedanib is unlikely to differ substantially from that in patients with IPF or SSc-ILD, and will raise no new safety concerns.

Comparisons with the safety profile in patients with IPF from the Periodic Benefit-Risk Evaluation Report (PBRER, October 16, 2018 to October 15, 2019) identified no particular safety concerns in patients with PF-ILD.

Table 12 presents a summary of the safety of nintedanib in the Japanese subpopulation of Study 1199.247. There were no clear differences in the safety profile of nintedanib, except for the incidences of hepatic disorder-related adverse events and interstitial lung disease, between the Japanese subpopulation and the overall population. The incidence of hepatic disorder-related adverse events tended to be higher in the Japanese

6) The reference ranges for the transaminases used in a clinical study in patients with PF-ILD were as follows: AST, 11 to 36 for males and 9 to 34 for females; ALT, 6 to 43 for males aged 18 to 68 years, 6 to 35 for males aged ≥69 years, 6 to 34 for females aged 18 to 68 years, and 6 to 32 for females aged ≥69 years. The reference ranges for the transaminases used in clinical studies in patients with SSc-ILD or IPF were as follows: AST, 0 to 42 for males and females, aged 18 to 64 years and 0 to 55 in males and females aged ≥65 years; ALT, 0 to 48, regardless of sex or age.

subpopulation than in the overall population. However, the higher incidence in the Japanese subpopulation was attributable to the more frequent occurrence of hepatic function abnormal, a non-specific term, mainly represented by elevated liver enzyme levels (Table 7). The severity of the hepatic disorder-related adverse events and the extent of the increases in transaminases (AST and ALT) did not differ substantially between the Japanese subpopulation and the overall population. In addition, the incidence of interstitial lung disease was higher in the Japanese subpopulation than in the overall population, while the incidence of interstitial lung disease in the nintedanib group did not exceed that in the placebo group in the Japanese subpopulation, as in the case of the overall population. This suggested that interstitial lung disease was attributable to the progression of underlying ILD in the patients. Taken together, the results of Study 1199.247 showed that the safety profile of nintedanib in the Japanese subpopulation was comparable to that in the overall population.

Table 12. Summary of the safety of nintedanib (safety analysis sets, up to Week 52)

	PF-ILD				SSc-ILD	IPF
	Study 1199.247				Study 1199.214	2 global studies pooled[a)]
	Japanese subpopulation		Overall population		Nintedanib	Nintedanib
	Nintedanib	Placebo	Nintedanib	Placebo		
N	52	56	332	331	288	638
Total exposure (patient-years)	46.3	50.0	285.8	310.6	253.0	548.0
Summary of adverse events						
Adverse events	51 (98.1) 1227.1	56 (100.0) 431.8	317 (95.5) 766.6	296 (89.4) 356.4	283 (98.3) 1208.7	609 (95.5) 632.1
Serious adverse events	19 (36.5) 49.2	27 (48.2) 66.5	107 (32.2) 42.9	110 (33.2) 41.0	69 (24.0) 29.3	194 (30.4) 36.6
Deaths	0	4 (7.1) 8.0	11 (3.3) 3.8	17 (5.1) 5.4	5 (1.7) 1.9	37 (5.8) 6.2
Adverse events leading to treatment discontinuation	11 (21.2) 24.4	10 (17.9) 20.3	65 (19.6) 23.0	34 (10.3) 11.0	46 (16.0) 18.2	123 (19.3) 21.3
Adverse drug reactions	47 (90.4) 560.3	21 (37.5) 58.5	262 (78.9) 280.9	126 (38.1) 55.7	238 (82.6) 338.8	455 (71.3) 185.7
Adverse events leading to dose reduction	23 (44.2) 83.4	0	110 (33.1) 50.7	14 (4.2) 4.6	98 (34.0) 49.9	101 (15.8) 19.0
Adverse events of special interest						
Diarrhoea (PT)	41 (78.8) 257.0	18 (32.1) 48.4	222 (66.9) 166.0	79 (23.9) 31.3	218 (75.7) 235.2	393 (61.6) 128.7
Nausea (PT)	15 (28.8) 41.5	1 (1.8) 2.0	96 (28.9) 43.7	31 (9.4) 10.5	91 (31.6) 46.4	156 (24.5) 32.8
Vomiting (PT)	8 (15.4) 19.4	0	61 (18.4) 24.5	17 (5.1) 5.6	71 (24.7) 33.7	74 (11.6) 13.5
Abdominal pain (HLT)	4 (7.7) 8.9	3 (5.4) 6.1	60 (18.1) 24.0	16 (4.8) 5.2	53 (18.4) 23.4	96 (15.0) 18.2
Serious gastrointestinal symptoms[b)]	1 (1.9) 2.1	0	10 (3.0) 3.5	4 (1.2) 1.3	11 (3.8) 4.3	19 (3.0) 3.2
Hepatic disorders combined[c)]	31 (59.6) 130.0	3 (5.4) 6.1	91 (27.4) 38.8	25 (7.6) 8.3	50 (17.4) 22.1	113 (17.7) 21.6
Arterial thromboembolism (SMQ·narrow)	0	0	3 (0.9) 1.0	3 (0.9) 1.0	2 (0.7) 0.8	16 (2.5) 2.7
Venous thromboembolism (SMQ·narrow)	1 (1.9) 2.1	1 (1.8) 2.0	3 (0.9) 1.0	5 (1.5) 1.6	4 (1.4) 1.5	7 (1.1) 1.2
Platelets decreased[d)]	0	1 (1.8) 2.0	1 (0.3) 0.3	2 (0.6) 0.6	2 (0.7) 0.8	2 (0.3) 0.3
Gastrointestinal perforation (SMQ·narrow)	1 (1.9) 2.1	0	1 (0.3) 0.3	1 (0.3) 0.3	0	2 (0.3) 0.3
Interstitial lung disease (SMQ)	9 (17.3) 20.3	18 (32.1) 39.8	27 (8.1) 9.6	44 (13.3) 14.7	20 (6.9) 7.7	65 (10.2) 11.2
Severe cutaneous adverse reactions (SMQ·narrow)	0	0	0	0	0	1 (0.2) 0.2
Haemorrhage (SMQ·narrow)	5 (9.6) 11.2	10 (17.9) 21.6	37 (11.1) 13.6	42 (12.7) 14.3	32 (11.1) 13.1	66 (10.3) 11.8
Osteonecrosis of jaw (PT)	0	0	0	0	0	0
Impaired healing (PT)	0	0	0	0	0	1 (0.2) 0.2

