Report on the Deliberation Results

June 3, 2015

Evaluation and Licensing Division, Pharmaceutical and Food Safety 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 14, 2014

[Results of review]
In the meeting held on May 28, 2015, the Second Committee on New Drugs concluded that 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 10 years, the drug substance and the drug product are both classified as powerful drugs, and the product is not classified as a biological product or a specified biological product.

[Conditions for approval]
The applicant is required to:
1. Develop a risk management plan and ensure that the plan is implemented appropriately.
2. Conduct a post-marketing drug use-results survey targeting all patients treated with the product until data from a specified number of the patients are gathered for better understanding of the characteristics of patients using the product, because of the limited number of patients enrolled in the Japanese clinical studies; and ensure that safety and efficacy data of the product are collected early, thereby taking necessary measures for the proper use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

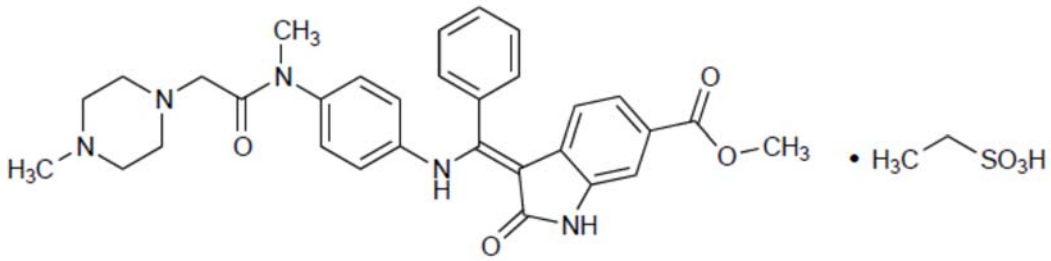
May 20, 2015

Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Ofev Capsules 100 mg, Ofev Capsules 150 mg
[Non-proprietary name]	Nintedanib Ethanesulfonate
[Name of applicant]	Nippon Boehringer Ingelheim Co., Ltd.
[Date of application]	October 14, 2014
[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 (1), Drug with a new active ingredient

[Chemical structure]



Molecular formula: $C_{31}H_{33}N_5O_4 \cdot C_2H_6O_3S$

Molecular mass: 649.76

Chemical name:

Methyl(3*Z*)-3-[({4-[*N*-methyl-2-(4-methylpiperazin-1-yl)acetamido]phenyl}amino)(phenyl)methylidene]-2-oxo-2,3-dihydro-1*H*-indole-6-carboxylate monoethanesulfonate

[Items warranting special mention]

Orphan drug (Drug Designation No. 254 of 2011 [*23 yaku*], Notification No. 0908-6 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated September 8, 2011)

[Reviewing office] Office of New Drug IV

Review Results

May 20, 2015

[Brand name]	Ofev Capsules 100 mg, Ofev Capsules 150 mg
[Non-proprietary name]	Nintedanib Ethanesulfonate
[Name of applicant]	Nippon Boehringer Ingelheim Co., Ltd.
[Date of application]	October 14, 2014

[Results of review]
Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in the treatment of patients with idiopathic pulmonary fibrosis has been demonstrated, and its safety is acceptable in view of its observed benefits. Observed adverse events such as gastrointestinal events and hepatic enzyme increased indicate the potential risks of serious adverse events including gastrointestinal perforation and myocardial infarction. Healthcare professionals should be advised to monitor patients closely during treatment with the product and to respond to adverse events by taking appropriate measures such as treatment interruption and dose reduction. The clinical studies of the product enrolled a limited number of Japanese patients with idiopathic pulmonary fibrosis. Given this situation and the potential risks of serious adverse events including hepatic impairment, gastrointestinal perforation, and myocardial infarction, the safety and efficacy of the product should be further investigated through post-marketing surveillance that involves all patients treated with the product until data of a specified number of the patients are gathered, so that sufficient information can be accumulated as early as possible.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indication and the dosage and administration as shown below, with the following conditions.

[Indication] Idiopathic pulmonary fibrosis

[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.

[Conditions for approval] The applicant is required to:

1. Develop a risk management plan and ensure that the plan is implemented appropriately.
2. Conduct a post-marketing drug use-results survey targeting all patients treated with the product until data from a specified number of the patients are gathered for better understanding of the characteristics of patients using the product, because of the limited number of patients enrolled in the Japanese clinical studies; and ensure that safety and efficacy data of the product are collected early, thereby taking necessary measures for the proper use of the product.

Review Report (1)

April 20, 2015

I. Product Submitted for Registration

[Brand name]	Ofev Capsules 100 mg, Ofev Capsules 150 mg (proposed)
[Non-proprietary name]	Nintedanib Ethanesulfonate
[Name of applicant]	Nippon Boehringer Ingelheim Co., Ltd.
[Date of application]	October 14, 2014
[Dosage form/Strength]	Soft capsules: Each capsule contains 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 indication]	Treatment of idiopathic pulmonary fibrosis and slowing of disease progression
[Proposed dosage and administration]	The usual adult dosage is 150 mg of nintedanib administered orally twice daily after meal in the morning and evening at intervals of approximately 12 hours. The dose may be reduced to 100 mg of nintedanib twice daily for patients experiencing an adverse drug reaction.

II. Summary of the Submitted Data and the Outline of Review by Pharmaceuticals and Medical Devices Agency

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

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, was discovered through exploratory research for antiangiogenic compounds inhibiting tumor cell growth by Boehringer Ingelheim GmbH (Germany). Nintedanib is considered to bind competitively to the ATP binding site of receptor tyrosine kinases such as platelet-derived growth factor receptor, fibroblast growth factor receptor, and vascular endothelial growth factor receptor, and inhibit ligand-mediated autophosphorylation of the receptor tyrosine kinases, thereby inhibiting intracellular signaling.

Idiopathic pulmonary fibrosis (IPF) is a subtype of idiopathic interstitial pneumonia and is characterized by inflammatory and fibrotic changes in the alveolar septum. The mechanism of development of IPF remains unknown. However, IPF is assumed to be caused by various an exogenous or endogenous insult to the lung that leads to injury of the alveolar epithelium or basal membrane and the subsequent restoration involving fibroblast growth and extracellular matrix deposition, promoting the formation of fibrotic lesion. The resulting lung consolidation would impair lung function. As the disease progresses, the patient may present worsened symptoms such as dyspnea, aggravated pulmonary function, and acute deterioration of respiratory function. IPF is thus a refractory disease with poor prognosis and often results in fatal outcome. According to a report, the median survival after diagnosis of IPF is 2 to 3 years (Raghu G et al., *Am J Respir Crit Care Med*. 2011;183:788-824). In Japan, the only approved drug for the treatment of IPF is pirfenidone (brand name, Pirespa Tablets 200 mg) at present. Other pharmacotherapies used in clinical practice include corticosteroid, azathioprine, cyclophosphamide hydrate, and acetylcysteine. Lung transplantation is a non-drug therapeutic option but has been applied to only limited cases in Japan. New therapeutic agents for IPF are in great demand in clinical settings.

Nintedanib inhibits intracellular signaling mediated by the platelet-derived growth factor, a fibroblast growth factor. Thus, nintedanib is expected to inhibit the formation of fibrous tissue, thereby slowing the progression of IPF. For this reason, nintedanib has been developed as therapeutic agent for IPF.

Nintedanib was approved with the indication for the treatment of IPF in October 2014 in the US and in January 2015 in the EU. As of February 2015, it has been approved in 31 countries.

In 2010, a foreign phase II study in patients with IPF was completed. In the same year, the clinical development of nintedanib for the treatment of IPF was started in Japan. Based on the results from global phase III studies including Japan and other studies, the marketing application has been submitted.

Nintedanib was designated as an orphan drug with the intended indication for "idiopathic pulmonary fibrosis" in September 2011 (Drug Designation No. 254 of 2011 [*23 yaku*], Notification No. 0908-6 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated September 8, 2011).

To prevent medication error, the proposed Japanese brand names of nintedanib were changed with the English brand names remaining unchanged.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

[redacted].

The chemical structure of the drug substance has been elucidated by nuclear magnetic resonance spectrometry (^{1}H-NMR, ^{13}C-NMR), mass spectrometry, ultraviolet-visible spectrophotometry (UV/VIS), infrared spectrophotometry (IR), and elemental analysis.

2.A.(1).2) Manufacturing process

[redacted].

2.A.(1).3) Control of drug substance

[redacted].

2.A.(1).4) Stability of drug substance

The stability studies conducted on the drug substance are shown in Table 1. The data showed that the drug substance was photostable.

Table 1. Stability studies of drug substance

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long term testing	3 commercial scale batches	25°C	60%RH	Low-density polyethylene bag (double) + fiber drum	60 months
Accelerated testing	3 commercial scale batches	40°C	75%RH		6 months

Based on the results, a retest period the drug substance was determine as [redacted] months when packed in doubled low-density polyethylene bags and stored in a fiber drum at room temperature.

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product and formulation development

The drug product is a soft capsule containing 120.4 mg or 180.6 mg of the drug substance (equivalent to 100 mg or 150 mg of nintedanib). The drug product contains medium chain fatty acid triglyceride, hard fat, soybean lecithin, gelatin, glycerin, titanium oxide, red ferric oxide/glycerin (1:1) slurry, and yellow ferric oxide/glycerin (1:2) slurry as excipients.

2.A.(2).2) Manufacturing process

[redacted].

2.A.(2).3) Control of drug product

The proposed specification for the drug product include content, description, identification (HPLC/UV), purity (HPLC), dissolution (UV/VIS), uniformity of dosage units (content uniformity), and assay (HPLC).

2.A.(2).4) Stability of drug product

The stability studies conducted on the drug product are as shown in Table 2. The accelerated stability data showed decreases in dissolution at 3 months and 6 months. Photostability data showed that the drug product is photostable.

Table 2. Stability studies of drug product

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long term testing	3 commercial scale batches	25°C	60%RH	PTP package + aluminum pillow package	36 months
Intermediate testing	3 commercial scale batches	30°C	75%RH		12 months
Accelerated testing	3 commercial scale batches	40°C	75%RH		6 months

[redacted].

2.B Outline of the review by PMDA

Based on the submitted data and the following review, PMDA has concluded that the quality of the drug substance and the drug product is controlled in an appropriate manner.

2.B.(1) New excipients

The drug product contains hard fat as an excipient, which has never been used in any oral preparation.

2.B.(1).1) Specifications and stability

The hard fat is listed in the Japanese Pharmaceutical Excipients, and thus PMDA has concluded that the specifications and the stability are acceptable.

2.B.(1).2) Safety

Based on the submitted data, PMDA has concluded that no particular safety issues are posed by the maximum daily intake of hard fat due to the administration of nintedanib.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

The primary pharmacodynamic studies of nintedanib ethanesulfonate (hereinafter referred to as "nintedanib") consist of *in vitro* studies on the inhibitory effect of nintedanib on receptor tyrosine kinases and *in vivo* studies using animal models of a bleomycin- or silica-induced lung fibrosis. As the secondary

pharmacodynamic studies, the effects of nintedanib on receptors and ion channels were investigated. The safety pharmacology studies consist of studies on the effects on the central nervous system, cardiovascular system, and respiratory system. The submitted safety pharmacology data also included data from studies of the effects of nintedanib on renal, hepatic, and gastrointestinal functions, for which nintedanib hydrochloride was used. In this section, the doses and the blood concentrations of nintedanib (as the ethanesulfonate salt) and its metabolite BIBF1202 (m1), and nintedanib hydrochloride are expressed as the free base.

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) *In vitro* pharmacology

(a) Inhibition against receptor tyrosine kinases (4.2.1.1-2, 4.2.1.1-5, 4.2.1.1-12)

The inhibitory effect of nintedanib on the kinase activities of the platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and vascular endothelial growth factor receptor (VEGFR) families was investigated by enzyme assay using their recombinant human protein kinase domains. The 50% inhibitory concentrations (IC_{50}) of nintedanib against PDGFR-α and PDGFR-β were 59 and 65 nmol/L, respectively. IC_{50} against FGFR-1, 2, 3, and 4 was 69, 37, 108, and 610 nmol/L, respectively; and IC_{50} against VEGFR-1, 2, and 3 was 34, 21, and 13 nmol/L, respectively. Other than PDGFR, FGFR, and VEGFR families, 20 kinases were used to investigate the inhibitory effect of nintedanib. In the non-receptor proto-oncogene tyrosine kinase homologue (Src) family, IC_{50} was 156 nmol/L against Src, 16 nmol/L against lymphocyte-specific protein tyrosine kinase (Lck), 195 nmol/L against V-yes-1 Yamaguchi sarcoma virus oncogene homologue (Lyn), and 41 nmol/L against wild-type Abelson tyrosine kinase (Abl). IC_{50} values of nintedanib against the kinases other than the above were ≥1 μmol/L.

The applicant's explanation:
The inhibition of Abl kinase activity by nintedanib would make minor contribution to its *in vivo* pharmacological effect because nintedanib inhibited the proliferation of the human chronic myelogenous leukemia cell line K562 with an IC_{50} of 433 nmol/L. The proliferation of the K562 cells is considered to depend on wild-type Abl signaling. In addition, nintedanib inhibited Src, Lck, and Lyn with IC_{50} values of 156, 16, and 195 nmol/L, respectively. C_{max} of nintedanib was 73.6 nmol/L in Japanese patients with idiopathic pulmonary fibrosis (IPF) receiving nintedanib 150 mg twice daily. These results suggest that Lck may be inhibited at the clinical dose of nintedanib. However, in the global phase III studies (pooled data from Studies 1199.32 and 1199.34), the incidences of adverse events under the System Organ Class "immune system disorders" which may be induced by the inhibition of Lck were comparable between the nintedanib group (0.6%, 4 of 638 subjects) and the placebo group (0.2%, 1 of 423 subjects), and no serious adverse events were reported. Therefore, the inhibition of Abl kinase activity by nintedanib is unlikely to pose safety concerns.

(b) Inhibition of receptor phosphorylation, cell proliferation, and cell migration (4.2.1.1-3, 4.2.1.1-4, 4.2.1.1-6, 4.2.1.1-17 to 4.2.1.1-20)

The inhibitory effects of nintedanib and its metabolite (m1) on the autophosphorylation of PDGFR-α and PDGFR-β induced by a PDGF subtype BB (PDGF-BB) (50 ng/mL) were investigated in lung fibroblasts derived from healthy subjects. IC_{50} values of nintedanib against PDGFR-α and PDGFR-β were 21.6 and 38.7 nmol/L, respectively, and those of m1 were 5717 and 23,510 nmol/L, respectively. Nintedanib inhibited cell proliferation induced by PDGF-BB (50 ng/mL), with IC_{50} of 64 nmol/L.

The inhibitory effect of nintedanib on cell proliferation induced by PDGF-BB (10 ng/mL), basic FGF (bFGF) (10 ng/mL), or VEGF (10 ng/mL) was investigated in lung fibroblasts derived from patients with IPF and non-fibrotic control donors. IC_{50} values in patient-derived cells were 11, 5.5, or <1 nmol/L, respectively, and those in donor-derived cells were 13, 0.6, or <1 nmol/L, respectively. The inhibitory effect of nintedanib against fibroblast migration stimulated by PDGF-BB (5 ng/mL), bFGF (5 ng/mL), or VEGF (5 ng/mL) was investigated in lung fibroblasts derived from patients with IPF and control donors. Nintedanib inhibited the PDGF-BB-, bFGF-, and VEGF-stimulated migration of the patient-derived cells at the concentrations of ≥100, ≥1000, and ≥100 nmol/L, respectively, and that of the donor-derived cells at the concentrations of ≥1000, ≥100, and ≥1000 nmol/L, respectively.

Human PDGFR-α was expressed in mouse embryonic fibroblast cells (NIH3T3 cells), and the inhibitory effect of nintedanib on the autophosphorylation of human PDGFR-α stimulated by PDGF-AB (100 ng/mL) was investigated using the NIH3T3 cells. IC_{50} of nintedanib was 54 nmol/L by Western blot and was 60 nmol/L by enzyme-linked immunosorbent assay.

Mouse VEGFR-3 was expressed in porcine aortic endothelial cells, and the inhibitory effect of nintedanib on the autophosphorylation of the mouse VEGFR-3 was investigated by Western blot in the presence of the culture supernatants of human embryonic kidney cell line (HEK293 cells) expressing VEGF-C. Nintedanib almost completely inhibited the autophosphorylation of VEGFR-3 at the concentration of ≥10 nmol/L, with IC_{50} of <10 nmol/L.