Upper row, n (%); lower row, total exposure-adjusted number of events per 100 patient-years

a) Studies 1199.32 and 1199.34

b) Serious adverse events categorized under gastrointestinal disorders (SOC)

c) A safety topic defined by the applicant, which comprised an aggregation of events categorized under "cholestasis and jaundice of hepatic origin (SMQ, narrow)," "drug-related hepatic disorders-comprehensive search (SMQ, narrow)," "non-infectious hepatitis (SMQ, narrow)," or "liver-related investigations, signs and symptoms (SMQ, broad)"

d) An aggregation of events categorized under "immune thrombocytopenic purpura (PT)," "platelet count decreased (PT)," and "thrombocytopenia (PT)"

As above, the currently available data on the safety profile of nintedanib in patients with PF-ILD raised no new concerns, compared with the safety profiles in patients treated for the approved indications, IPF and SSc-ILD.

Therefore, the safety risks associated with the use of nintedanib in patients with PF-ILD will be manageable by continuing the same safety measures as those taken for the approved indications.

PMDA's view:
The applicant's explanation was accepted. The safety profile of nintedanib in patients with PF-ILD was assessed based on the available clinical study results. The risk of hepatic disorders in association with the use of nintedanib in patients with PF-ILD is considered comparable to that in patients treated for the approved indications, and the safety profile of nintedanib in patients with PF-ILD has raised no particular concerns compared with the safety profile of nintedanib for the approved indications.

However, given that only a small number of Japanese patients with PF-ILD have been treated with nintedanib, and that patients with PF-ILD have a variety of underlying ILD diagnoses, the applicant should continue to collect safety information on the risk of hepatic disorders in association with the long-term use of nintedanib in patients with PF-ILD, and should appropriately communicate new findings to healthcare professionals. Patients with PF-ILD during treatment with nintedanib should be monitored carefully for the risk of developing the known adverse drug reactions including hepatic disorders, and the same safety measures as those used for the approved indications should be taken, such as advising that nintedanib be used under the supervision of a physician with expertise in the treatment of PF-ILD.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.4 Clinical positioning

The applicant's explanation about the clinical positioning of nintedanib in the treatment of PF-ILD:
In Study 1199.247, patients with ILD who exhibited a progressive fibrosing phenotype as a shared pathological feature were grouped together for enrollment in the study, regardless of their clinical ILD diagnoses. Although there are no generally accepted criteria to define "progressive fibrosing ILD," based on the current treatment algorithm and clinical practice for PF-ILD, Study 1199.247 included patients who were diagnosed with "fibrosing ILD" other than IPF, had the extent of lung fibrosis >10% on HRCT, had a %FVC of ≥45% and a %DLco of ≥30% and <80%, and met at least one of the following criteria for progression of ILD within 24 months before screening, despite disease management considered appropriate by physicians:

i) A relative decline in %FVC of ≥10%
ii) A relative decline in %FVC of ≥5% to <10% combined with worsening of respiratory symptoms
iii) A relative decline in %FVC of ≥5% to <10% combined with increasing extent of fibrotic changes on chest imaging
iv) Worsening of respiratory symptoms and increasing extent of fibrotic changes on chest imaging