The persistence of inhibitory effect of nintedanib on receptor activation was investigated. VEGFR-2 was expressed in NIH3T3 cells, and the cells were treated with nintedanib (200 nmol/L) for 1 hour. Receptor phosphorylation stimulated by VEGF (50 ng/mL) was then measured 8, 24, or 32 hours after the removal of nintedanib. The ≥90% inhibitory effect persisted until 32 hours after the removal of nintedanib. The persistence of inhibitory effect of nintedanib on PDGFR-α and -β activation was also investigated in normal human lung fibroblasts (NHLFs). NHLFs were treated with nintedanib (50 nmol/L) for 30 minutes, then PDGF-BB (50 ng/mL) was added to the cells 2 to 32 hours after the removal of nintedanib. The inhibition rates at 8, 24, and 32 hours after the removal of nintedanib were 16.9% to 27.3%, 8.6% to 16.2%, and 3.6% to 8.0%, respectively, and the inhibitory effect partially remained until 24 hours after the removal of nintedanib.

(c) Inhibition against transformation (4.2.1.1-9)

The inhibitory effect of nintedanib on the transformation of fibroblasts into myofibroblasts induced by transforming growth factor-β (TGF-β) (0.4 nmol/L) was investigated using primary human fibroblasts. The mRNA expression of α-smooth muscle actin (αSMA), a myofibroblast differentiation marker, was inhibited in a nintedanib-concentration dependent manner with IC_{50} values of 100 to 1000 nmol/L.

(d) Inhibition against growth and intracellular signaling of endothelial cells and perivascular cells (4.2.1.1-13)

The inhibitory effect of nintedanib on the proliferation of human umbilical vein endothelial cells (HUVEC) stimulated by VEGF (5 ng/mL), human umbilical artery smooth muscle cells (HUASMC) stimulated by PDGF-BB (15 ng/mL), and bovine retinal pericytes (BRP) stimulated by PDGF-BB (15 ng/mL) was investigated and their IC_{50} values were 9, 43, and 79 nmol/L, respectively. In addition, the inhibitory effect of nintedanib on mitogen-activated protein kinase (MAPK) and serine/threonine protein kinase (Akt) signal transduction pathways was investigated. Nintedanib inhibited the phosphorylation of MAPK and Akt and induced apoptosis in a concentration dependent manner.

3.(i).A.(1).2) *In vivo* pharmacology studies

(a) Investigation of prophylactic and therapeutic treatments in a rat bleomycin-induced lung fibrosis model (4.2.1.1-8, 4.2.1.1-10)

The effects of nintedanib administered before and after the onset of pulmonary fibrosis were investigated using a rat model of bleomycin-induced lung fibrosis. Bleomycin was intratracheally administered to male rats (n = 10/group) in a single dose of 2.2 mg/kg to induce lung fibrosis. Starting on the day after the administration of bleomycin, nintedanib was orally administered once daily for 21 days at 0 (vehicle, 0.1% hydroxyethylcellulose), 10, 30, or 50 mg/kg (prophylactic treatment). In the nintedanib groups, pulmonary fibrotic change (qualitative) and the expression of TGF-β1 and procollagen I mRNAs, which are considered associated with the fibrotic change, were inhibited in a dose-dependent manner as compared with the vehicle group. Starting at 10 days after the administration of bleomycin, nintedanib was orally administered once daily for 12 days at 0 (vehicle, 0.1% hydroxyethylcellulose) or 50 mg/kg (therapeutic treatment). In the nintedanib 50 mg/kg group, no pulmonary fibrotic change was observed and the expression of TGF-β1 and procollagen I mRNAs were inhibited as compared with the vehicle group.

(b) Investigation of prophylactic and therapeutic treatments in a mouse bleomycin-induced lung fibrosis model (4.2.1.1-16)

The effects of nintedanib administered before and after the onset of pulmonary fibrosis were investigated using a mouse model of bleomycin-induced lung fibrosis. Bleomycin was intranasally administered to female mice (n = 10/group) in a single dose of 3 mg/kg to induce lung fibrosis. Starting on the day of the administration of bleomycin, nintedanib was orally administered once daily for 15 days at 0 (vehicle, normal saline), 30, or 60 mg/kg (prophylactic treatment). In the nintedanib ≥30 mg/kg groups, lung inflammation was reduced as compared with the vehicle group. This was demonstrated by findings such as decreases in lymphocyte count in bronchoalveolar lavage fluid (BALF) and interleukin (IL)-1β level in lung tissue. Reduced pulmonary fibrosis was also demonstrated by decreases in tissue inhibitor of metalloproteinase 1 (TIMP-1) and total collagen levels in lung tissue. Starting at 7 days after the administration of bleomycin, nintedanib was orally administered once daily for 15 days at a dose of 0 (vehicle, normal saline), 30, or 60 mg/kg (therapeutic treatment). In the 60 mg/kg group, lung inflammation was reduced as compared with the vehicle group. This was demonstrated by decreases in lymphocyte count in the BALF and IL-1β level in lung tissue. Reduced pulmonary fibrosis was also demonstrated by decreases in TIMP-1 and total collagen levels in lung tissue.

(c) Investigation of prophylactic and therapeutic treatments in a mouse silica-induced lung fibrosis model (4.2.1.1-15)

The effects of the nintedanib administered before and after the onset of pulmonary fibrosis were investigated using a mouse model of silica-induced lung fibrosis. Silica was intranasally administered to female mice (n = 10/group) in a single dose of 2.5 mg to induce lung fibrosis. Starting on the day of the administration of silica, nintedanib was orally administered once daily for 31 days at 0 (vehicle, normal saline), 30, or 100 mg/kg (prophylactic treatments). In the nintedanib ≥30 mg/kg groups, lung inflammation accompanied by granuloma and fibrosis was reduced as compared with the vehicle group. This was demonstrated by findings such as decreases in neutrophil and lymphocyte counts in the BALF, IL-1β, chemokine ligand-1/keratinocyte chemoattractant (CXCL1/KC), TIMP-1, and total collagen levels in lung tissue. Further, nintedanib was orally administered once daily at 0 (vehicle, normal saline), 30, or 100 mg/kg (therapeutic treatment) for 21 days starting at 10 days after the administration of silica or for 11 days starting at 20 days after the administration of silica. In the nintedanib ≥30 mg/kg groups, neutrophil and lymphocyte counts in the BALF and total collagen level in lung tissue decreased as compared with the vehicle group. Changes in IL-1β, CXCL1/KC, and TIMP-1 levels in lung tissue were smaller than those following the prophylactic administration.

3.(i).A.(2) Secondary pharmacodynamics

3.(i).A.(2).1) Effects on the receptors and ion channels (4.2.1.1-1, 4.2.1.1-11)

The effects of nintedanib at 5 μmol/L on 50 types of receptors and ion channels were investigated *in vitro*. Nintedanib produced a ≥50% inhibition of ligand binding to the following receptors and ion channels: serotonin 1B receptor (102%), neurokinin 2 receptor (84%), adenosine A3 receptor (66%), L-type Ca^{2+} channel (65%), A2A adenosine receptor (56%), M2 muscarine receptor (54%), and H2 histamine receptor (51%). The concentration of nintedanib (5 μmol/L) was ≥60 times C_{max} (73.6 nmol/L) of nintedanib in IPF patients receiving oral nintedanib 150 mg twice daily.

3.(i).A.(3) Safety pharmacology

3.(i).A.(3).1) Effects on central nervous system (4.2.1.3-2)

Following a single oral administration of nintedanib at 0 (vehicle, 0.5% hydroxyethylcellulose), 3, 20, or 100 mg/kg to rats (n = 4/sex/group), the effects on general symptoms, behavior, body temperature, and locomotor activity were investigated by modified Irwin test. In any group, there were no effects on the general symptoms, behavior, locomotor activity, body temperature, or the other physiological conditions.

3.(i).A.(3).2) Effects on cardiovascular system

(a) *In vivo* Study (4.2.3.2-18, 4.2.1.2-6, 4.2.1.2-9)

The effects of nintedanib on the cardiovascular system was investigated in the 4-week repeated oral dose toxicity study in cynomolgus monkeys (n = 3-5/sex/group). Nintedanib (as ethanesulfonate) was orally administered at 0 (vehicle, 0.5% hydroxyethylcellulose), 3, 15, or 60 mg/kg for 28 days. In the nintedanib 60 mg/kg group, mildly increased heart rate was observed at 2 hours after the first dose (5.7%

as compared with the vehicle group), but no effects on the cardiovascular parameters such as systolic and diastolic blood pressure, heart rates, and electrocardiogram (ECG) parameters were observed in the ≤15 mg/kg groups. In the 60 mg/kg group, C_{max} of nintedanib was 272 ng/mL, which was approximately 6.9 times that (39.7 ng/mL) in Japanese patients with IPF receiving oral nintedanib 150 mg twice daily.

The effects of nintedanib on the cardiovascular system were investigated following a single oral administration of nintedanib hydrochloride at 0 (vehicle, 1% hydroxyethylcellulose), 10, 30, or 100 mg/kg to male rats (n = 8/group). Systemic arterial blood pressure increased in a dose dependent manner at 2 hours post-dose. In the 100 mg/kg group, increased systolic blood pressure was observed (by a maximum of 10 mm Hg as compared with the vehicle group), but heart rates remained unchanged despite the increased blood pressure. In the 100 mg/kg group, C_{max} of nintedanib was estimated to be 210 ng/mL,[1] which was approximately 5.3 times that (39.7 ng/mL) in Japanese patient with IPF receiving oral nintedanib 150 mg twice daily.

The effects of nintedanib on the cardiovascular system were investigated following a single continuous intravenous infusion of nintedanib hydrochloride at 0 (vehicle, 5% glucose), 3, 10, or 30 mg/kg to male pigs (n = 5/group). In the ≤10 mg/kg groups, no effects on heart rates and systolic and diastolic blood pressure were observed. In the 30 mg/kg group, decreased systolic and diastolic blood pressures at 30 minutes post dose (a decrease of 15 to 20 mm Hg compared with the control group) and increased heart rate associated with the decreased blood pressure (a rise of 10 bpm compared with the control group) were observed. The QT interval was shortened in the ≥3 mg/kg groups, and the QRS duration tended to prolong in the 30 mg/kg group but these parameters returned to normal immediately after the end of administration. In the 30 mg/kg group, C_{max} of nintedanib was 8538 ng/mL, which was approximately 220 times that (39.7 ng/mL) in Japanese patients with IPF receiving oral nintedanib 150 mg twice daily.

(b) Effects on hERG current and action potential (4.2.1.2-5)

The effects of nintedanib on hERG current were investigated in HEK293 cells expressing hERG potassium channel by whole-cell patch clamping. Nintedanib at 0.1, 1, 3, and 10 μmol/L inhibited the hERG current in a concentration dependent manner. IC_{50} of nintedanib was 4.0 μmol/L and was ≥50 times C_{max} (73.6 nmol/L) in patients with IPF receiving oral nintedanib 150 mg twice daily.

The effects of nintedanib at 0.1, 0.3, 1, 3, or 10 μmol/L on action potential waveform were investigated in isolated guinea pig papillary muscle cells, based on action potential duration (APD) 10%, 30%, and 90% repolarization (APD10, APD30, and APD90, respectively). At any concentration, no effects were observed on the action potential duration, resting membrane potential, action potential amplitude, or maximum depolarization rate.

3.(i).A.(3).3) Effects on respiratory system (4.2.1.3-1)

The effects of nintedanib on the respiratory function were investigated by whole-body plethysmography following a single oral administration of nintedanib (as ethanesulfonate) at 0 (vehicle, 0.5% hydroxyethylcellulose), 3, 20, or 100 mg/kg to rats (n = 4/sex/group). In any group, there were no effects on the respiratory rate, tidal volume, or minute ventilation.

3.(i).A.(3).4) Effects on renal and hepatic functions (4.2.1.2-4, 4.2.1.2-10)

The effects of nintedanib on the hepatic functions were investigated following a single oral administration of nintedanib hydrochloride at 0 (vehicle, 1% hydroxyethylcellulose), 30, 100, or 300 mg/kg to rats (n = 10/sex/group). Findings included decreases in blood magnesium and chloride concentrations at 8 hours post dose and increases in alanine aminotransferase (ALT), glutamate dehydrogenase (GLDH), and free fatty acid at 24 hours post dose in the ≥100 mg/kg groups, and increased free calcium at 8 hours post dose and increases in triglycerides and total bilirubin at 24 hours post dose in the 300 mg/kg group.

The effects of nintedanib on renal and hepatic functions were investigated following oral administration of nintedanib hydrochloride at 0 (vehicle, 1% hydroxyethylcellulose), 10, 30, or 100 mg/kg to rats (n = 5/sex/group) for 7 days. In the 100 mg/kg group, increased serum ALT, triglyceride, and calcium

[1] As the exposure to nintedanib hydrochloride was comparable to that to nintedanib ethanesulfonate (4.2.2.2-1), the value was estimated from the toxicokinetics study data on nintedanib (4.2.3.2-6, 4.2.3.2-7, 4.2.3.2-9, 4.2.3.2-8, 4.2.3.4.1-2).

concentrations were observed 7 days after dosing. Increased urine calcium at 4 to 8 hours post dose was observed in the ≥30 mg/kg groups, and increased urine volume, urine sodium, and urine β-N-acetylglucosaminidase at 4 to 8 hours post dose in the 100 mg/kg group. In the 30 mg/kg group, C_{max} of nintedanib was estimated to be 210 ng/mL,[2] which was approximately 5.3 times that (39.7 ng/mL) in Japanese patients with IPF receiving oral nintedanib 150 mg twice daily.

3.(i).A.(3).5) Effects on gastrointestinal transit (4.2.1.2-2, 4.2.1.2-3)

The effect of nintedanib on gastric emptying was investigated. Fasted rats (n = 5/sex/group) received oral nintedanib hydrochloride at a single dose of 0 (vehicle, 1% hydroxyethylcellulose), 10, 30, or 100 mg/kg and were fed with a specified amount of food 30 minutes later. At 1 hour after the start of feeding, the stomach weight was measured. In the ≤30 mg/kg groups, there were no effect on the gastric emptying, but in the 100 mg/kg group, suppressed gastric emptying (+232% as compared with the vehicle group) was observed. In the 100 mg/kg group, C_{max} of nintedanib was estimated to be 210 ng/mL,[2] which was approximately 5.3 times that (39.7 ng/mL) in Japanese patients with IPF patients receiving oral nintedanib 150 mg twice daily.

The effect of nintedanib on gastrointestinal propulsion was investigated based on the intestinal transit rate of barium sulfate as an indicator. Rats (n = 5/sex/group) received oral nintedanib hydrochloride at a single dose of 0 (vehicle, 1% hydroxyethylcellulose), 10, 30, or 100 mg/kg, and received oral barium sulfate 30 minutes later. In the 10 mg/kg group, there was no effect on the gastrointestinal transit. In the 30 mg/kg and 100 mg/kg groups, however, the gastrointestinal propulsion was suppressed in a dose-dependent manner (decreases of 28% and 40%, respectively, compared with the vehicle group). In the 30 mg/kg group, C_{max} of nintedanib was estimated to be 57 ng/mL,[2] which was approximately 1.4 times that (39.7 ng/mL) in Japanese patients with IPF receiving oral nintedanib 150 mg twice daily.

3.(i).B Outline of the review by PMDA

3.(i).B.(1) Pharmacologic effects of nintedanib

The applicant's explanation the mechanism of the action of nintedanib on IPF:

According to a report, fibrosis such as IPF is caused by the unregulated proliferation of fibroblasts. Fibroblasts differentiate into myofibroblasts that secrete extracellular matrix (ECM) proteins, and excessive ECM depositing on the alveolar wall causes alters alveolar architecture and impairs gas exchange (King TE et al., *Lancet*. 2011;378:1949-1961.). Other reports explained that PDGF, which promotes the proliferation, migration, and survival of myofibroblasts, is involved in the development of pulmonary fibrosis (Bonner JC, *Cytokine Growth Factor Rev.* 2004;15:255-273), that patients with IPF showed enhanced FGF and FGFR-1 expressions in epithelial, endothelial, and smooth muscle cells/myofibroblast-like cells and enhanced FGFR-2 expression in the interstitial cells in lung tissue (Inoue Y et al., *Am J Respir Crit Care Med.* 2002;166:765-773), and that patients with IPF having high serum VEGF concentrations tended to have lower survival rates (Ando M et al., *Lung.* 2010;188:247-252).

Pharmacology data showed that nintedanib selectively inhibited PDGFR, FGFR, and VEGFR, thereby suppressed PDGF-, bFGF-, or VEGF-stimulated cell proliferation and migration and the transformation of fibroblasts. The data also showed that nintedanib slowed disease progression in the animal models of pulmonary fibrosis. This suggested that nintedanib slows the progression of IPF by inhibiting receptor tyrosine kinases such as PDGFR, FGFR and VEGFR.

Based on the submitted data, PMDA has concluded that nintedanib inhibits PDGFRα and β, FGFR1 to 3, and VEGFR and that the results from studies using animal models have indicated potential therapeutic effect of nintedanib on IPF.