The results of the study demonstrated the superiority of nintedanib to placebo in the primary endpoint, the annual rate of decline in FVC over 52 weeks [see Section 7.1]. Furthermore, subgroup analyses by patient characteristics for the primary endpoint (Table 10) suggested the efficacy of nintedanib in the treatment of PF-

ILD, regardless of patient characteristics, such as underlying ILD diagnoses, HRCT patterns, and criteria (i) to (iv) defined for progression of ILD.[7)]

Study 1199.247 employed an inclusion criterion specifying that patients who had specific symptoms despite off-label treatment with immunomodulatory therapies[8)] were eligible for the study to include patients with ILD in who pulmonary fibrosis progressed despite management with pharmacotherapies or non-pharmacotherapies that were deemed by the investigators to be appropriate in clinical practice for the patient's ILD. However, patients with underlying ILD diagnoses such as asbestosis, who were expected by the investigators to have resistance to immunomodulatory therapies, were enrolled in the study, regardless of whether they had actually received immunomodulatory therapies. During the study, the concomitant use of immunomodulatory therapies was restricted to only when specific conditions were met,[9)] to prevent these therapies from affecting the assessment of the efficacy or safety of nintedanib. The proportions of patients who used any immunomodulatory therapy during the study were 11.7% (39 of 332 patients) in the nintedanib group and 24.2% (80 of 331 patients) in the placebo group. The medications concomitantly used with nintedanib are shown in Table 13. Although the incidences of adverse events with or without the concomitant use of immunomodulatory therapies should be interpreted carefully due to the small numbers of patients using such therapies and adverse events reported by the patients, the incidences of adverse events were generally similar, regardless of the concomitant use of immunomodulatory therapies (Table 14). The incidences of respiratory adverse events, particularly interstitial lung disease (PT), respiratory failure (PT), and acute respiratory failure (PT), were higher in patients using restricted concomitant medications than in those using no restricted concomitant medications. This was probably because the use of such concomitant medications was restricted to only when the disease was worsening. In Study 1199.247, respiratory failure (PT) and acute respiratory failure (PT) were required to be reported as serious adverse events, thus resulting in a higher incidence of serious adverse events in patients using restricted concomitant medications than in those using no restricted concomitant medications (Table 15). Table 16 shows the incidences of adverse events with or without the use of low-dose concomitant corticosteroids that were allowed at baseline. There were no differences in the incidences of adverse events between patients with and without the use of corticosteroids at baseline.

7) In Table 10, subgroup analyses by "criteria for progression of ILD" were conducted for patients with a decline in %FVC of ≥10% (criterion (i)), those with a decline in %FVC of ≥5% and <10% combined with increasing extent of fibrotic changes on chest imaging or worsening of symptoms (criteria (ii) and (iii)), and those with increasing extent of fibrotic changes on chest imaging or worsening of symptoms (criterion (iv)).

8) The unapproved immunomodulatory medications included, but were not limited to, corticosteroids, azathioprine, mycophenolate mofetil, N-acetylcysteine, rituximab, cyclophosphamide, cyclosporine, and tacrolimus.

9) The use of DMARDs (e.g., methotrexate) or TNF inhibitors was allowed, if they had been used at a stable dose for the 6 months before the start of study treatment. The DMARDs had to be used at the same dose during the study period. The use of immunomodulatory therapies (e.g., azathioprine, cyclosporine, tacrolimus, rituximab, cyclophosphamide, mycophenolate mofetil, high-dose corticosteroids) was prohibited at the time of randomization and during the 6 months after the start of study treatment, and allowed after 6 months of study treatment only in patients with a clinically significant deterioration of ILD or collagen disorder.

Table 13. Immunomodulatory therapies concomitantly used with nintedanib (Study 1199.247, TS)

Concomitant medications	Number of patients with concomitant medications N = 39
Corticosteroids	34 (10.2)
Mycophenolate mofetil	5 (1.5)
Tacrolimus	3 (0.9)
Rituximab	3 (0.9)
Azathioprine	1 (0.3)

n (%)

Table 14. Adverse events reported by ≥5.0% of patients in either treatment group, with or without use of restricted/prohibited concomitant medications (Study 1199.247, TS)