3.(i).B.(2) Effects of nintedanib on gastrointestinal transit

PMDA asked the applicant to explain how nintedanib affected the gastrointestinal transit in the safety pharmacology studies.

[2] As the exposure to nintedanib hydrochloride was comparable to that of nintedanib (4.2.2.2-1), the value was estimated from the toxicokinetics study data on nintedanib (4.2.3.2-6, 4.2.3.2-7, 4.2.3.2-9, 4.2.3.2-8, 4.2.3.4.1-2).

The applicant's explanation:
In the safety pharmacology studies, gastrointestinal transit was reduced in a dose-dependent manner in the ≥30 mg/kg groups. However, in the repeat-dose toxicity study in rats (4.2.3.2-9), there were no findings suggesting ingested substances or feces retained in the gastrointestinal tract following the 26-week administration of nintedanib at 80 mg/kg/day.

According to several reports, gastrointestinal motility is regulated intricately by various cells such as intestinal cells of Cajal (ICC) and PDGFRα-expressing fibroblast-like cells. The administration of Kit-neutralizing antibody, a PDGFR-like structured receptor tyrosine kinase, to rats removes the ICC located in the plexuses between the circular layer and longitudinal muscular layer in the small intestine, leading to the disappearance of slow waves generated by the ICC (Sanders KM et al., *Annu Rev Physiol.* 2006;68307-68343, Grover M et al., *Neurogastroenterol Motil*. 2012;24:844-852, Vannucchi MG et al., *J Cell Mol Med.* 2013;17:1099-1108). Given these findings, the inhibition of PDGFRα may have affected the gastrointestinal transit.

PMDA's view:
It is unknown whether the inhibitory effect of nintedanib on gastrointestinal transit is relevant to humans. However, gastrointestinal disorders such as diarrhea were also reported in association with the use of PDGFR, FGFR, and EGFR inhibitors. Risks of adverse drug reactions associated with the pharmacological effects of nintedanib in clinical use should be carefully assessed based on the clinical study data [see "4. Clinical data"].

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

The results of studies of oral or intravenous nintedanib in mice, rats, rabbits, and monkeys were submitted as data on absorption, distribution, metabolism, excretion, and drug interaction of nintedanib. In the pharmacokinetic studies, ^{14}C-labeled or non-radiolabeled nintedanib was used. The plasma concentrations of unchanged nintedanib were determined by high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) (lower limit of quantitation: 2.50 ng/mL in mouse plasma; 1.00 ng/mL in rat, rabbit, and cynomolgus monkey plasma; 0.500 ng/mL in rhesus monkey plasma). Radioactivity concentrations in plasma, urine, feces, and bile were determined by liquid scintillation counter, and tissue radioactivity concentrations by whole-body autoradiography and liquid scintillation counter.

Unless otherwise specified, the dose of nintedanib is expressed as the free base, and the pharmacokinetic parameters are expressed as the mean or mean ± standard deviation (SD).

3.(ii).A.(1) Absorption

3.(ii).A.(1).1) Single dose studies (4.2.2.2-1, 4.2.2.2-3, 4.2.3.2-16, 4.2.3.2-19)

Pharmacokinetic parameters of plasma concentrations of unchanged nintedanib in female and male mice, male rats, female and male cynomolgus monkeys, and female and male rhesus monkeys following a single oral or intravenous administration of nintedanib are shown in Table 3. C_{max} and AUC increased with the increasing dose. There were no clear sex-related differences, although exposure to nintedanib tended to be higher in females than in males in some studies. The bioavailability of oral nintedanib was 11.9% in rats, 23.8% in rhesus monkeys, and was 13.2% in cynomolgus monkeys. Following a single dose of 50 mg/kg of nintedanib, C_{max} values of a metabolite of nintedanib (m1) were 61.2 ± 10.1 ng/mL in male mice and 88.6 ± 59.7 ng/mL in female mice. $AUC_{0-\infty}$ values in male and female mice were 324 ± 67.9 and 423 ± 162 ng·h/mL, respectively, and $t_{1/2}$ values were3.18 ± 0.82 and 3.88 ± 0.63 hours, respectively. T_{max} (median [range]) was 2 (1-2) hours in both male and female mice.

Table 3. Pharmacokinetic parameters of unchanged nintedanib in mice, rats, and monkeys following a single-dose administration of nintedanib

Animal	Dose (mg/kg)	Number of animals	Route of administration	Unchanged nintedanib					
				C_{max} (ng/mL)	T_{max} (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	CL (mL/min/kg)	Vss (L/kg)
Mouse	50	5 males	p.o.	402 ± 69.2	2	2230 ± 247	5.17 ± 1.16	-	-
		5 females		692 ± 270	2	3220 ± 951	5.13 ± 1.73	-	-
Rat	2	4 males	i.v.	124	ND	181	3.95	202	41.2
	30		p.o.	48.6	2	293[a)]	-	-	-
	50			105	2	375[a)]	-	-	-
	100			180	3	1330[a)]	-	-	-
	300			299	8	4290[a)]	-	-	-
Rhesus monkey	5	2 males	i.v.	1100	ND	2940	7.03	29.9	10.5
		2 females		1080	ND	2730	7.15	30.6	10.3
	10	2 males	p.o.	93.3	3	740[a)]	ND	-	-
		2 females		72.6	2	529[a)]	ND	-	-
	40	2 males		384	3	5630[a)]	ND	-	-
		2 females		238	3	3250[a)]	ND	-	-
	80	1 male		597	8	10,300[a)]	ND	-	-
		1 female		588	8	8850[a)]	ND	-	-
Cynomolgus monkey	1	1 male	i.v.	153	ND	346	9.89	48.2	19.3
		1 female		310	ND	429	6.27	38.9	8.85
	5	1 male		956	ND	1970	5.73	42.3	10.0
		1 female		1640	ND	2550	6.17	32.6	7.27
	20	1 male	p.o.	107	2	1040[a)]	ND	-	-
		1 female		127	4	1340[a)]	ND	-	-
	40	1 male		140	4	1570[a)]	ND	-	-
		1 female		210	8	3200[a)]	ND	-	-
	80	1 male		351	8	6540[a)]	ND	-	-
		1 female		284	8	4870[a)]	ND	-	-
	160	1 male		629	24	12,600[a)]	ND	-	-
		1 female		759	8	15,600[a)]	ND	-	-

Mean or mean ± SD, T_{max} is expressed in median.
ND, not determined; -, no data available; C_{max}, maximum plasma concentration; T_{max}, time to reach the maximum concentration; AUC, area under the concentration-time curve; $t_{1/2}$, elimination half-life; CL, systemic clearance; Vss, volume of distribution at a steady state; p.o., oral dose; i.v., intravenous dose
a) AUC_{0-24} (ng·h/mL)

3.(ii).A.(1).2) Repeat-dose studies (toxicokinetics) (4.2.3.2-2, 4.2.3.2-9, 4.2.3.2-17 to 4.2.3.2-18, 4.2.3.2-20 to 4.2.3.2-21, 4.2.3.4.1-2)

Toxicokinetics was investigated in oral dose toxicity studies, etc. over 13 weeks in mice, 26 and 104 weeks in rats, 4 and 52 weeks in rhesus monkeys, 4 and 13 weeks in cynomolgus monkeys. The pharmacokinetic parameters following repeat-dose administration are shown in Table 4. There was no accumulation of nintedanib after repeated dosing.

Table 4. Pharmacokinetic parameters of unchanged nintedanib and its metabolite in mice, rats, and monkeys following repeat-dose administration

	Treatment period	Dose (mg/kg/day)	Number of animals	Route of administration	Measurement time point	Male		Female	
						C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)
Unchanged nintedanib									
Mouse	13 weeks	10	4	p.o.	Day 1	51.9	207	53.9	257
					Day 87	57.7	225	56.2	231
		30	4		Day 1	217	1280	426	2260
					Day 87	262	1280	241	1350
		100	4		Day 1	1100	7700	1350	6210
					Day 87	1450	5630	600	3840
Rat	26 weeks	5	6	p.o.	Day 1	3.38	13.7	5.76	24.6
					Day 179	5.12	16.4	9.70	29.2
		20	6		Day 1	29.7	154	61.6	232
					Day 179	41.1	184	78.4	316
		80	6		Day 1	378	1270	465	1960
					Day 164	173	1240	168	1030
	104 weeks	5	4	p.o.	Week 1	0.71	1.06	1.13	3.63
					Week 52	7.16	37.7	2.71	14.0
		10	4		Week 1	4.74	12.1	7.32	22.6
					Week 52	8.36	78.0	11.3	87.9
Rhesus monkey	4 weeks	10	3	p.o.	Day 1	71.7	537	91.1	624
					Day 28	51.4	357	75.2	529
		20	3		Day 1	151	1060	104	938
					Day 28	121	755	151	1360
		60	5		Day 1	280	3270	256	2600
					Day 28	222	2830	285	3620
	52 weeks	10	4	p.o.	Day 1	120	979	67.8	595
					Day 363	77.6	786	53.7	506
		20	4		Day 1	133	1150	189	1730
					Day 363	92.0	831	132	1220
Cynomolgus monkey	4 weeks	3	3	p.o.	Day 1	24.2	228	17.8	176
					Day 28	15.1	158	18.7	185
		15	3		Day 1	102	1170	124	1490
					Day 28	135	1600	93.6	1030
		60	4-5		Day 1	321	4920	275	4520
					Day 14	299	4980	245	4740
	13 weeks	3	3	p.o.	Day 1	38.5	307	33.5	330
					Day 91	38.3	305	37.2	345
		15	3		Day 1	137	1430	103	1100
					Day 91	140	1370	131	1310
		30/20[a)]	5		Day 1	224	2300	177	2070
					Day 91	170	1870	119	1320
m1									
Mouse	13 weeks	10	4	p.o.	Day 1	5.68	7.68	10.2	36.2
					Day 87	4.38	10.4	16.6	71.4
		30	4		Day 1	27.3	186	81.6	369
					Day 87	29.8	162	78.2	458
		100	4		Day 1	139	847	263	1030
					Day 87	339	1010	410	1800
Rat	104 weeks	5	4	p.o.	Week 1	3.37	7.27	7.18	16.7
					Week 52	16.4	115	13.0	96.5
		10	4		Week 1	14.2	37.6	22.6	73.9
					Week 52	18.5	199	51.2	287
Rhesus monkey	52 weeks	10	3-4	p.o.	Day 1	8.21	81.9	4.32	50.8
					Day 363	5.95	85.7	3.64	47.9
		20	3-4		Day 1	8.39	85.4	12.0	147
					Day 363	4.80	59.7	7.17	90.6
m2 (glucuronate conjugate of m1)									
Mouse	13 weeks	10	4	p.o.	Day 1	61.9	197	58.4	194
					Day 87	46.6	159	79.9	236
		30	4		Day 1	199	844	202	1100
					Day 87	215	757	242	1180
		100	4		Day 1	491	2480	626	2850
					Day 87	951	4510	1070	5590
Rat	104 weeks	5	4	p.o.	Week 1	135	568	261	1000
					Week 52	572	2920	762	3050
		10	4		Week 1	338	1150	383	1450
					Week 52	1150	4650	1340	6480

Mean

C_{max}, maximum plasma concentration; AUC, area under the concentration-time curve

[a)] 30 mg/kg/day until Day 13, withdrawal from Day 14 to Day 16, 20 mg/kg/day from Day 17 to Day 91

3.(ii).A.(2) Distribution

3.(ii).A.(2).1) Tissue distribution (4.2.2.3-1, 4.2.2.3-4)

A single dose of 30 mg/kg of ^{14}C-labeled nintedanib was orally administered to male albino rats (n = 1/time point). Radioactivity was distributed throughout the body until 8 hours. The maximum radioactivity concentration was achieved in blood at 30 minutes post-dose; in the tongue, myocardium, liver, and kidney at 2 hours post dose; and in the eyes, Harderian gland, pituitary gland, brown adipose tissue, salivary gland, thymus, lungs, spleen, adrenal gland, bone marrow, muscle, testis, and skin at 8 hours post-dose. Radioactivity was detected in the eyes, Harderian gland, pituitary gland, salivary gland, liver, spleen, kidney, and bone marrow at 24 hours post-dose but was not detected in any tissue at 168 hours post-dose. In the brain and spinal cord, radioactivity was below the lower limit of quantitation (158 ng eq./g) at any time point.

A single dose of 5 mg/kg of ^{14}C-labeled nintedanib was intravenously administered to male pigmented rats. Radioactivity was distributed in most tissues as observed in albino rats, but the radioactivity concentration in each tissue tended to be higher than that in albino rats. Especially, the radioactivity concentrations in the eyes and pituitary gland were higher than those in albino rats. At 168 hours post-dose, the radioactivity concentrations in the eyes and pituitary gland decreased to approximately 4% and 9%, respectively, as compared to those at 2 hours after dosing.

Repeated doses of 30 mg/kg/day of ^{14}C-labeled nintedanib were orally administered to male albino rats (n = 3/time point) for 13 days. Radioactivity concentrations in the testes, submandibular gland, liver, and epididymis were 7.9, 4.2, 3.3, and 3.2 times, respectively, higher than those following a single oral administration.

3.(ii).A.(2).2) Plasma protein binding and distribution in blood cells (4.2.2.3-2, 4.2.2.5-2, 5.3.2.1-1)

Human plasma protein-bound fractions of ^{14}C-labeled nintedanib at 50, 200, 1000, and 2000 ng/mL ranged from 97.7% to 98.0%, which were not clearly different from those in mice, rats, cynomolgus monkeys, and rhesus monkeys. Bound fractions of ^{14}C-labeled nintedanib to human serum albumin at 50 and 200 ng/mL ranged from 97.3% to 97.7%, while those in α1-acid glycoprotein (0.14-3.4 g/L) ranged from 50.8% to 93.5%, increasing with the increasing concentration of α1-acid glycoprotein.

Rat and human samples were treated with ^{14}C-labeled nintedanib at 500 ng/mL for 3 hours. The blood/plasma concentration ratios decreased time-dependently from 2.76 at 2 minutes post-treatment to 0.58 at 3 hours post-treatment in rats, and from 0.7 at 2 minutes post-treatment to 0.27 at 3 hours post-treatment in humans. In addition, a single dose of 30 mg/kg of ^{14}C-labeled nintedanib was orally administered to rats. The blood/plasma concentration ratios at 0.25 and 8 hours post-dose were 0.043 and 1.89, respectively.

3.(ii).A.(2).3) Plasma protein binding to nintedanib metabolite (5.3.2.1-2 to 5.3.2.1-3)

Plasma protein-bound fractions of ^{14}C-labeled m1, a metabolite of nintedanib, at 5, 100, and 1000 ng/mL in rats, rhesus monkeys, and humans were 75.0% to 79.3%, 51.8% to 57.2%, and 73.5% to 81.8%, respectively. Plasma protein binding rates of ^{14}C-labeled m2, a glucuronate conjugate of m1, at 0.1, 1, and 10 μmol/L in rats and rhesus monkeys were 94.9% to 96.2% and 83.1% to 83.8%, respectively. Human plasma protein binding rates of ^{14}C-labeled m2 at 0.1, 1, 10, and 100 μmol/L were 89.8% to 97.6%.

3.(ii).A.(3) Metabolism

3.(ii).A.(3).1) *In vitro* studies (5.3.2.2-1, 5.3.2.2-3, 5.3.2.2-5, 5.3.2.3-2)

In human liver microsomes incubated with ^{14}C-labeled nintedanib at 100 μmol/L, unchanged nintedanib, m1, m3, m4, and the hydroxy form of nintedanib were detected. The main components were unchanged nintedanib (approximately 72%) and m1 (23%). The formation of m1 was inhibited by approximately 98% in the presence of bis(p-nitrophenyl)phosphate sodium (BNPP), an esterase inhibitor, at 100 μmol/L. The metabolite m3 and hydroxy form of nintedanib are formed in the presence of BNPP. The formation of metabolite m3 and hydroxy form of nintedanib was inhibited by approximately 77% and 30%, respectively, in the presence of 1 μmol/L of ketoconazole that inhibits cytochrome P450 (CYP)3A.

The formation of both components were inhibited by approximately 50% in the presence of 100 μmol/L of quercetin that inhibits CYP2C8. In the presence of both ketoconazole and quercetin, the formation of the metabolite m3 and hydroxy form of nintedanib was inhibited by approximately 90% and 65%, respectively. In the presence of 20 μmol/L of furafylline that inhibits CYP1A2, 50 μmol/L of sulfaphenazole inhibiting CYP2C9, and 10 μmol/L of quinidine inhibiting CYP2D6, the formation of the metabolite m3 and the hydroxy form of nintedanib was inhibited by <10%. To identify CYP isoforms involved in the metabolism of nintedanib, 50 μmol/L of ^{14}C-labeled form of nintedanib was incubated with the recombinant human CYP expression system. The results suggested that CYP3A4 plays a main role in and CYP2C8 also contributes somewhat to the formation of m3. These findings indicate that nintedanib in humans is mainly metabolized through hydrolysis by esterase, and CYP3A4 and CYP2C8 are not largely involved.