Events	With concomitant medications N = 39	Without concomitant medications N = 293	Events	With concomitant medications N = 39	Without concomitant medications N = 293
Diarrhoea	27 (69.2)	195 (66.6)	Malaise	3 (7.7)	5 (1.7)
Bronchitis	14 (35.9)	27 (9.2)	Disease progression	3 (7.7)	3 (1.0)
Nausea	12 (30.8)	84 (28.7)	Hypoxia	3 (7.7)	3 (1.0)
Vomiting	8 (20.5)	53 (18.1)	Sputum increased	3 (7.7)	2 (0.7)
Dyspnoea	8 (20.5)	28 (9.6)	Hypotension	3 (7.7)	2 (0.7)
Interstitial lung disease	8 (20.5)	8 (2.7)	Constipation	2 (5.1)	21 (7.2)
Decreased appetite	6 (15.4)	42 (14.3)	Asthenia	2 (5.1)	16 (5.5)
ALT increased	6 (15.4)	37 (12.6)	Dizziness	2 (5.1)	14 (4.8)
AST increased	6 (15.4)	32 (10.9)	Hypertension	2 (5.1)	11 (3.8)
Acute respiratory failure	6 (15.4)	4 (1.4)	Rash	2 (5.1)	9 (3.1)
Cough	5 (12.8)	28 (9.6)	Musculoskeletal pain	2 (5.1)	8 (2.7)
Weight decreased	4 (10.3)	37 (12.6)	Dry mouth	2 (5.1)	6 (2.0)
Headache	4 (10.3)	31 (10.6)	Sinusitis	2 (5.1)	6 (2.0)
Fatigue	4 (10.3)	29 (9.9)	Alopecia	2 (5.1)	5 (1.7)
Upper respiratory tract infection	4 (10.3)	20 (6.8)	Blood LDH increased	2 (5.1)	4 (1.4)
Back pain	4 (10.3)	15 (5.1)	Respiratory failure	2 (5.1)	4 (1.4)
GGT increased	4 (10.3)	15 (5.1)	Rheumatoid arthritis	2 (5.1)	2 (0.7)
Nasopharyngitis	3 (7.7)	41 (14.0)	Transaminases increased	2 (5.1)	2 (0.7)
Abdominal pain	3 (7.7)	31 (10.6)	Vertigo	2 (5.1)	2 (0.7)
Abdominal pain upper	3 (7.7)	27 (9.2)	Migraine	2 (5.1)	0
Urinary tract infection	3 (7.7)	17 (5.8)	Bacterial pneumonia	2 (5.1)	0
Pneumonia	3 (7.7)	16 (5.5)	Hypersensitivity pneumonitis	2 (5.1)	0
Pyrexia	3 (7.7)	13 (4.4)	Hepatic function abnormal	1 (2.6)	18 (6.1)
Dyspepsia	3 (7.7)	10 (3.4)	Chest pain	1 (2.6)	15 (5.1)

n (%)

Table 15. Summary of adverse events, with or without use of restricted/prohibited concomitant medications (Study 1199.247, up to Week 52, TS)

	With concomitant medications N = 39	Without concomitant medications N = 293
Adverse events	39 (100)	278 (94.9)
Serious adverse events	27 (69.2)	80 (27.3)
Deaths	3 (7.7)	8 (2.7)
Adverse events leading to treatment discontinuation	8 (20.5)	57 (19.5)
Adverse drug reactions	32 (82.1)	230 (78.5)

n (%)

Table 16. Summary of adverse events, with or without concomitant use of low-dose corticosteroids (Study 1199.247, TS)

	With concomitant corticosteroids N = 174	Without concomitant corticosteroids N = 155
Adverse events	165 (94.8)	149 (96.1)
Serious adverse events	57 (32.8)	48 (31.0)
Deaths	7 (4.0)	4 (2.6)
Adverse events leading to treatment discontinuation	28 (16.1)	37 (23.9)
Adverse drug reactions	134 (77.0)	126 (81.3)

n (%)

Based on the above, nintedanib can be used in the treatment of PF-ILD, regardless of patient characteristics such as underlying ILD diagnoses, HRCT patterns, and criteria (i) to (iv) defined for progression of ILD.

PMDA's view:

The available data regarding the efficacy and safety profile of nintedanib have suggested that nintedanib is expected to be used to suppress the progression of ILD and slow the decline in lung function in patients with PF-ILD. For the use of nintedanib, physicians with sufficient knowledge and experience in the treatment of PF-ILD should carefully determine the eligibility of each patient for nintedanib therapy based on the expected benefits and risks, after understanding the clinical study results including the target patient population and concomitant medications used in the study, evaluating the progression of pulmonary fibrosis in individual patients, and identifying the underlying etiologies. At the same time, the physicians should administer concomitant therapies to adequately manage the symptoms of individual patients. In Study 1199.247, the concomitant use of immunomodulatory therapies was limited to patients with a clinically significant deterioration of ILD,[9)] and available information on the efficacy and safety of nintedanib in combination with immunomodulatory medications is limited. Therefore, such information should continue to be collected from published literature and other sources in the post-marketing setting.