Liver microsomes from rats, dogs, cynomolgus monkeys, and humans were incubated with m1, a metabolite of nintedanib, at 300 μmol/L at pH 7.0. The glucuronidation reaction rate was 330, 17, 57, and 96 pmol/min/mg, respectively. The investigation in insect cells expressing various human UDP-glucuronosyltransferases (UGTs) suggested that UGT1A1 is involved in the glucuronidation reaction of m1.

Small intestinal microsomes from rats and humans were incubated with m1 at 5 to 300 μmol/L. Glucuronate conjugates were detected in a dose-dependent manner. Insect cells expressing human UGT1A7, UGT1A8, and UGT1A10 were incubated with m1, and the Michaelis constants for the glucuronidation reaction of m1 were 31, 184, and 88 μmol/L, respectively.

3.(ii).A.(3).2) *In vivo* Studies (4.2.2.4-2 to 4.2.2.4-5, 5.3.3.1-2)

A single dose of ^{14}C-labeled nintedanib was orally administered at 30 mg/kg to male and female mice (n = 5/sex for feces and urine samples, n = 12/sex for plasma samples). In the males, unchanged nintedanib, m2 (glucuronate conjugate of m1), and m3 were detected in plasma until 4 hours post-dosing, m1 and m4 in urine until 48 hours post-dose, and unchanged nintedanib, m1, m3, and m4 in bile until 6 hours and in feces until 48 hours post-dose. In the females, unchanged nintedanib, m1, and m2 were detected in plasma until 4 hours post-dose, m1 in urine until 48 hours post-dose, unchanged nintedanib, m1, m3, m4, and m15 in bile until 6 hours post-dose, and unchanged nintedanib, m1, m3, and m4 in feces until 48 hours post-dose.

A single dose of ^{14}C-labeled nintedanib was administered intravenously at 5 mg/kg or orally at 30 mg/kg to male and female rats (n = 2/group). Unchanged nintedanib, m1, m2, and m3 were detected in urine until 24 hours post-dosing and in bile until 6 hours post-dose, and unchanged nintedanib, m1, m3, and m4 in feces until 24 hours post-dose, irrespective of administration route. Unchanged nintedanib, m1, m2, and m4 were detected in plasma until 4 hours post-oral dose, and unchanged nintedanib, m1, and m2 in plasma post-intravenous dose. No clear sex-related differences were observed.

A single dose of ^{14}C-labeled nintedanib was orally administered at 60 mg/kg to male rats (n = 1). Unchanged nintedanib was detected in plasma at 1 to 4 hours post-dose. Unchanged nintedanib, m1, m2, m4, m5, m7, and one unknown metabolite were detected in urine until 24 hours post-dose, and unchanged nintedanib, m1, m5, m7, and one unknown metabolite in bile until 6 hours post-dose.

A single dose of ^{14}C-labeled nintedanib was administered intravenously at 5 mg/kg or orally at 20 mg/kg to male and female rhesus monkeys (n = 3/sex), and metabolites were investigated. In the intravenous administration group, unchanged nintedanib, m1, and m2 were detected in plasma at 1 hour post-dose, unchanged nintedanib, m1 to m8, and m12 in urine until 24 hours post-dose, and unchanged nintedanib, m1, m3, m4, m5, m7, m9, and m14 in feces until 72 hours post-dose. In the oral administration group, unchanged nintedanib, m2, m3, and m13 were detected in plasma at 3 hours post- dose; unchanged nintedanib and m1 to m11 in urine until 24 hours post-dose, and unchanged nintedanib, m1, m3, m4, m5, m9, and m14 in feces until 72 hours post-dose. No clear sex-related differences were observed.

A single dose of 100 mg of ^{14}C-labeled nintedanib was orally administered to humans (8 male subjects). Unchanged nintedanib, m1, m2, and m7 were detected in plasma until 6 hours post-dose, unchanged

nintedanib, m1 to m5, and m7 to m10 in urine until 24 hours post-dose, and unchanged nintedanib, and m1 to m5 in feces until 72 hours post-dose.

From these studies, the metabolic pathways of nintedanib in mice, rats, monkeys, and humans are inferred as shown in Figure 1.

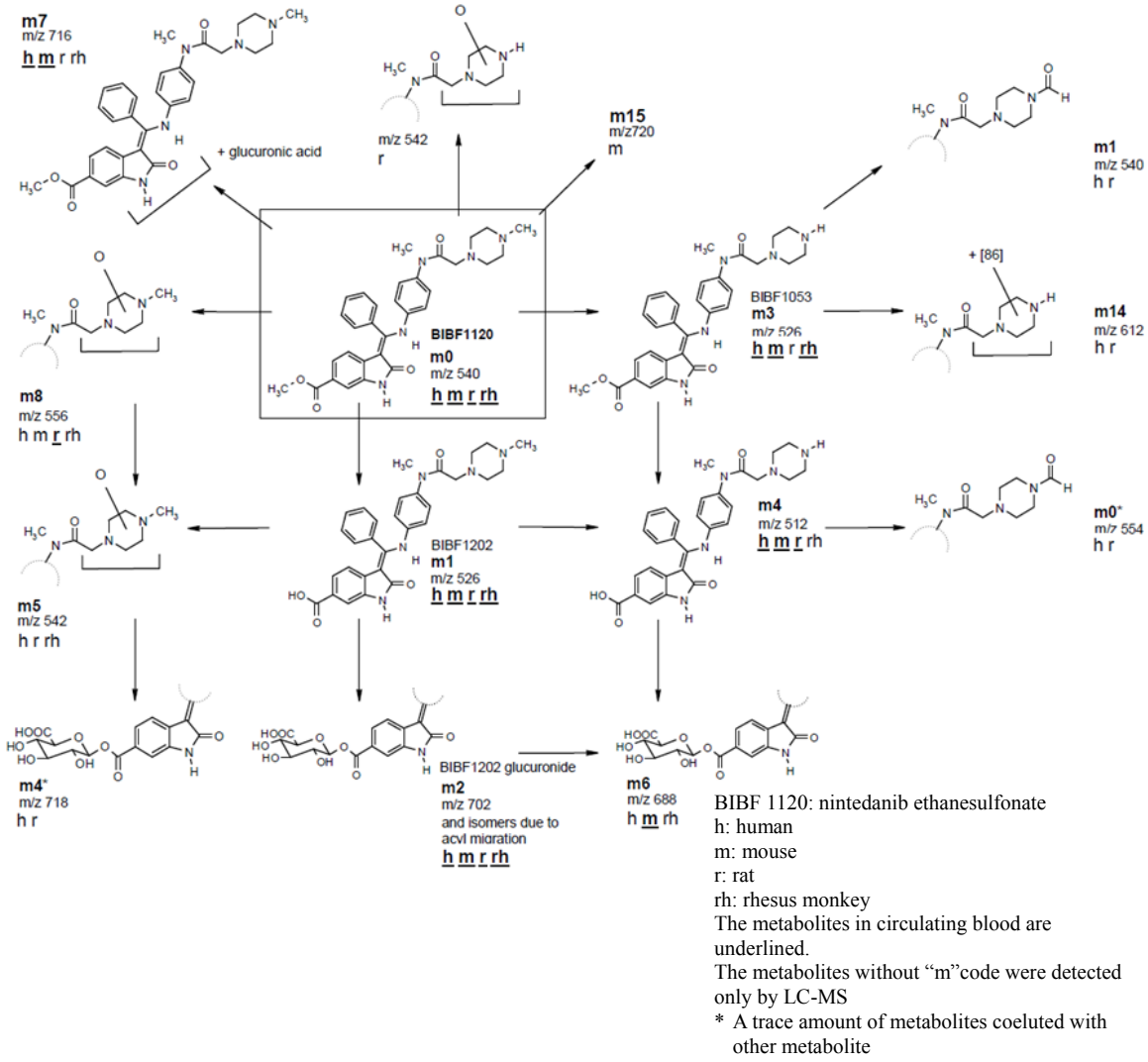


Figure 1. Inferred metabolic pathways of nintedanib in mice, rats, monkeys, and humans

3.(ii).A.(4) Excretion

3.(ii).A.(4).1) Excretion into urine, feces, and bile (4.2.2.3-4, 4.2.2.4-2 to 4.2.2.4-3, 4.2.2.4-5, 4.2.2.5-2, 5.3.3.1-1)

A single dose of ^{14}C-labeled nintedanib was orally administered at 30 mg/kg to male and female mice (n = 1/sex for urine and feces samples, n = 3/sex for bile samples). In the females and males, urinary excretion rates (% of the administered radioactivity) until 48 hours post-dose were 1.8% and 2.2%, respectively, and the fecal excretion rates were 90.6% and 99.3%, respectively. A single dose of ^{14}C-labeled nintedanib was administered intraduodenally at 30 mg/kg. The biliary excretion rates in the females and males until 6 hours post-dose were 20.3% and 10.1%, respectively.

A single dose of ^{14}C-labeled nintedanib was intravenously administered at 5 mg/kg or orally at 30 mg/kg to male rats (n = 4). The urinary and fecal excretion rates were 5.1% and 89.2%, respectively, until 168 hours post-intravenous dose and 1.3% and 98.5%, respectively, until 96 hours post-oral dose. When a single dose of ^{14}C-labeled nintedanib was intravenously administered at 5 mg/kg or intraduodenally at 30 mg/kg, the biliary excretion rates until 6 hours post-dose were 65.2% and 8.3%, respectively.

Repeated oral doses of ^{14}C-labeled nintedanib were administered at 30 mg/kg once daily to male rats (n = 3) for 13 days. The urinary and fecal excretion rates at 24 hours post-dose were 1.6% and 91.2%, respectively, showing no changes associated with the number of repeated doses.

A single of ^{14}C-labeled nintedanib was administered intravenously at 5 mg/kg or orally at 20 mg/kg to male and female rhesus monkeys (n = 3/sex). The urinary excretion rates until 168 hours post-intravenous and oral doses were 4.7% and 1.5%, respectively, and the fecal excretion rates were 84.4% and 85.7%, respectively. No clear sex-related differences were observed for either administration route.

A single dose of ^{14}C-labeled nintedanib was orally administered to humans (8 male subjects) at 100 mg. The urine excretion rate until 72 hours post-dosing was 0.65%, and the fecal excretion rate until 120 hours post-dosing was 93.4%.

3.(ii).A.(4).2) Excretion into milk (4.2.2.3-5)

A single dose of ^{14}C-labeled nintedanib was administered orally to lactating rats (n = 5/time point) at 30 mg/kg. The serum and milk radioactivity concentrations in maternal animals at 1 hour post-dose were 2260 ± 1020 and 269 ± 197 ng/mL, respectively, and $AUC_{0\text{-}24}$ values were 12,400 ± 5500 and 14,000 ± 5760 ng·h/mL, respectively, indicating that nintedanib is excreted into milk. The radioactivity excretion rates in milk at 24 hours post-dose were 0.18% to 0.45% of the dose.

3.(ii).A.(5) Pharmacokinetic drug interactions

3.(ii).A.(5).1) Enzyme inhibition and induction (4.2.2.6-1, 5.3.2.2-2, 5.3.2.2-5 to 5.3.2.2-9)

The inhibitory effect of nintedanib at 0.1, 1, 10, and 100 μmol/L (50 μmol/L for CYP2B6) on human CYP activities was investigated in human liver microsomes. The IC_{50} value of nintedanib against CYP3A4 activity was 70.1 μmol/L, and those on CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP4A11 activities were estimated to be greater than the defined maximum concentration (100 μmol/L or 50 μmol/L). M1, a metabolite of nintedanib, and m2, its glucuronate conjugate, did not inhibit the CYP activity at up to 100 μmol/L.

The inhibitory effect of nintedanib at 30, 75, and 150 μmol/L on the glucuronidation reaction of m1 mediated by human UGT1A1 was investigated in human liver microsomes. The IC_{50} of nintedanib was estimated to be 1.7 μmol/L.

The inhibitory effect of nintedanib at 0, 10, 25, 50, 75, 100, and 200 μmol/L was investigated in human liver microsomes. The IC_{50} value of nintedanib was 24.5 μmol/L against estradiol-3-glucuronidation reaction mediated by human UGT1A1 and was 77.6 μmol/L against estradiol-17-glucuronidation reaction mediated by UGT2B7.

The induction of human CYPs by nintedanib was investigated in human primary hepatocytes. Nintedanib at dose levels ranging from 0.001 to 2 μmol/L did not affect mRNA expression or enzymatic activity of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A.

Liver microsomes were prepared from male rats (n = 5) treated with nintedanib orally at 5 or 20 mg/kg/day for 4 days. A substrate of each CYP was added to the liver microsomes to investigate the impact of nintedanib on the CYP activities. Nintedanib did not affect any of CYP1A, CYP2B, CYP2E1, and CYP3A activities.

3.(ii).A.(5).2) Transporter (5.3.2.3-1, 5.3.2.3-3, 5.3.2.3-6)

The efflux ratios ($P_{app\ B\rightarrow A}/P_{app\ A\rightarrow B}$) of nintedanib at 29.5 μmol/L and m1 at 31.1 μmol/L in P-glycoprotein (P-gp)-expressing porcine kidney cell line were 23.3 and 1.12, respectively, suggesting that nintedanib is a substrate of P-gp. The inhibitory effect of nintedanib at 0.3, 3, and 30 μmol/L on the uptake of digoxin, a substrate of P-gp, was investigated in the same cell line. The uptake of digoxin decreased by approximately 23%, 27%, and 0%, respectively.

The efflux ratios ($P_{app\ B\rightarrow A}/P_{app\ A\rightarrow B}$) of nintedanib at 29.5 μmol/L and m1 at 31.1 μmol/L in Madin-Darby Canine Kidney (MDCK) II cell lines expressing multidrug resistance associated protein (MRP2) were

1.90 and 1.64, respectively, suggesting that neither nintedanib nor m1 is a substrate of MRP2. The inhibitory effect of nintedanib at 0.3, 3, and 30 μmol/L on the uptake of vinblastine, a substrate of MRP2, was investigated. The uptake of vinblastine remained nearly unaffected, with decreases approximately 0%, 5%, and 2%, respectively.

The efflux ratios ($P_{app\ B\rightarrow A}/P_{app\ A\rightarrow B}$) of nintedanib at 29.5 μmol/L and m1 at 31.1 μmol/L in breast cancer resistance protein (BCRP)-expressing MDCKII cell line were 2.65 and 0.82, respectively, suggesting that neither nintedanib nor m1 is a substrate of BCRP. The inhibitory effect of nintedanib at 0.3, 3, and 30 μmol/L on the uptake of prazosin, a substrate of BCRP, was investigated. The uptake of prazosin decreased by approximately 8%, 63%, and 51%, respectively.

The uptake of ^{14}C-labeled nintedanib at 11.8 μmol/L and ^{14}C-labeled m1 at 12.6 μmol/L was investigated using HEK293 cell line expressing human organic cation transporter (hOCT) 1, hOCT2, human organic anion transport polypeptide (hOATP) 1B1, hOATP1B3, or hOATP2B1. The results suggested that m1 is a substrate of hOATP1B1 and hOATP2B1. The inhibitory effects of nintedanib at 0.3 to 30 μmol/L and m1 at 1 to 100 μmol/L against the substrates of each transporter were investigated. The IC_{50} values of nintedanib against hOATP1B1, hOATP1B3, and hOATP2B1 were estimated to be ≥10 μmol/L, and those against hOCT1 and hOCT2 were estimated to be 0.88 μmol/L and ≥30 μmol/L, respectively. The IC_{50} values of m1 against hOATP1B1, hOATP1B3, hOATP2B1, hOCT1, and hOCT2 were estimated to be 14, 79, 50, 16 μmol/L, and ≥100 μmol/L, respectively.

The membrane transport assay indicated that m2 is a substrate of MRP2 and BCRP, not of hOCT1, hOATP1B1, hOATP1B3, or hOATP2B1. Up to 100 μmol/L of m2 did not inhibit P-gp, BCRP, MRP2, human organic anion transporter (hOAT) 1, hOAT3, hOATP1B1, hOATP1B3, or hOCT2.

3.(ii).B Outline of the review by PMDA

PMDA's view:

Following intravenous administration of ^{14}C-labeled nintedanib at a dose of 5 mg/kg to albino or pigmented rats, radioactivity concentrations at 2 hours post-dose were determined to analyze concentrations of radioactivity in tissues relative to blood. Radioactivity concentrations in the skin and eyes were 3.7 and 11 times, respectively, that in blood in albino rats, and 4.2 and 36 times, respectively, that in blood in pigmented rats, indicating more concentrated tissue distribution in pigmented rats than in albino rats. The results suggest that nintedanib potentially binds to melanin. Given these findings, nintedanib may be accumulated in the skin, etc. in Japanese patients than in Caucasian patients; and *in vitro* phototoxicity study has shown that nintedanib is phototoxic [see "3.(iii) Summary of toxicology studies"]. Therefore, the occurrence of phototoxicity-related events should be further investigated in patients treated with nintedanib through post-marketing surveillance.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

Toxicity studies of nintedanib include the studies on single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance, and other toxicities (studies on phototoxicity, hemolysis, and genotoxicity of impurities). In this section, the doses and blood concentrations of nintedanib are expressed as the free base.

3.(iii).A.(1) Single-dose toxicity (4.2.3.1-1 to 4.2.3.1-5, 4.2.3.2-15, 4.2.3.2-16, 4.2.3.2-19)

Oral and intravenous dose studies in mice and rats were conducted. The approximate lethal doses in both mice and rats were determined to be >2000 mg/kg in oral administration and >40 mg/kg in intravenous administration. In clinical observations, no changes related to nintedanib were observed in mice treated orally or intravenously or in rats treated intravenously. In rats treated orally, sedation, staggering gait, diarrhea, etc. were observed. Although single oral dose toxicity studies were not conducted in non-rodent animals, the approximate lethal doses in cynomolgus monkeys and rhesus monkeys were determined to be 80 to 160 mg/kg and 120 mg/kg, respectively, based on the results of the dose escalating studies in these animals.

3.(iii).A.(2) Repeat-dose toxicity

Repeated oral dose toxicity studies were conducted in mice (up to 13 weeks), rats (up to 26 weeks), beagle dogs (up to 2 weeks), cynomolgus monkeys (up to 13 weeks), and rhesus monkeys (up to 52 weeks). Major findings included thickening of the epiphyseal growth plate and decreased bone marrow cell count potentially attributable to the inhibition of cell proliferation by nintedanib in both rats and rhesus monkeys, dentopathy of the incisors in rats, and decreased spleen lymphocyte count in rhesus monkeys. The no observed adverse effect levels (NOAELs) are considered to be 5 mg/kg/day in the 26-week oral dose toxicity study in rats and 10 mg/kg/day in the 52-week oral dose toxicity study in rhesus monkeys. The ratios of animal to human exposures to nintedanib at the maximum recommended human dose were calculated by comparing the exposures of the animal species with the clinical data (C_{max}, 39.7 ng/mL; AUC_{τ}, 218 ng·h/mL; values obtained from Japanese patients with IPF receiving oral nintedanib 150 mg twice daily). The animal/human exposure ratios based on C_{max} and AUC were 0.13 to 0.24 and 0.075 to 0.13, respectively, for rats; and 1.35 to 1.95 and 2.32 to 3.61, respectively, for rhesus monkeys. Beagle dogs were found to be most sensitive to nintedanib among the studied animals due to many fatal cases resulting from gastrointestinal toxicity such as diarrhea and vomiting noted in a study. Nevertheless, given the tolerability to nintedanib observed in patients in early clinical studies, beagle dogs were considered inappropriate for the assessment of potential adverse effects on humans. The metabolite profiles in cynomolgus monkeys and rhesus monkeys were similar to those in humans. Increased hepatic enzymes were observed in a clinical study. On the basis of all these findings, the rhesus monkey was determined to be the appropriate non-rodent animal for the assessment of the effect of nintedanib on humans because of its substantially variable liver function parameters.

3.(iii).A.(2).1) Thirteen-week repeated oral dose toxicity study in mice (4.2.3.2-2)

Nintedanib was orally administered at 0 (vehicle, 0.5% hydroxyethylcellulose), 10, 30, or 100 mg/kg/day[3] for 13 weeks to male and female ICR mice. Piloerection was observed in males in the 100 mg/kg/day group. Whitened incisor was observed in the 100 mg/kg/day group from Week 7, and broken tooth was observed in 1 of 12 females at Week 10/11. Across the dose groups, reduced body weight gain was observed in a dose-dependent manner. In females in the 100 mg/kg/day group, decreased food consumption was observed. In the ≥30 mg/kg/day groups, hematology findings included decreases in red blood cell count and reticulocyte count (female) as well as increases in mean corpuscular hemoglobin (MCH) and mean corpuscular volume (MCV) in the ≥30 mg/kg/day groups, and anisocytosis or macrocytosis was observed in some animals. Other findings included decreased neutrophil count in females in the ≥10 mg/kg/day groups as well as increases in basophil count, monocyte count, achromatic large cell count, and lymphocyte count (female) and decreased platelet count in the 100 mg/kg/day group, and all these changes were mild.

Clinical chemistry findings included decreased blood glucose in females in the ≥30 mg/kg/day groups and increased total bilirubin in males in the 100 mg/kg/day group. Other findings included decreased calcium in females in all dose groups, increased potassium in females in the ≥30 mg/kg/day groups, and decreases in inorganic phosphorus, total protein and albumin, and albumin/globulin (A/G) ratio in females in the 100 mg/kg/day group.

Absolute weight of the spleen and relative weights of the spleen to body and brain increased males in the ≥30 mg/kg/day groups. The relative weight of the spleen to body was slightly high in females in the 100 mg/kg/day group. Absolute weight, relative weights of the liver to body and brain decreased in females in all dose groups and males in the ≥30 mg/kg/day groups. Absolute weight, relative weights of the heart to body and brain decreased in females in the 100 mg/kg/day group. Histopathological findings included thickening of the growth plates due to increased hypertrophic chondrocyte count and chondrocyte swelling (sternum, femur) in the basal layers of the articular cartilage in the ≥30 mg/kg/day groups; and cellular depletion in the bone marrow, various dentopathy of the incisors, enhanced extramedullary hematopoiesis in the spleen and liver (male), slight or mild diffuse cortical hyperplasia (male) in the adrenals, decreased mature corpora lutea count and increased luteinized follicles in the ovaries (female) in the 100 mg/kg/day group. Based on these findings, 30 mg/kg/day was considered close to the maximum tolerated dose, but the NOAEL has not been established.

[3] In the 2-week repeated-oral-dose toxicity study in mice (4.2.3.2-1), nintedanib has been demonstrated to be tolerable up to 100 mg/kg/day. This study was conducted as a preparatory study for a mouse carcinogenicity study to determine the maximum tolerated dose.

3.(iii).A.(2).2) Four-week repeated oral dose toxicity study in rats (4.2.3.2-6)

Nintedanib was orally administered at 0 (vehicle, 0.5% hydroxyethylcellulose), 3, 20, or 100 mg/kg/day[4] for 4 weeks to male and female Wistar Hannover rats. Although no deaths occurred, decreases in body weight and food consumption were observed in the 100 mg/kg/day group during the recovery period following the treatment period. Decreased body weight and food consumption resolved after feeding of pellets softened with water to the animals. These changes were thus considered attributable to the inflammation and fracture of the upper and lower incisors, which caused the animals a difficulty in consuming pellets. Decreased thymus weight was observed in the 100 mg/kg/day group. Histopathological findings included thickening of the epiphyseal growth plate, dentopathy (whitened tooth, fracture, bleeding, focal necrosis, etc.), slight hypertrophy of glomerular vascular endothelial cells, and hyaline granules detected in glomerular podocytes and endothelial cells in the kidneys by intracytoplasmic periodic acid Schiff stain (PAS) in the 100 mg/kg/day group. In addition, an increasing apoptosis cell count was observed in the thymus, spleen, mesentery, and axillary lymph nodes. Because of the inhibitory effect of nintedanib on Lck, Lyn, and Src, the immunological effect of nintedanib was investigated. The findings included decreased T cells/B cells ratios in peripheral blood and in the spleen, decreased helper T cell (CD3+CD4+) count in blood, and mildly increased NK cell activity in the spleen in all the males in the 100 mg/kg/day group (10 of 10 male animals). The changes observed in the teeth and bones were likely to be class effects of the drugs inhibiting VEGFR-mediated intracellular signaling. The NOAEL was thus determined to be 20 mg/kg/day.

3.(iii).A.(2).3) Thirteen-week repeated oral dose toxicity study in rats (4.2.3.2-7)

Nintedanib was orally administered at 0 (vehicle, 0.5% hydroxyethylcellulose), 3, 20, or 100 mg/kg/day for 13 weeks to male and female Wistar Hannover rats. In the 100 mg/kg/day group, 2 of 10 male animals died mainly due to food consumption affected by severe dentopathy in the incisor (1 of 10 animals) and chronic progressive nephrosis (1 of 10 animals). In females in the 20 mg/kg/day group and in the 100 mg/kg/day group, decreases in body weight and food consumption and changes on the incisors were observed. Hematology findings included decreases in red blood cell count, hematocrit, and hemoglobin, and increases in reticulocyte count, white blood cell count, and platelet count in the 100 mg/kg/day group. Findings in bone marrow smear preparations included increases in lipid droplet count, reticular cell count, megakaryocyte count, lymphocyte count, and plasma cell count, and mildly increased erythropoiesis/granulocytopoiesis ratio. Clinical chemistry findings included increases in γ-glutamyltransferase (γ-GT), aldolase, and ALT in the 100 mg/kg/day group, increases in aspartate aminotransferase (AST), leucine arylamidase, and globulin, and decreases in albumin and total protein in females in the 100 mg/kg/day group. The increases in ALT, AST (females) and GLDH (females) were observed even after the recovery period. Other findings included decreased thymus weight in males of the ≥20 mg/kg/day groups and increased mesenteric lymph node weight in the 100 mg/kg/day group. Histopathological findings other than dose-dependent dentopathy of the incisors included thickening of the epiphyseal growth plate in the long bones due to increased hypertrophic chondrocyte count, slight to moderate cellular depletion in the bone marrow, increased extramedullary hematopoiesis in the spleen, and hemosiderosis in the liver (females) in the ≥20 mg/kg/day groups; and glomerulopathy in the kidney and deposition of PAS positive/hyaline droplet granules, mineralization, increased extramedullary hematopoiesis, and depletion of lymphocytes in the spleen, slight to moderate hemosiderosis associated with microgranuloma in the liver, degenerative changes in the thymus and mesenteric lymph node, and slight to moderate atrophy of corpora lutea and luteinized follicles in the ovaries (females) in the 100 mg/kg/day group. These findings were reversible or tended to be reversible after the recovery period. Accordingly, the NOAEL was determined to be 3 mg/kg/day.

3.(iii).A.(2).4) Thirteen-week repeated oral dose toxicity study in rats (4.2.3.2-8)

Nintedanib was orally administered at 0 (vehicle, 0.5% hydroxyethylcellulose), 5, 20, or 60 mg/kg/day for 13 weeks to male and female Wistar Hannover[5] rats. In the ≥20 mg/kg/day groups, dentopathy of the incisors (whitened tooth, fracture, defect, malocclusion, etc.) and reduced body weight gain were observed. In males in the 60 mg/kg/day group, mildly decreased food consumption was observed.

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[4] In a 2-week repeated oral dose exploratory toxicity study in rats (4.2.3.2-3 to 4.2.3.2-5), histopathological changes were observed in the bones, bone marrow, kidney, spleen, thymus, thyroid, parathyroid gland, and trachea at the doses of ≥300 mg/kg/day.

[5] This study was conducted as a dose-finding study for a 2-year carcinogenicity study in rats, and thus HsdHan; WIST rats of the same strain as that to be used in the future study were used.

Hematology findings after 6 weeks of dosing included decreased red blood cell count and subsequent increases in MCH and MCV in the ≥20 mg/kg/day groups, and decreases in hemoglobin and mean corpuscular hemoglobin concentration (MCHC) and increased platelet count in females in the 60 mg/kg/day group. In males in the 60 mg/kg/day group, slight increases in lymphocyte, basophil, and monocyte counts were observed. After 13 weeks of dosing, findings after 6 weeks of dosing still remained. Besides, decreases in red blood cell count and MCHC and increased MCH in the 5 mg/kg/day group; mild increases in lymphocyte basophil, and monocyte counts were also observed in males in the 20 mg/kg/day group; and increased platelet count in the 60 mg/kg/day group. Clinical chemistry findings included increased blood glucose in females in the ≥5 mg/kg/day groups; increased triglyceride and decreased sodium in females in the ≥20 mg/kg/day groups; and increases in alkaline phosphatase, ALT, AST, urea nitrogen (males), and potassium (females), and decreases in total protein (males), albumin (males), and A/G ratio (females) in the 60 mg/kg/day group. Weight-related findings included decreased liver weight in females in the ≥5 mg/kg/day groups; decreased kidney weight in females in the ≥20 mg/kg/day groups; and decreased weights of the heart, liver, spleen (males), lung (females), and pituitary gland (females) in the 60 mg/kg/day group. These changes are considered to reflect the low body weight. In the ≥5 mg/kg/day groups, discoloration in the lungs and bronchus and dose-dependent increase in the incidence of ovarian enlargement were observed. Other findings included dentopathy (fracture, defect, malocclusion, discolored pale white tooth, overgrowth, etc.) in the ≥20 mg/kg/day groups, and discoloration of thyroid and hypertrophic duodenum in the 60 mg/kg/day group.

Histopathological findings included pulp cavity necrosis in females in the ≥5 mg/kg/day groups; and peripheral pigmentation in the liver, decreased cell count and sinus dilatation/cystic formation in the mesenteric lymph node, vacuolation of the adrenal cortex, thickening of the growth plates in the sternum and femur (increased cell count in the hypertrophic chondrocyte layer), increased chondrocyte enlargement in the basal layers of the articular cartilage, cell depletion in the bone marrow, pulp cavity necrosis (males), and increased mature corpora lutea count in the ovaries (females) in the 60 mg/kg/day group. Based on these findings, the dose of 60 mg/kg/day was considered close to the maximum tolerated dose, in light of the demonstrated tolerability to nintedanib up to 20 mg/kg/day. However, the NOAEL has not been determined because of pulp cavity necrosis occurred at any dose.

3.(iii).A.(2).5) Twenty-six-week repeated oral dose toxicity study in rats (4.2.3.2-9)

Nintedanib was orally administered at 0 (vehicle, 0.5% hydroxyethylcellulose), 5, 20, or 80 mg/kg/day for 26 weeks to male and female Wistar Hannover rats.

One of 20 males and 1 of 20 females in the 20 mg/kg/day group and 5 of 20 males and 3 of 20 females in the 80 mg/kg/day group died or were prematurely sacrificed due to the deteriorated systemic condition during the study. The cause of deaths was determined to be deteriorated general condition attributable to broken incisors and associated deceased food consumption. The surviving animals in the 80 mg/kg/day group were prematurely sacrificed on Day 165/166 due to deteriorated general condition and lack of body weight gain (males). Reduced body weight gain was observed in males in the ≥20 mg/kg/day groups, and no body weight gain was observed in males in the 80 mg/kg/day group from Day 50 onward. Clinical observation revealed broken incisors in 3 of 20 males and 9 of 20 females and swelling and reddening of the gingiva in almost all animals in the 20 mg/kg/day group. Broken incisors, swelling and reddening of the gingiva were observed in all animals in the 80 mg/kg/day group.

Hematology findings included decreased red blood cell count and increases in reticulocyte, white blood cell (lymphocyte), and platelet counts in the 80 mg/kg/day group. Clinical chemistry findings included increases in ALT, aldolase, and GLDH in the 80 mg/kg/day group, which remained even after the 8-week recovery period. The urinalysis revealed that microbial count and inorganic phosphorus tended to increase during a part of the study period in the ≥20 mg/kg/day groups, and increased urine protein and presence of white blood cells were observed in some animals in the 80 mg/kg/day group. Decreased thymus weight was observed in males in the ≥20 mg/kg/day groups and increased adrenal gland weight in males in the 80 mg/kg/day group. At the histopathological examination, in the ≥20 mg/kg/day groups, slight to severe changes were observed in the liver, spleen, kidney, adrenal gland, bone marrow, thymus, ovaries, epiphyseal growth plate, articular cartilage, incisors, common bile duct, and adjacent organs in a dose-dependent manner. These changes were similar to those observed in the 13-week repeated oral dose toxicity study in rats [see "3.(iii).A.(2).3) Thirteen-week repeated oral dose toxicity study in rats

(4.2.3.2-7)"]. Almost all changes were reversible or tended to be reversible. New findings or worsening in known findings in this study included peripheral hemosiderosis and extramedullary hematopoiesis in the liver, moderate to severe calcinosis of the capsule and trabeculae in the spleen, slight to mild lymphoid depletion, and increased extramedullary hematopoiesis in the spleen, thickening of epiphyseal cartilage (extended hypertrophic chondrocyte layer) in the knee, increased swelling of chondrocyte in the basal layers of the knee joint cartilage, mild to severe cellular depletion in the bone marrow; corpora lutea atrophy, increased corpora lutea count, and decreased angiogenesis in the ovaries in the ≥20 mg/kg/day groups; and severe dilation of the main extrahepatic bile duct accompanied by a moderate to severe inflammation and a pronounced hyperplasia of the bile duct epithelial cells, slight to mild unspecific tubular injury findings in the kidney, moderate involution of the thymus, and mild to severe sinusoid dilatation/angiectasis as well as diffuse hyperplasia (males) of the adrenal cortex in the 80 mg/kg/day group. Based on these findings, the NOAEL was determined to be 5 mg/kg/day.