The treatment algorithm for PF-ILD and the clinical positioning of nintedanib in the treatment of PF-ILD will need to be discussed at relevant academic societies, based on the available clinical study data and the results of post-marketing surveillance, etc.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.5 Patient population and indication

PMDA's view:

Based on the submitted data and the reviews in Sections 7.R.2, 7.R.3, and 7.R.4, "progressive fibrosing ILD" may be added as a new indication.

As discussed in Section 7.R.4, despite there being no generally accepted criteria to defined "progressive fibrosing ILD," nintedanib is intended to be used in patients with ILD who have been diagnosed as having progressive pulmonary fibrosis based on the comprehensive assessment of lung function, respiratory symptoms, and chest images. Therefore, the "Precautions for Indications" section should include a cautionary statement

that nintedanib should be administered to patients with progressive fibrosing ILD who have been confirmed by the comprehensive assessment of lung function, respiratory symptoms, and chest images.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.6 Dosage and administration

The applicant's explanation about the dosage and administration of nintedanib in the treatment of PF-ILD:
In Study 1199.247, in which nintedanib was administered at a dose of 150 mg twice daily, with an option of reducing the dose to 100 mg twice daily or interrupting the treatment if needed to manage adverse events, the superiority of nintedanib to placebo was demonstrated in the annual rate of decline in FVC over 52 weeks, which was the primary endpoint [see Section 7.1], and the results of other efficacy endpoints supported the efficacy of nintedanib [see Section 7.R.2].

Table 17 shows the proportions of patients requiring treatment interruption or dose reduction in Study 1199.247 involving patients with PF-ILD, Study 1199.214 involving patients with SSc-ILD, and 2 global phase III studies involving patients with IPF (Studies 1199.32 and 1199.34). The proportions of patients with PF-ILD requiring treatment interruption or dose reduction did not tend to differ substantially from those treated for the approved indications, IPF and SSc-ILD. Table 18 shows the adverse events leading to permanent dose reduction in Study 1199.247. Diarrhoea was the most common adverse event that led to permanent dose reduction; however, most of the cases were mild or moderate in severity, and resolved after dose reduction. The proportions of patients who discontinued the study drug during the 52 weeks were 24.1% (80 of 332 patients) in the nintedanib group and 14.8% (49 of 331 patients) in the placebo group. In Study 1199.247, the dose intensity[10)] of the study drug was 92.5% in the nintedanib group and 98.6% in the placebo group, whereas in patients experiencing dose reduction, the dose intensity of the study drug was 79.4% (112 patients) in the nintedanib group and 82.3% (18 patients) in the placebo group. The annual rates [95% CIs] of decline in FVC over 52 weeks by dose intensity were −61.8 [−97.5, −26.1] mL/year in the subgroup of patients with a dose intensity of >90% (234 patients) and −72.8 [−129.5, −16.0] mL/year in the subgroup of patients with a dose intensity of ≤90% (90 patients), suggesting that nintedanib is expected to be effective even in patients requiring dose reduction or treatment interruption.

Table 19 shows the baseline characteristics of patients who required or did not require dose reduction in Study 1199.247. Patients requiring dose reduction tended to have a slightly lower body weight and included more females than those requiring no dose reduction. However, it is difficult to select the dose of nintedanib according to baseline patient characteristics, because more than half of the patients enrolled in Study 1199.247 did not require dose reduction. Since only a few approved drugs are available for patients with PF-ILD in Japan, and in view of the irreversibility of the disease, treatment of pulmonary fibrosis should aim at slowing its progression as much as possible. Accordingly, the dosage regimen for the treatment of PF-ILD should be the

[10)] A value obtained by dividing the total dose of the study drug actually administered, taking into account the study drug used in patients who underwent dose reduction or treatment interruption, by the total dose of the study drug that was supposed to be administered during the planned treatment period or until treatment discontinuation

same as that for the approved indications. Specifically, the usual adult dosage of nintedanib in the treatment of PF-ILD is 150 mg twice daily, and the dose may be reduced to 100 mg twice daily according to the patient's condition, such as adverse drug reactions.

Table 17. Numbers and percentages of patients requiring treatment interruption or dose reduction (safety analysis set, up to Week 52)

Indication (Study)	PF-ILD (Study 1199.247)		SSc-ILD (Study 1199.214)		IPF (2 global studies pooled[a)])	
Treatment group N	Nintedanib N = 332	Placebo N = 331	Nintedanib N = 288	Placebo N = 288	Nintedanib N = 638	Placebo N = 423
Treatment interruption	110 (33.1)	34 (10.3)	109 (37.8)	33 (11.5)	151 (23.7)	42 (9.9)
Dose reduction to 100 mg	112 (33.7)	18 (5.4)	117 (40.6)	13 (4.5)	178 (27.9)	16 (3.8)
Dose reduction to 100 mg, followed by re-escalation to 150 mg	34 (10.2)	8 (2.4)	25 (8.7)	2 (0.7)	40 (6.3)	7 (1.7)
Dose intensity	92.5%	98.6%	90.3%	98.4%	93.7%	98.9%

n (%) or mean
a) Studies 1199.32 and 1199.34

Table 18. Adverse events leading to permanent dose reduction, reported by ≥1.0% of patients in either treatment group (Study 1199.247, safety analysis set, up to Week 52)