3.(iii).A.(2).6) Two-week repeated oral dose toxicity study in dogs (Reference 4.2.3.2-12)

Nintedanib was orally administered at 0 (vehicle, 0.5% hydroxyethylcellulose), 3, 10, 30, or 100 mg/kg/day for 2 weeks to male and female beagle dogs. One of 2 females in the 10 mg/kg/day group and all the animals in the ≥30 mg/kg/day groups (2 of 2 animals for each sex) were sacrificed moribund due to deteriorated general condition caused by gastrointestinal toxicity such as diarrhea before the end of treatment. In the 3 mg/kg/day group, liquid stool, decreased food consumption, and emaciation were observed Histopathological findings observed in the 3 mg/kg/day group included decreased large intestine goblet cell count, basophilic changes accompanied by increased nuclei in the crypt epithelium and mitotic, and slight erosion in the rectal mucosa only in females. In the sacrificed animals, histopathological changes such as erosion in the intestinal mucosa suggestive of intestinal epithelium cell injury and villous atrophy in the intestinal mucosa were observed. In the ≥30 mg/kg/day groups, moderately increased hepatic transaminase activity was observed.

3.(iii).A.(2).7) Four-week repeated oral dose toxicity study in cynomolgus monkeys (4.2.3.2-17)

Nintedanib was orally administered at 0 (vehicle, 0.5% hydroxyethylcellulose), 3, 15, or 60 mg/kg/day[6] for 4 weeks to male and female cynomolgus monkeys. One of 5 males in the 60mg/kg/day group was sacrificed moribund due to deteriorated systemic condition on Day 14. Furthermore, 3 of 5 males and 4 of 5 females were subjected to necropsy on Day 15, and 1 male and 1 female withdrew from treatment for the remaining 2 weeks to investigate the reversibility.

Gastrointestinal symptoms such as diarrhea and vomiting were observed in the ≥15 mg/kg/day groups. Severe gastrointestinal symptoms, decreases in food consumption and body weight, and deteriorated systemic condition were observed in the 60 mg/kg/day group. In the 60 mg/kg/day group, changes after 2-week withdrawal included decreases in red blood cell count, hematocrit, or hemoglobin and increases in reticulocyte, platelet, and band-form neutrophil counts; and clinical chemistry findings included increases in triglyceride, urea nitrogen, and GLDH activity. In the 60 mg/kg/day group, decreases in submaxillary lymph nodes, spleen (males) and thymus (males) weights, and slight increases in kidney (females) and liver (females) weights were observed. Histopathological changes in the 60 mg/kg/day group included atrophy of the lymphoid tissue, spleen, and thymus, decreases in thymus and bone marrow cell counts, renal tubular dilation in the kidney, gastrointestinal erosion, epithelial atrophy of the esophagus, tongue, and skin, and atrophy of the exocrine pancreas gland, submandibular gland, parotid gland, and serous gland of the tongue as well as villous atrophy of the small intestine. Based on these findings, the NOAEL was determined to be 3 mg/kg/day.

3.(iii).A.(2).8) Thirteen-week repeated oral dose toxicity study in cynomolgus monkeys (4.2.3.2-18)

Nintedanib was orally administered at 0 (vehicle, 0.5% hydroxyethylcellulose), 3, 15, or 30 mg/kg/day for 13 weeks to male and female cynomolgus monkeys. In the 30 mg/kg/day group, observed loose stool/liquid stool indicated poor tolerability to nintedanib. Thus, nintedanib was administered at a dose of 30 mg/kg/day for 13 days followed by 3-day withdrawal, and then the dose was reduced to 20 mg/kg/day from Day 17 (30/20 mg/kg/day group).

[6] In the dose escalating oral toxicity study in cynomolgus monkeys (4.2.3.2-15) as well as the toxicokinetics study in cynomolgus monkeys that compared oral and intravenous doses (4.2.3.2-16), diarrhea, vomiting, and decreased body weight were observed at the nintedanib dose of 80 mg/kg/day, and further severe gastrointestinal signs were observed at 160 mg/kg/day.

In the ≥3 mg/kg/day groups, loose stool/liquid stool and excessive salivation were observed, and the incidences of these symptoms increased in a dose-dependent manner. In the ≥15 mg/kg/day groups, reduced body weight gain or decreased body weight was observed. In the 30/20 mg/kg/day group, decreased food consumption was observed especially in females. In the 30/20 mg/kg/day group, transient decrease in reticulocyte count was observed at Week 2. Increased thymus weight and atrophy of the thymus were observed in 1 of 3 females each in the 3 and 15 mg/kg/day groups and 2 of 3 females in the 30/20 mg/kg/day group.

At the histopathological examination, slightly decreased thymic cortex cell count was observed in 1 of 3 females in the 3 mg/kg/day group, 1 of 3 males and 1 of 3 females in the 15 mg/kg/day group, and 2 of 3 males and 1 of 3 females in the 30/20 mg/kg/day group. Mild to moderate fatty replacement in the femur bone marrow was observed in the ≥3 mg/kg/day groups, and severe one in 1 of 3 females in the 30/20 mg/kg/day group. Slight to mild fatty replacement in the sternum bone marrow was observed in the ≥3 mg/kg/day groups, including the control group, but the incidence or severity in the control group was low. As these changes remained even after the 4-week recovery period, they were considered possibly attributable to nintedanib. Although there were no changes in CD4 and CD8 positive T cells or NK cells, a slight decrease in B cell count (males) was observed in the peripheral blood and was found reversible. All the bone marrow smear preparations showed normal cell density, distribution, and morphology.

The NOAEL in this study was determined to be 3 mg/kg/day, although loose stool/liquid stool and salivation occurred in the 3 mg/kg/day group. This is due to the incidence of the stool-related events lower than that in the control group and the incidence of salvation apparently lower than that in the 15 mg/kg/day group.

3.(iii).A.(2).9) Four-week repeated oral dose toxicity study in rhesus monkeys (4.2.3.2-20)

Nintedanib was orally administered at 0 (vehicle, 0.5% hydroxyethylcellulose), 10, 20, or 60 mg/kg/day[7] for 4 weeks to male and female rhesus monkeys. No nintedanib-associated death occurred. In the 60 mg/kg/day group, liquid stool and vomiting (all animals), decreased food consumption (1 of 3 males, 1 of 3 females), and remarkably decreased body weight (2 of 3 males, 1 of 3 females) were observed. Decreases in red blood cell count and hematocrit were observed in males of the ≥10 mg/kg/day groups, and reduced prothrombin time was observed in males of the 60 mg/kg/day group. Increased ALT and decreased γ-GT were observed in the ≥20 mg /kg/day groups, and a slight to mild increase in AST was observed in the 60 mg/kg/day group. Based on the above, the NOAEL was determined to be 10 mg/kg/day.

3.(iii).A.(2).10) Fifty-two-week repeated oral dose toxicity study in rhesus monkeys (4.2.3.2-21)

Nintedanib was orally administered at 0 (vehicle, 0.5% hydroxyethylcellulose), 10, 20, or 60 mg/kg/day for 52 weeks to male and female rhesus monkeys. In the 60 mg/kg/day group, nintedanib 60 mg/kg/day was withdrawn on Day 30 due to toxicological changes in general condition, followed by a 20-day withdrawal period. Nintedanib was administered at the reduced dose of 45 mg/kg/day from Week 7 to Week 25. From Week 26 onward, the dose was further reduced to 30 mg/kg/day. The treatment was then discontinued after 55 weeks of administration so that the treatment duration was the same as that in the ≤20 mg/kg/day groups.

In the 60/45/30 mg/kg/day group, 1 of 4 males and 1 of 4 females were prematurely sacrificed due to severely deteriorated general conditions including liquid stool, decreased activity, emaciation, and stooping position. In these animals, decreased plasma electrolyte, increased red blood cell count, decreases in spleen and thymus weights, thymus atrophy, adrenal cortex hypertrophy, and inflammatory cells in the small intestine were observed at sacrifice.

In the ≥20 mg /kg/day groups, reduced body weight gain and salivation occurred, and in the 60/45/30 mg/kg/day group, liquid stool, vomiting, decreased activity, stooping position, pale white gingival, and decreased body weight occurred. The incidence or severity of these events decreased with the reduced

[7] In the toxicokinetics study in rhesus monkeys that compared oral and intravenous doses (4.2.3.2-19), remarkably decreased food consumption was observed at a dose of 80 mg/kg/day for 7 days.

dose. Mixed *coliform spp.* (especially, *E.coli*) and/or *Campylobactor spp.* bacteria were detected by microbiological examination with a rectum or fecal swab, and were considered related to the severity of liquid stool. No treatment-related effects were revealed by electrocardiography, ophthalmological examination, urinalysis, peripheral white blood cell examination, or necropsy.

Hematology and clinical chemistry findings included decreases in neutrophil count, eosinophil count, basophil count, monocyte count, and achromatic large cell count in females and decreased lymphocyte count in males at Week 13; and decreased lymphocyte count only in females at Week 26 in the 60/45/30 mg/kg/day group. Decreased platelet count (males) and increased chlorine concentration (females) at Weeks 52 and 55 were reversible. Slight decreases in albumin and total protein (females) were observed at Weeks 40, 52, and 55 and remained even after the 8-week recovery period. Weight-related findings included decreased spleen weight in females in the ≥10 mg/kg/day groups, and decreases in lung (including the bronchus) and adrenal gland weights in females in the 60/45/30 mg/kg/day group. Histopathological findings included thickening of the growth plate in the femur/tibia and sternum and atrophy of adrenal zona fasciculata in the ≥10 mg/kg/day groups, and thinning of the cortical bone in the sternum and decreased trabecular bone mass in the 60/45/30 mg/kg/day group, which were reversible.

In the immunological examination, no consistent changes were observed in monocytes, the subsets of B and T cells, and NK cells in peripheral blood. Although there were no changes in the proportion of the subsets of B and T cells and NK cells in the spleen in the 60/45/30 mg/kg/day group, the number of cells per unit of tissue weight decreased in each cell type but the change was reversible. The NK cell activity per unit tissue weight also tended to decrease. The NOAEL was determined to be 10 mg/kg/day, because the changes observed in the 10 mg/kg/day group were considered to have no toxicological significance or to be associated with the pharmacological effect.

3.(iii).A.(3) Genotoxicity (4.2.3.3.1-1 to 4.2.3.3.1-4, 4.2.3.3.2-1)

A bacterial reverse mutation assay (Ames test) and a mouse lymphoma TK assay were performed *in vitro* on nintedanib and its major metabolite, m1. A rat bone marrow micronucleus assay was performed *in vivo* on nintedanib. Both nintedanib and m1 were considered non genotoxic.

3.(iii).A.(4) Carcinogenicity

3.(iii).A.(4).1) Two-year oral dose carcinogenicity study in mice (4.2.3.4.1-1)

Nintedanib was orally administered at 0 (vehicle, 0.5% hydroxyethylcellulose), 5, 15, or 30 mg/kg/day for 104 weeks to male and female CD1 mice. The survival rate in males in the 30 mg/kg/day group decreased to 23% at Week 103. The treatment was discontinued and the male animals were necropsied. Many male mice were sacrificed during the study primarily due to severe abrasion on the auricle and neck skin. Abrasion occurred only in males, and the incidence of the event in the nintedanib groups was similar to that in the control group. The microbiological examination has not yielded definite results. Thus, the cause of abrasion remains unknown. The frequent deaths in the males in the 30 mg/kg/day group were considered attributable to the treatment, but macroscopic or histopathological findings were not consistent among individual animals, and thus, the cause of deaths remains unknown. Although reduced body weight gain was observed in the 30 mg/kg/day group, food consumption was not affected. Hematology findings included slight increases in MCH and MCV in the ≥15 mg/kg/day groups, slightly decreased red blood cell count in the 30 mg/kg/day group, slightly increased lymphocyte count in females in the 30 mg/kg/day group, and increased achromatic large cell count in males in ≥15 mg/kg/day groups and females in the 30 mg/kg/day group. Macroscopically, mass in the gallbladder was observed in many females in the ≥15 mg/kg/day groups. There were no nintedanib-related neoplastic lesions, but non-neoplastic changes including ulceration, responsive epithelial hyperplasia, and fibrotic changes in the gallbladder were observed in the ≥15 mg/kg/day groups. The epithelial hyperplasia and fibrotic changes are indicating regeneration and restoration processes subsequent to the ulceration and are thus considered to show the aggravation of background lesions which would also be observed in the control group (Lewis DJ, *J Comp Pathol.* 1984;94:263-271). There were no nintedanib-related lesions in the intrahepatic bile duct or liver, and epithelial hyperplasia, and fibrotic changes were not observed in a preliminary study of this study, a 13-week repeated oral dose toxicity study in mice (4.2.3.2-2). Based on the the results of the 2-year oral dose study of nintedanib in mice, the compound is considered non-carcinogenic.

3.(iii).A.(4).2) Two-year oral dose carcinogenicity study in rats (4.2.3.4.1-2)

Nintedanib was orally administered at 0 (vehicle, 0.5% hydroxyethylcellulose), 2.5, 5, or 10 mg/kg/day for 104 weeks to male and female Wistar Hannover rats. Hematology findings included increases in reticulocyte count (females), MCH, and MCV, and decreased MCHC (females) in the ≥2.5 mg/kg/day groups; and decreased red blood cell count in females in the ≥5 mg/kg/day groups and males in the 10 mg/kg/day group. In the 10 mg/kg/day group, reduced prothrombin time was observed. In the ≥2.5 mg/kg/day groups, decreased urine volume, increases in urine protein and urine specific gravity, and decreases in sodium and chlorine concentrations were observed. Increased plasma concentrations of creatinine, potassium, and phosphorus and decreased A/G ratio suggested changes in renal function. There was no nintedanib-related tumorigenesis. The incidences of neoplastic and non-neoplastic lesions in the adrenal gland, mammary gland (females), thyroid (females), and pituitary gland (males) tended to decrease in a dose dependent manner. In the ≥5 mg/kg/day groups, chronic progressive nephrosis or arteritis/periarteritis (mainly on the blood vessels in the tongue, testis, and pancreatic tissues) was sporadically observed. These findings were, however, recognized as advanced cases of spontaneous diseases occurring in rats (Hard GC et al., *Toxicol Sci*. 2013;132:268-275, Percy DH and Bathold SW, *Pathology of laboratory rodents and rabbits*. 2007) or secondary changes in the diseases, and thus were unlikely to be relevant to humans. The other findings included decreased local cortical hypertrophy/vacuolation in the adrenal gland, hemosiderosis in Kupffer cells in the liver, and macrophage accumulation in the lung, all of which are considered unlikely to be relevant to humans or to have no toxicological significance. Based on the results of the 2-year oral dose study of nintedanib in rats, the compound is considered non-carcinogenic.

3.(iii).A.(5) Reproductive and developmental toxicity

To evaluate the reproductive and developmental toxicity of nintedanib, studies on fertility and early embryonic development to implantation in rats, embryo-fetal development studies in rats and rabbits, and a study on pre- and postnatal development, including maternal function in rats were conducted.

The applicant explained that nintedanib was contraindicated in pregnant women or in women who may be pregnant because of its teratogenicity observed in the embryo-fetal development studies in rats and rabbits.

3.(iii).A.(5).1) Fertility and early embryonic development to implantation

(a) Study of the effects on male rats (4.2.3.5.1-1)

Nintedanib was orally administered to male Wistar Hannover rats at 0 (vehicle, 0.5% hydroxyethylcellulose), 3, 20, or 100 mg/kg/day daily from 92 days prior to mating. Female rats received vehicle orally from Gestation Day 1 to Gestation Day 6 (the day of mating was deemed as Gestation Day 1). Dentopathy of the incisors was observed in 4 of 24 rats in the 20 mg/kg/day group and in 23 of 24 rats in the 100 mg/kg/day group. In the 20 mg/kg/day group, decreased food consumption was observed in 4 weeks of the 13-week treatment period, and reduced body weight gain was observed during the first half of the treatment period. In the 100 mg/kg/day group, decreases in body weight and food consumption were observed during the pre-mating period. Nintedanib had no effect on mating ability or fertility in males, as no treatment-related changes were observed in the male reproductive organs (testis, epididymis, prostate, vesicular gland, coagulating gland). Based on the above, the NOAELs in paternal animals were determined to be 3 mg/kg/day for general toxicity and >100 mg/kg/day for fertility and early embryonic development.

(b) Study of the effects on female rats (4.2.3.5.1-2)

Nintedanib was orally administered to female Wistar Hannover rats at 0 (vehicle, 0.5% hydroxyethylcellulose), 3, 20, or 100 mg/kg/day from 15 days prior to mating through Gestation Day 7 (the day of mating was deemed as Gestation Day 1). Although no death occurred, reduced or a trend towards reduced body weight gain was noted in the 100 mg/kg/day group and decreased food consumption was observed during the pre-mating period in the same group. Although the mating rate with untreated male rats was 100% in all the dose groups, pregnancy was established in 19 of 24 animals in the 100 mg/kg/day group (fertility rate, 79.2%), and delivery was achieved only in 11 of 19 maternal animals (delivery rate, 57.9%) due to total resorption. Findings included increased corpora luteum count and increased post-implantation loss associated with an increased number of early resorption in the 20 mg/kg/day group; and increases in the number of early resorption and embryonic resorption rate as well

as a decreased number of live fetuses in the 100 mg/kg/day group. Histopathological findings included decreased secretion from the mammary gland and decreased proportion of the glandular structure relative to the adipose tissue of the mammary gland in the ≥20 mg/kg/day groups, and these findings were remarkable in the 100 mg/kg/day group. Based on the above, the NOAEL in maternal animals was determined to be 20 mg/kg/day for general toxicity, copulation, and fertility and 3 mg/kg/day for early embryonic development.

3.(iii).A.(5).2) Embryo-fetal development

(a) Rat embryo-fetal development study (4.2.3.5.2-3)

Nintedanib was orally administered to pregnant Wistar Hannover rats at 0 (vehicle, 0.5% hydroxyethylcellulose), 2.5, 5, or 10 mg/kg/day[8] from Gestation Day 7 to Gestation Day 16. No maternal toxicity was observed. In the ≥2.5 mg/kg/day groups, treatment-related skeletal variation and malformation occurred. In the 10 mg/kg/day group, increases in the number of early resorption and the embryonic resorption rate and decreased fetal body weight were observed. Teratogenic changes occurred mainly in the axial skeleton and aortic arch in animals of this group. Based on these findings, the NOAEL for embryo-fetal development in rats has not been established. At 2.5 mg/kg/day, exposure to nintedanib was below the lower limit of quantitation (1.0 ng/mL) while exposure to m2 was detected, and m1 was shown to inhibit various tyrosine kinase receptors, albeit weakly. Thus, the teratogenicity was considered to have been induced by nintedanib, m1, and m2.

(b) Rabbit embryo-fetal development study (4.2.3.5.2-5)

Nintedanib was orally administered to pregnant Himalayan rabbits at 0 (vehicle, 0.5% hydroxyethylcellulose), 15, 30, or 60 mg/kg/day[9] from Gestation Day 6 to Gestation Day 18. No toxicologically significant changes related to nintedanib occurred in body weight, body weight gain, or general condition. In the 15 and 30 mg/kg/day groups, no effects were observed in corpora luteum count, the number of implantation, pre-implantation loss, the number of live fetuses, or the number of dead fetuses. In the 60 mg/kg/day group, total resorption occurred in 3 of 20 animals and total abortion in 1 of 20 animals, and increases in the numbers of early resorption and total resorption, embryonic resorption rate, and female fetal ratio were observed. Fetal body weight was not affected by the treatment. In the ≥15 mg/kg/day groups, teratogenic changes occurred in the axial skeleton (unilateral centrum ossification, centrum fusion, spinal displacement) and dermal skull (additional irregular suture line). In the ≥30 mg/kg/day groups, further morphologic abnormalities were frequently observed in the aortic arches and heart (subclavian artery defect, aortic arch defect), urogenital system (kidney defect, ureter defect, absence of ductus deferens, uterus agenesis), and axial skeleton system (hemivertebrae, centrum cleft). Distal forelimb (unilateral brachydactyly) was affected in some fetuses. Based on these findings, the NOAEL for embryo-fetal development in rabbits has not been established. C_{max} and $AUC_{0\text{-}24}$ at 15 mg/kg/day were 461 ng/mL and 1920 ng·h/mL, respectively, which were 11.6 and 8.8 times, respectively, those values (C_{max}, 39.7 ng/mL; AUC_{τ}, 218 ng·h/mL) in Japanese patients with IPF receiving oral nintedanib 150 mg twice daily.

3.(iii).A.(5).3) Rat study for effects on pre- and postnatal development, including maternal function (4.2.3.5.3-1)

Nintedanib was orally administered to female Wistar Hannover rats at 0 (vehicle, 0.5% hydroxyethylcellulose), 2.5, 5, or 10 mg/kg/day from 6 days after mating to Lactation Day 20. In the plasma sample from the F1 rats in the 10 mg/kg/day group, m2 was measurable, but exposures to nintedanib and its metabolites were low.

No nintedanib-related changes in clinical observations were noted in maternal animals. In the 5 mg/kg/day group, slightly reduced body weight gain was observed from Gestation Day 14 to Gestation Day 20 and slightly decreased food consumption from Gestation Day 17 to Gestation Day 19, as compared with the vehicle control group. In the 2.5 and 5 mg/kg/day groups, nintedanib had no effect on the gestational period and pre- and post-natal viability/litter size of offspring. In the 10mg/kg/day group, many maternal animals had a gestational period of 23 to 23.5 days. The number of implantations

[8] In dose-finding studies, the doses ≥20 mg/kg/day induced total resorption in all maternal animals (4.2.3.5.2-1, 4.2.3.5.2-2).

[9] In a dose-finding study, 3 of 6 maternal animals at 180 mg/kg/day died or were sacrificed moribund, and the remaining 3 survived maternal animals had no live fetus. At 75 mg/kg/day, 2 of 6 maternal animals had total abortion, and increased embryonic resorption rate was also observed (4.2.3.5.2-4).

was not affected by nintedanib, but decreased post-implantation embryonic viability including total resorption and decreased litter size were observed in 3 of 22 dams. The death of a whole litter of pups occurred in 2 of 19 dams in the 10 mg/kg/day group during the early post-natal phase. The sex ratio was not affected by nintedanib. In F1 offspring, the administration of nintedanib to the maternal animals had no effect on the body weight on 1 day postnatal, body weight gain until weaning (21 days postnatal), and body weight gain until 25 days postnatal, and had no effect on general condition, sexual maturation, locomotor activity, learning and memory, and fertility. Based on these findings, the NOAEL was determined to be 5 mg/kg/day for fertility of maternal animals and pre- and post-natal development of F1 offspring.

3.(iii).A.(6) Local tolerance

3.(iii).A.(6).1) Skin irritation study (4.2.3.6-1)

Acute skin irritation/corrosivity of nintedanib) was investigated in NZW rabbits. Approximately 0.5 g of nintedanib was mixed with deionized water into paste and applied to the skin. Nintedanib was determined to be non-irritative.

3.(iii).A.(6).2) Eye mucosal irritation study (4.2.3.6-2)

Nintedanib was administered as a single dose of 20 mg (powder) to the conjunctival sac of NZW rabbits. Mild changes were induced in the conjunctiva, eyelid, and iris and completely resolved within 72 hours after dosing. Based on the above, nintedanib was determined to be non-irritative.

3.(iii).A.(6).3) Local tolerance study by intravenous/intraarterial/intramuscular injection (4.2.3.6-3, 4.2.3.6-4)

A single dose of nintedanib 2 mg/mL (pH 4.5, 5% glucose solution) was administered intravenously, intraarterially, or intramuscularly to NZW rabbits. While intravenous nintedanib was well tolerated, the intraarterial and intramuscular doses induced local irritation.

3.(iii).A.(6).4) Local irritation study by parasinoidal injection (4.2.3.6-5)

Nintedanib at 2 mg/mL (pH 4.5, 5% glucose solution) was perivenously injected to Wistar Hannover rats. Local irritation was observed.

3.(iii).A.(7) Other toxicity studies

An *in vitro* phototoxicity study in Balb/c 3T3 cells, hemolysis study with human blood, genotoxicity studies of the impurities potentially present in the drug substance or drug product were conducted.

3.(iii).A.(7).1) *In vitro* phototoxicity study (4.2.3.7.1-1)

Phototoxicity of nintedanib was investigated in Balb/c 3T3 cells. Nintedanib was considered to have phototoxicity, based on its photo irritation factor (PIF) of 18.4 and the mean photo effect (MPE) of 0.554 to 0.560. The phototoxicity-induction threshold is estimated to be 0.5 μg/mL.

3.(iii).A.(7).2) Hemolysis study with human blood (4.2.3.7.3-1)

The hemolysis of nintedanib with human blood was investigated in undiluted injection solution (2 mg/mL) and diluted solutions (7.7%, 10%, 14.3%, 25%, and 50%), positive control (1% saponin solution), and the vehicle (0.9% sodium chloride). The *in vitro* hemolysis rate was ≤0.5%, and thus the intravenous administration of nintedanib injection solution to humans is acceptable.

3.(iii).A.(7).3) Toxicity and genotoxicity of the impurities (4.2.3.7.6-1 to 4.2.3.7.6-29)

None of the impurities in the drug substance and drug product has acceptance criteria exceeding the threshold that can be justified by safety data. To predict mutagenicity of the organic impurities present in the drug substance, synthetic intermediate, and starting materials as well as degradation products expected to be present in the drug substance or drug product, their chemical structures were further subjected to *in silico* analysis using DEREK (version 13) and MC4PC (version 2.3 and 2.4) and literature search on mutagenicity and carcinogenicity using various databases (e.g., MDL toxicity database, SciFinder, Toxnet, Leadscope). Chemical substances for which no referable published data were available and a structural alert for mutagenicity was shown by the *in silico* analysis were subjected to the Ames test. Impurities tested negative or those tested positive despite having robust data showing no genotoxicity are regarded as impurities for which reporting and identification thresholds should be

specified. Impurities tested positive are controlled with the specification limit so as not to exceed the Threshold of Toxicological Concern (<1.5 μg/day). The levels of Impurity A and Impurity B that are known to be mutagenic and carcinogenic are demonstrated to be not more than the acceptable level and dietary intake level.

3.(iii).B Outline of the review by PMDA

3.(iii).B.(1) Effects on bones and teeth

There was a report on jawbone necrosis occurring in the clinical use of sorafenib tosylate and sunitinib malate that have a similar pharmacological effect to nintedanib. PMDA asked the applicant to explain the nintedanib's mechanism of toxicity development on the bones and teeth as well as its potential effects on the bones and teeth in patients other than growing children.

The applicant's explanation:
A report explains that VEGF and VEGFR play important roles in various processes of bone development and growth (Yang Y-Q et al., *Int J Oral Sci.* 2012;4:64-68.). Thickening of the epiphyseal growth plate in growing bones is a class effect of chemical compounds inhibiting VEGF signaling. This is considered attributable to decreased osteoblast activity subsequent to disturbed removal of hypertrophic chondrocytes, which is due to inhibited vascular invasion into the hypertrophic chondrocyte layer. The effects on tooth growth such as bleeding and tooth fracture associated with necrosis, as observed in rat toxicity studies, are considered a result of decreased physical strength of the teeth by the following biological responses: the inhibition of VEGFR-mediated intracellular signaling leading to suppressed angiogenesis in the dental pulp and the inhibition of PDGFR-mediated intracellular signaling leading to decreased collagen fiber formation in the gingival result in the degeneration and disappearance of odontoblasts and ameloblasts, subsequently inducing morphological changes of enamel and cementum. As described, the pharmacological effects of nintedanib on the teeth and bones induced by the inhibition of VEGFR, PDGFR, and FGFR are manifested only during the bone growth period. Children and adolescents are therefore at risk of nintedanib-induced disorders, but the risk should be low in adults considering low growth potential of bones in this population.

Jaw bone necrosis has been highlighted as one of potential adverse reactions to drugs with a similar pharmacological effect to nintedanib. The mechanism by which jaw bone necrosis develops is considered unrelated to the inhibition of VEGFR, PDGFR, and FGFR because the impact of the inhibition of such receptor tyrosine kinases on bones is mostly seen in children and adolescents. The majority of patients who experienced jaw bone necrosis in the studies were the elderly, and some of them were also receiving bisphosphonate agents, which are reported to be related to jaw bone necrosis. Jaw bone necrosis seen in patients receiving a drug with the similar pharmacological effect to nintedanib is therefore considered attributable to the concomitant drug. In the toxicity studies of nintedanib, jaw bone necrosis was not reported, and pooled data from global phase III studies (Study 1199.32, Study 1199.34) in patients with IPF do not include any adverse events classified as osteonecrosis (MedDRA SMQ). Jaw bone necrosis was reported by 1 patient (0.2%) of the nintedanib group in a phase III study, in which the nintedanib/docetaxel combination regimen was used in patients with non-small cell lung cancer (Study 1199.13), but not in a phase III study in cancer patients, which was conducted to evaluate the efficacy and safety of the nintedanib/pemetrexed sodium hydrate combination regimen (Study 1199.14). Therefore, nintedanib is unlikely to induce jaw bone necrosis in humans.

PMDA's view:
The teeth and bones are known to be the toxicological target tissues of nintedanib. Nintedanib inhibits multiple receptor tyrosine kinases and may induce adverse events due to its unknown pharmacologic effects or through interaction with concomitant drugs. Jawbone necrosis occurred in the clinical studies of nintedanib. Taking account of these factors, the possibility cannot be ruled out that jaw bone necrosis occurs in patients to be treated with nintedanib. The occurrence of the adverse event should be further investigated through post-marketing surveillance, etc.

3.(iii).B.(2) Phototoxicity

PMDA asked the applicant to explain the phototoxicity risk of nintedanib in humans, in response to the positive results of the *in vitro* phototoxicity study of nintedanib in Balb/c 3T3 cells.

The applicant's explanation:
The phototoxicity threshold determined in the *in vitro* phototoxicity study of nintedanib in Balb/c 3T3 cells (approximately 500 ng/mL) is as far as approximately 12.6 times C_{max} (39.7 ng/mL) of nintedanib in Japanese IPF patients orally treated twice daily at the dose of 150 mg. The whole body autoradiography in rats showed that the concentrations of nintedanib in the skin and eyes of orally treated albino rats were ≤3 times that in blood, and that the distribution of nintedanib in the pigmented skin of pigmented rats was not significantly different from that in the non-pigmented skin of albino rats. These tissue distribution data indicated no particular concerns for phototoxicity. Global phase III studies (Study 1199.32, Study 1199.34) were conducted without any protective measures taken for the skin. The pooled data from the studies showed that no adverse events classified under "Photosensitivity and photodermatosis conditions" (HLT) occurred in the nintedanib or placebo group, and the incidence of rash (SSC) in the nintedanib group (6.9%, 44 of 638 subjects) was lower than that in the placebo group (9.0%, 38 of 423 subjects). Accordingly, a risk of phototoxicity is considered low in patients treated with nintedanib.

PMDA's view:
Although the clinical studies have not suggested a risk of phototoxicity-related events, the occurrence of photosensitivity-related adverse events should be further investigated through post-marketing surveillance, etc. Nintedanib has been shown to have melanin affinity and to be distributed into the skin and eyes in the pigmented animals, suggesting that the accumulation of nintedanib may be seen more prominently in Japanese than in Caucasians. Pirfenidone, a drug potentially used in combination with nintedanib, is known to have a risk of phototoxicity and may increase the risk when used concomitantly with nintedanib.

The toxicity profile of nintedanib has been identified based on the submitted toxicity data. From the viewpoint of safety in clinical use, however, general toxicity such as gastrointestinal and bone marrow toxicity as well as reproductive and developmental toxicity are of concern. In light of the seriousness of the target disease, the clinical use of nintedanib is acceptable. Due to its toxicity profile, nintedanib should be used appropriately, considering a potential risk in target patients and paying close attention to the possible development of adverse events related to gastrointestinal toxicity, bone marrow toxicity, and reproductive and developmental toxicity.

4. Clinical data

4.(i) Summary of biopharmaceutical studies and associated analytical methods

4.(i).A Summary of the submitted data

As evaluation data, the results from absolute bioavailability study (Study 1199.75 [5.3.1.1-2]), bioequivalence study (Study 1199.21 [5.3.1.2-1]), and food effect study (Study 1199.17 [5.3.1.1-1]) conducted overseas were submitted. Concentrations of unchanged nintedanib ethanesulfonate (hereinafter referred to as "nintedanib") and its metabolites (BIBF 1202 [m1]; m2, glucuronate conjugate of m1) in plasma and urine were determined by high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) (lower limit of quantitation: unchanged nintedanib in plasma and urine, 0.500 ng/mL and 0.0500 ng/mL; and its metabolites m1 and m2 in plasma and urine, 1.00 ng/mL and 0.100 ng/mL, respectively).

Unless otherwise specified, the dose and concentration of nintedanib ethanesulfonate are expressed as the free base, and those of m1 are expressed as the amphoteric-ion basis. Unless otherwise specified, the pharmacokinetic parameters are expressed as the mean or mean ± SD.