Events	Nintedanib N = 332	Placebo N = 331
Diarrhoea	53 (16.0)	3 (0.9)
ALT increased	18 (5.4)	2 (0.6)
AST increased	16 (4.8)	1 (0.3)
Nausea	11 (3.3)	2 (0.6)
Vomiting	8 (2.4)	3 (0.9)
Hepatic function abnormal	8 (2.4)	1 (0.3)
Decreased appetite	7 (2.1)	2 (0.6)
Weight decreased	6 (1.8)	1 (0.3)
GGT increased	4 (1.2)	0

n (%)

Table 19. Baseline characteristics of patients requiring and not requiring dose reduction (Study 1199.247, overall population, up to Week 52)

		With dose reduction N = 112	Without dose reduction N = 220
Sex	Male	50 (44.6)	129 (58.6)
	Female	62 (55.4)	91 (41.4)
Race	Asian	33 (29.5)	50 (22.7)
	White	78 (69.6)	164 (74.5)
	Black/African American	1 (0.9)	4 (1.8)
Age (years)		66.4 ± 9.0	64.6 ± 10.0
Body weight (kg)		73.0 ± 15.5	78.9 ± 17.3
Time since the initial diagnosis of ILD (years)		3.6 ± 3.6	3.7 ± 3.9
ILD type	iNSIP	22 (19.6)	42 (19.1)
	Unclassifiable IIPs	31 (27.7)	33 (15.0)
	Hypersensitivity pneumonitis	27 (24.1)	57 (25.9)
	Autoimmune ILDs	23 (20.5)	59 (26.8)
	Other ILDs	9 (8.0)	29 (13.2)
Baseline FVC (mL)		2,163.5 ± 684.7	2,430.0 ± 752.6
Baseline %FVC		68.3 ± 16.1	68.9 ± 16.1
Baseline %DLco		43.0 ± 10.2	45.0 ± 12.7

n (%) or mean ± SD

PMDA's view:
Based on the applicant's explanation, the submitted data, and the reviews in Sections 7.R.2 and 7.R.3, the following dosage regimen proposed by the applicant is acceptable: The usual adult dosage is 150 mg of nintedanib administered orally twice daily. The dose may be reduced to 100 mg of nintedanib twice daily according to the patient's condition.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.7 Post-marketing investigations

The applicant's explanation:
As described in the review in Section 7.R.3, the currently available data raised no new specific concerns about the safety profile of nintedanib in patients with PF-ILD, as compared with that in patients treated for the approved indications, IPF and SSc-ILD. However, the assessment of the safety profile of nintedanib in Japanese patients with PF-ILD was limited. As such, post-marketing surveillance will be conducted to demonstrate the safety and other aspects of nintedanib in clinical practice.

PMDA's view:
In light of the review in Section 7.R.3, the applicant explained that the currently available information regarding the safety profile of nintedanib in patients with PF-ILD had raised no new concerns that clearly outweigh the safety risks associated with the use of nintedanib for its approved indications, IPF and SSc-ILD. The applicant's explanation is understandable. However, the safety and other aspects of nintedanib, including the incidence of hepatic disorder-related adverse events, in patients with PF-ILD in clinical practice should continue to be evaluated in post-marketing surveillance, etc., because (a) only a limited number of Japanese patients with PF-ILD were evaluated in the clinical study, (b) patients with PF-ILD have different underlying ILD diagnoses, and (c) the incidence of hepatic disorder-related adverse events in Study 1199.247 involving patients with PF-ILD tended to be higher than that in in the clinical studies involving patients with IPF or SSc-ILD. Furthermore, the same safety measures as those specified for the approved indication, IPF, should be taken, such as advising that nintedanib be used under the supervision of a physician with expertise in the treatment of PF-ILD.

The above conclusion of PMDA will be discussed at the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The inspections are ongoing, and the results and PMDA's conclusion will be reported in the Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The inspections are ongoing, and the results and PMDA's conclusion will be reported in the Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that nintedanib has efficacy in the treatment of PF-ILD, and that nintedanib has acceptable safety in view of its benefits. Nintedanib is clinically meaningful because it offers a new treatment option for patients with PF-ILD. The safety and other aspects of nintedanib in Japanese patients with PF-ILD in clinical practice should be further evaluated in post-marketing surveillance, etc.

PMDA has concluded that nintedanib may be approved if nintedanib is not considered to have any particular problems based on comments from the Expert Discussion.

10. Others

The table below shows the methods of efficacy assessment and the definitions of the efficacy endpoints used in the clinical study with nintedanib in patients with PF-ILD.

Endpoints	Definition
Annual rate of decline in FVC over 52 weeks	The estimated change from baseline in FVC at Week 52, assuming that FVC changes linearly with time
%FVC	The ratio (%) of an FVC value to the predicted normal FVC value calculated based on age, sex, and height
K-BILD total score	A health status questionnaire for patients with ILD, composed of 15 questions across 3 domains (breathlessness and activities, psychological symptoms, and chest symptoms). Each question has a 7-point response scale, resulting in a total score ranging from 0 to 100, with higher scores representing better health status.
L-PF symptoms score	A questionnaire developed for patients with pulmonary fibrosis. It is composed of 23 items covering the following 3 domains: 1) dyspnea, 2) cough, and 3) fatigue. An L-PF symptoms score is calculated from responses to the 23 questions, ranging from 0 to 100, with higher scores indicating greater impairment.

Review Report (2)

April 10, 2020

Product Submitted for Approval	
Brand Name	Ofev Capsules 100 mg, Ofev Capsules 150 mg
Non-proprietary Name	Nintedanib Ethanesulfonate
Applicant	Nippon Boehringer Ingelheim Co., Ltd.
Date of Application	October 24, 2019

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy, clinical positioning, indication, and dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusions as to the efficacy, clinical positioning, indication, and dosage and administration of nintedanib in the treatment of progressive fibrosing interstitial lung disease (PF-ILD) as presented in the Review Report (1), and made the following comments on the clinical positioning.

- For the use of nintedanib, physicians with full knowledge of nintedanib and sufficient knowledge and experience in the treatment of the proposed indication (PF-ILD) should identify patients with interstitial lung diseases (ILDs) with a progressive fibrosing phenotype, as confirmed by the comprehensive assessment of lung function, respiratory symptoms, and chest images, while taking account of the inclusion criteria used in Study 1199.247.
- PF-ILD usually originates from a variety of underlying ILD diagnoses, including idiopathic non-specific interstitial pneumonia (iNSIP), unclassifiable idiopathic interstitial pneumonias (IIPs), rheumatoid arthritis, systemic sclerosis (SSc), polymyositis/dermatomyositis, Sjogren's syndrome, systemic lupus erythematosus, ILDs associated with collagen disorders such as mixed connective tissue disease, chronic hypersensitivity pneumonitis, sarcoidosis, and occupational/environmental fibrosing pulmonary diseases. Therefore, information on the safety and efficacy of nintedanib in patients with these

underlying ILD diagnoses should be collected in post-marketing surveillance, etc. and appropriately communicated to healthcare professionals.

- In Japan, in addition to nintedanib approved for the treatment of IPF and SSc-ILD, pirfenidone is approved for the treatment of IPF, and corticosteroids and immunosuppressive agents (e.g., tacrolimus) are approved for the treatment of polymyositis/dermatomyositis-associated ILDs. Recommendations for the use of nintedanib or other drugs in patients with different underlying ILD diagnoses will need to be discussed at relevant academic societies, etc., based on experience in clinical practice.

PMDA's view:

A conclusion has been drawn based on the comments from the Expert Discussion. Physicians with expertise in the treatment of PF-ILD should carefully determine the eligibility of each patient for nintedanib therapy based on the expected benefits and risks, after understanding the clinical study results including the target patient population and concomitant medications used in the study. Further, the applicant should collect information on underlying ILD diagnoses and the safety and efficacy of nintedanib in combination with existing therapies through the planned post-marketing surveillance, etc., and should appropriately communicate the information to healthcare professionals.

The applicant has agreed to respond appropriately to PMDA's conclusion.

1.2 Safety and risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusions as to the safety and post-marketing safety measures for nintedanib described in the Review Report (1).

In view of the discussions presented in Section "7.R.7 Post-marketing safety measures" in the Review Report (1) and the comments from the expert advisers at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for nintedanib should include the safety and efficacy specifications presented in Table 20, and that the applicant should conduct the additional pharmacovigilance activities, efficacy investigations/studies, and risk minimization activities presented in Table 21. In addition, PMDA has instructed the applicant to conduct post-marketing surveillance, etc. to evaluate the above-mentioned matters.

Table 20. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
▪ Gastrointestinal symptoms such as diarrhoea and nausea ▪ Hepatic function disorders ▪ Thromboembolism ▪ Platelets decreased ▪ Gastrointestinal perforation	▪ Interstitial pneumonia ▪ Serious skin disorders ▪ Haemorrhage ▪ Osteonecrosis of jaw ▪ Wound healing delayed ▪ Use of nintedanib in patients with moderate or severe hepatic impairment (Child Pugh B or C)	▪ None
Efficacy specification		
▪ Efficacy of nintedanib in clinical practice (IPF)		

(No change)

Table 21. Summary of additional pharmacovigilance activities, efficacy investigations/studies, and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy investigations/studies	Additional risk minimization activities
▪ Specified use-results survey (IPF) ▪ Specified use-results survey (long-term treatment) (SSc-ILD) ▪ Specified use-results survey (long-term treatment) (PF-ILD) ▪ Early post-marketing phase vigilance (SSc-ILD) ▪ Early post-marketing phase vigilance (PF-ILD) ▪ Post-marketing clinical study (PF-ILD)[a)]	▪ None	▪ Disseminate data gathered during early post-marketing phase vigilance (SSc-ILD) ▪ Disseminate data gathered during early post-marketing phase vigilance (PF-ILD) ▪ Prepare and distribute materials for healthcare professionals ▪ Prepare and distribute materials for patients

a) The study will evaluate the long-term safety of nintedanib in patients with PF-ILD who completed Study 1199.247. This post-marketing clinical study will be switched from Study 1199.247, which was being conducted as a clinical trial before the approval.

(Underline denotes additions.)

The applicant's response:

A specified use-results survey will be conducted in patients with PF-ILD to evaluate the long-term safety and efficacy of nintedanib (see Table 22): the observation period will be 104 weeks, the planned sample size will be 400, and the safety specification will be hepatic dysfunction.

Table 22. Outline of the specified use-results survey

Objective	To evaluate the long-term safety and efficacy of nintedanib in clinical practice
Survey method	Sequential enrollment system
Population	Patients with PF-ILD
Observation period	104 weeks
Planned sample size	400 patients (354 in the safety analysis set)
Main survey items	▪ Safety specification: hepatic dysfunction ▪ Patient characteristics (e.g., body weight, age, sex, clinical ILD diagnosis, timing and rationale for diagnosis of progressive phenotype, disease duration, clinical ILD symptoms, medical history, complications) ▪ Exposure to nintedanib ▪ Prior treatments for PF-ILD ▪ Concomitant drugs/therapies ▪ Laboratory tests ▪ Adverse events ▪ Efficacy assessments

PMDA accepted the above applicant's responses. PMDA considers that the information collected through the specified use-results survey should be appropriately and promptly communicated to healthcare professionals, etc.

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and

Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-01) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The clinical study was generally performed in accordance with GCP. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following issue regarding the sponsor, despite its minor impact on the overall assessment of the study. The sponsor was notified of the issue.

Issue requiring corrective action

Sponsor

- A portion of the information, including the occurrence of serious, unexpected adverse drug reactions, was not communicated in a timely manner to the investigators or the heads of study sites.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below. The product is a drug with a new indication; accordingly, the re-examination for the present application is 5 years and 10 months.

Indications Idiopathic pulmonary fibrosis
Systemic sclerosis-associated interstitial lung disease
Progressive fibrosing interstitial lung disease

(Underline denotes additions.[1)])

Dosage and Administration

The usual adult dosage is 150 mg of nintedanib administered orally twice daily, after breakfast and evening meal. The dose may be reduced to 100 mg of nintedanib twice daily according to the patient's condition.

(No change)

Approval Conditions

The applicant is required to develop and appropriately implement a risk management plan.

1) Dashed line denotes additions made with the partial change approval dated December 20, 2019.

Appendix

List of Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS	American Thoracic Society
DLco	Carbon monoxide diffusion capacity
DMARDs	Disease-modifying antirheumatic drugs
ERS	European Respiratory Society
FGF	Fibroblast growth factor
FVC	Forced vital capacity
%FVC	FVC % predicted value
GGT	gamma-glutamyl transferase
HLT	High-level term
HRCT	High resolution computed tomography
IIPs	Idiopathic interstitial pneumonias
IL	Interleukin
ILD	Interstitial lung disease
iNSIP	Idiopathic non-specific interstitial pneumonia
IPF	Idiopathic pulmonary fibrosis
K-BILD	King's Brief Interstitial Lung Disease Questionnairre
KC	Keratinocyte chemoattractant/chemokine (C-X-C motif) ligand 1
KL-6	Sialylated carbohydrate antigen Krebs von den Lungen - 6
LDH	Lactate dehydrogenase
L-PF	Living with Pulmonary Fibrosis
MedDRA	Medical Dictionary for Regulatory Activities
PDGF	Platelet derived growth factor
PF-ILD	Progressive fibrosing interstitial lung disease
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred term
QOL	Quality of life
SMQ	Standardized MedDRA query
SOC	System organ class
SSc	Systemic sclerosis
SSc-ILD	Systemic sclerosis-associated interstitial lung disease
TNF	Tumor necrosis factor
TS	Treated set
UIP	Usual interstitial pneumonia
VEGF	Vascular endothelial growth factor