4.(i).A.(1) Absolute bioavailability study (5.3.1.1-2, Study 1199.75 [June to August 2009])

In a single-blind or open-label study was conducted overseas in healthy adult subjects (n = 30), a single dose of nintedanib was administered intravenously at 1, 3, or 6 mg 30 minutes after consumption of a light meal, or orally at 100 mg. The C_{max} of unchanged nintedanib in plasma was 2.1 ± 0.4, 5.2 ± 1.5, 12.5 ± 2.4, and 8.9 ± 3.2 ng/mL, respectively, and $AUC_{0-\infty}$ (AUC_{0-tz} for the 1 mg intravenous dose group) was 6.0 ± 1.4, 34.1 ± 8.8, 74.4 ± 19.2, and 61.3 ± 23.6 ng·h/mL, respectively. The absolute bioavailability following the oral administration of nintedanib calculated from the adjusted geometric mean $AUC_{0-\infty}$ was 4.69% [90% confidence interval (CI); 3.615, 6.078].

4.(i).A.(2) Bioequivalence study (5.3.1.2-1, Study 1199.21 [September to November 2006])

A randomized, open-label, two-treatment, two-period, or three-treatment, three-period, crossover study was conducted overseas in healthy adult subjects (n = 36) to compare the bioequivalence of different formulations of nintedanib 150 mg administered after a standard meal. In the study, subjects received a soft capsule (150 mg) characterized by fast dissolution (>80% of the labeled amount was dissolved in 15 minutes in the dissolution test; hereinafter "fast formulation") and another soft capsule (150 mg) characterized by slow dissolution (>80% of the labeled amount was dissolved in 30 minutes in the dissolution test; hereinafter "slow formulation") in a crossover manner, and some of the subjects also received a liquid formulation (150 mg). Pharmacokinetic parameters were analyzed for tested formulations. The ratios (the fast formulation/the slow formulation) [90% CI] of the adjusted geometric mean C_{max} and $AUC_{0-\infty}$ 1.03 [0.918, 1.146] and 1.03 [0.966, 1.092], respectively. T_{max} (median [range]) was 3.00 (0.75-6.00) hours for the fast formulation and 2.00 (0.750-6.00) hours for the slow formulation. The parameter values were similar between the formulations. C_{max} and $AUC_{0-\infty}$ of nintedanib for the fast formulation to were 202.8% and 152.4%, respectively, of those for the liquid formulation and T_{max} (median [range]) of nintedanib for the liquid formulation was 4.00 (0.25-6.00) hours.

4.(i).A.(3) Food effect study (5.3.1.1-1, Study 1199.17 [October to November 2005])

In an open-label, two-treatment, two-period, crossover study conducted overseas, a single dose of soft capsules of nintedanib (i.e., the proposed product) was orally administered to healthy adults (n = 16) at 150 mg to investigate food effects (with high-fat diet). Pharmacokinetic parameter were analyzed. The ratios (fed/fasting state) [90% CI] of the adjusted geometric mean C_{max} and $AUC_{0-\infty}$ was 1.15 [0.85, 1.57] and 1.21 [0.95, 1.53], respectively. In the fed versus fasted state, C_{max} and $AUC_{0-\infty}$ increased by approximately 20%, and T_{max} (median [range]) increased to 3.98 (1.50-6.05) hours from 2.0 (1.48-3.98) hours.

Based on the above, the exposure to nintedanib in the fed state tended to be greater than that in the fasted state, showing food effect. The applicant therefore explained that nintedanib should be administered after meal.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

As evaluation data, the results from the multiple-dose study in Japanese patients with idiopathic pulmonary fibrosis (IPF) (Study 1199.31 [5.3.3.2-1]), mass balance study (Study 1199.20 [5.3.3.1-1]), population pharmacokinetic analysis in IPF patients (U13-2869 [5.3.3.5-4]), investigations of the drug interaction (Study 1199.161 [5.3.3.4-1], Study 1199.162 [5.3.3.4-2]), and investigation of the effects on QT interval in Japanese patients (5.3.5.3-6) were submitted. In addition, as reference data, the results from the population pharmacokinetic analysis (U13-1588 [5.3.3.5-3]) and investigation of the effects on QT interval (Study 1199.26 [5.3.5.4-1]) in patients with non-small cell lung cancer and patients with IPF were submitted.

4.(ii).A.(1) Studies in Japanese patients

4.(ii).A.(1).1) Japanese phase II study in IPF patients (5.3.3.2-1, Study 1199.31 [May 2010 to March 2011])

A placebo controlled, randomized, double-blind, parallel-group study in IPF patients (n = 50; 9 patients in the nintedanib 50 mg group, 9 patients in the 100 mg group, and 32 patients in the 150 mg group) was conducted to investigate the pharmacokinetics and safety of nintedanib monotherapy or the nintedanib plus pirfenidone combination therapy.

Nintedanib was orally administered twice daily after meal at 50 or 100 mg alone or in combination with pirfenidone for 14 days, or at 150 mg alone or in combination with pirfenidone for 28 days. The nintedanib + pirfenidone group included patients who had been receiving pirfenidone at a dose of 1800 mg/day for ≥3 months, and neither dose change nor starting of a new pirfenidone regimen was allowed during the study period.

The pharmacokinetic parameters of unchanged nintedanib on the day of the first dose of nintedanib monotherapy and those of unchanged nintedanib and its metabolites, m1 and m2, on the day of the last dose are shown in Table 5.

Table 5. Pharmacokinetic parameters of unchanged nintedanib and its metabolites following multiple oral doses of nintedanib alone to Japanese IPF patients for 14 days

	Dose	No. of subjects	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	AUC_{τ} (ng·h/mL)	AUC_{0-24} (ng·h/mL)
Unchanged nintedanib							
Day of the first dose	50 mg BID	3	6.1 ± 6.6	-	-	-	30.1 ± 2.7[a)]
	100 mg BID	3 or 4	14.9 ± 7.1	4.48 (1.97-12.0)	8.3 ± 1.2	-	102 ± 47.3
	150 mg BID	11	42.8 ± 39.9	3.90 (1.00-6.00)	9.3 ± 5.4	-	232 ± 191
Day of the last dose	50 mg BID	2	12.4 ± 12.0	-	-	45.4 ± 43.1	-
	100 mg BID	4	22.7 ± 12.6	3.42 (2.00-4.07)	23.8 ± 5.4	120 ± 36.5	167 ± 46.7
	150 mg BID	9	46.9 ± 30.3	3.87 (1.00-3.97)	27.9 ± 5.3	256 ± 193	364 ± 279
m1							
Day of the last dose	50 mg BID	2	11.8 ± 13.9	-	-	-	-
	100 mg BID	4	30.7 ± 27.5	3.92 (2.92-4.07)	23.2 ± 4.3	173 ± 80.5	239 ± 97.3
	150 mg BID	9	39.4 ± 23.9	3.97 (1.67-6.00)	23.2 ± 3.6	277 ± 182	395 ± 276
m2							
Day of the last dose	50 mg BID	2	31.6 ± 14.2	-	55.7 ± 5.3	334 ± 146	627 ± 244
	100 mg BID	4	105 ± 63.7	0.81 (0.43-3.92)	46.0 ± 3.7	889 ± 333	1670 ± 634
	150 mg BID	9	137 ± 56.0	3.92 (0.50-8.02)	60.6 ± 27.4	1470 ± 599	2840 ± 1230

Mean ± SD; T_{max} is expressed in median (range).
C_{max}, maximum plasma concentration; T_{max}, time to reach the maximum plasma concentration; $t_{1/2}$, elimination half-life; AUC, area under the concentration-time curve; BID, twice-daily
a) AUC_{0-12}

Oral doses of nintedanib 100 or 150 mg or placebo were administered twice daily for 28 days to patients with IPF (13 patients who had been receiving pirfenidone 1800 mg/day for ≥3 months, and 15 patients who had not received pirfenidone). The pharmacokinetic parameters are shown in Table 6. Exposure to nintedanib in the patients receiving pirfenidone tended to be low. The applicant explained that the exposure to nintedanib in the patients receiving pirfenidone is within the range of $AUC_{\tau, ss, norm}$[10] [90% CI] (1.18 [0.49, 2.80] ng·hr/mL/mg) in IPF patients estimated by the population pharmacokinetic analysis [see "4.(ii).A.(3) Population pharmacokinetic analysis"], thus the decreased exposure to nintedanib due to combination use with pirfenidone is unlikely to have a clinical impact. In patients in the nintedanib + pirfenidone group, the pharmacokinetic parameters after the pirfenidone monotherapy were comparable to those after the combination therapy with pirfenidone and nintedanib.

[10] Dose-adjusted AUC_{τ} at steady state

Table 6. Concentrations of unchanged nintedanib and pirfenidone in Japanese IPF patients with and without pirfenidone

	Dose	No. of subjects	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	$t_{1/2}$ (h)	No. of subjects	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	$t_{1/2}$ (h)
Unchanged nintedanib		With pirfenidone[a)]				Without pirfenidone			
Day of the last dose	Nintedanib 100 mg BID	3	17.6 ± 13.2	133 ± 65.7	30.9 ± 5.9	4	22.7 ± 12.6	167 ± 46.7	23.8 ± 5.4
	Nintedanib 150 mg BID	7	24.3 ± 7.1	218 ± 42.3	29.0 ± 6.9	9	46.9 ± 30.3	364 ± 279	27.9 ± 5.3
Pirfenidone[b)]		With nintedanib				Without nintedanib			
Day of the last dose	Nintedanib 100 mg BID	3	12,100 ± 1250	109,000 ± 24,300[c)]	-	3-4	15,300 ± 3070	131,000 ± 20,900[c)]	3.9 ± 2.1
	Nintedanib 150 mg BID	5-8	12,800 ± 3040	104,000 ± 24,100[c)]	3.4 ± 1.4	8-9	13,400 ± 4120	93,400 ± 17,800[c)]	3.3 ± 1.4

Mean ± SD

C_{max}, maximum plasma concentration; AUC, area under the concentration-time curve; $t_{1/2}$, elimination half-life

a) Pirfenidone 1800 mg/day

b) Blood concentration following the administration of pirfenidone 1800 mg/day

c) AUC_{0-12}

4.(ii).A.(2) Studies in non-Japanese subjects

4.(ii).A.(2).1) Mass balance study (5.3.3.1-1, Study 1199.20 [October to November 2005])

In an open-label, uncontrolled study conducted overseas in healthy adults (n = 8), the pharmacokinetic parameters of plasma unchanged nintedanib following a single dose of an oral solution containing 100 mg of ^{14}C-labeled nintedanib were determined. C_{max} was 11.5 ± 5.7 ng/mL, AUC_{0-12} was 67.4 ± 27.5 ng·h/mL, the median T_{max} was 1.29 hours, and λ_z was 0.053 ± 0.016 h^{-1}. In terms of the total plasma radioactivity, C_{max} was 40.5 ± 9.7 ng eq./mL, AUC_{0-12} was 352 ± 63.4 ng eq.·h/mL, the median T_{max} was 2.04 hours, and λ_z was 0.044 ± 0.015 h^{-1}. Radioactivity excreted in urine up to 72 hours post-dose accounted for 0.67% ± 0.17% of the total radioactivity and that in feces up to 120 hours post-dose accounted for 93.5% ± 2.4% of the total radioactivity.

4.(ii).A.(3) Population pharmacokinetic analysis

4.(ii).A.(3).1) Population pharmacokinetic analysis in patients with non-small cell lung cancer and patients with IPF (5.3.3.5-3, U13-1588)

A population pharmacokinetic analysis (NONMEM Version 6.2.0) was performed on data from 1191 subjects obtained at 5611 sampling points in the phase II study involving patients with non-small cell lung cancer (Study 1199.10), foreign phase II study in IPF patients (Study 1199.30), and phase III study in patients with advanced or recurrent non-small cell lung cancer (Studies 1199.13 and 1199.14). In these clinical studies, nintedanib was administered once daily at 50 mg, or twice daily at 50 to 250 mg. The basic pharmacokinetic model was a one-compartment model with assumed primary elimination, absorption lag-time, and primary absorption rates. The covariates[11] selected were body weight for the apparent clearance (CL/F), race, age, study, and smoking history for the relative bioavailability (F1), and study for the absorption rate constant (KA). The population pharmacokinetic parameters were estimated in the standard patients with IPF (Caucasian, 62 years, body weight of 71.5 kg, previous smoker or non-smoker) based on the final model. CL/F was 897 L/h, V2/F was 465 L, and KA was 0.0827 h^{-1}.

4.(ii).A.(3).2) Population pharmacokinetic analysis in patients with IPF (5.3.3.5-4, U13-2869)

A population pharmacokinetic analysis (NONMEM Version 7.2.0) was performed on data from 933 subjects obtained at 3501 sampling points in the foreign phase II study (Study 1199.30) and global phase III studies (Study 1199.32, Study 1199.34) involving patients with IPF. In these clinical studies, nintedanib was administered once daily at 50 mg, or twice daily at 50, 100, or 150 mg. The final model

[11] The covariates investigated for F1 and CL/F were age, sex, body weight, body mass index (BMI), body surface area, smoking history, alcohol use, non-small cell lung cancer tissue type (adenocarcinoma or non-adenocarcinoma), ECOG Performance Status in patients with non-small cell lung cancer, presence or absence of liver metastasis in patients with non-small cell lung cancer, race, creatinine clearance, ALT, AST, serum bilirubin, hepatic impairment (based on liver function tests), LDH, plasma total protein, UGT1A1 genetic polymorphism, concomitant use of P-gp inhibitor, and concomitant use of P-gp inducer. The concomitant use of cathartic was additionally investigated for F1. The covariates investigated for V2/F were age, sex, body weight, BMI, BSA, smoking history, alcohol use, non-small cell lung cancer tissue type (adenocarcinoma or non-adenocarcinoma), ECOG Performance Status in patients with non-small cell lung cancer, presence or absence of liver metastasis in patients with non-small cell lung cancer, race, hepatic impairment (based on liver function tests), and LDH. The covariates investigated for KA were age, sex, non-small cell lung cancer tissue type (adenocarcinoma or non-adenocarcinoma), race, concomitant use of P-gp inhibitor, concomitant use of P-gp inducer, and concomitant use of cathartic.

established in U13-1588 was used as the basic model. The covariates[12] selected were body weight and lactate dehydrogenase (LDH) for apparent clearance (CL/F), and race, study, age, and smoking history for relative bioavailability (F1). The population pharmacokinetic parameters were estimated in the standard patient with IPF (Caucasian, 66 years, body weight of 77.1 kg, LDH 205 U/L, previous smoker or non-smoker) based on the final model. CL/F was 994 L/h, V2/F was 265 L, and KA was 0.0814 h^{-1}. As compared with the standard patient with IPF, the estimated $AUC_{\tau,ss}$ decreased by 14% for patients aged 52 years and increased by 13% for those aged 79 years that increased by 24% for patients weighing 55 and decreased by 19% for those weighing 107 kg and that decreased by 10% for patients with LDH of 146 and increased by 20% for those with LDH of 294 U/L.

4.(ii).A.(4) Pharmacokinetic interactions

4.(ii).A.(4).1) Ketoconazole (5.3.3.4-1, Study 1199.161 [September to November 2012])

Non-Japanese healthy adults (n = 34) received a single dose of nintedanib orally at 50 mg (monotherapy), or ketoconazole, a P-gp and UGT1A1 inhibitor, orally at 400 mg once daily for 3 days, followed by a single dose of oral nintedanib 50 mg 1 hour after the last dose of ketoconazole (combination therapy). The pharmacokinetics of unchanged nintedanib following the nintedanib monotherapy and the combination therapy of nintedanib with ketoconazole was investigated. The pharmacokinetic parameters of unchanged nintedanib following nintedanib monotherapy and the combination therapy of nintedanib with ketoconazole are shown in Table 7. The ratios (combination therapy/monotherapy) of the adjusted geometric mean pharmacokinetic parameters [90% CI] was 1.80 [1.58, 2.05] for C_{max} and 1.61 [1.48, 1.74] for $AUC_{0-\infty}$.

Table 7. Pharmacokinetic parameters of unchanged nintedanib following the nintedanib monotherapy and the combination therapy of nintedanib with ketoconazole

Dose (mg)	No. of subjects	Route of administration	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)	CL (mL/min)	Vz (L)
Nintedanib 50	31	p.o.	5.6 ± 7.2	4.00 (3.00-6.00)	19.2 ± 6.8	42.1 ± 19.6	23,300 ± 8740	39,900 ± 26,100
Nintedanib 50 + ketoconazole	29	p.o	7.7 ± 3.2	3.00 (1.00-6.00)	16.7 ± 6.2	65.6 ± 23.1	14,700 ± 6790	19,900 ± 7970

Mean ± SD; T_{max} is expressed in median (range).
C_{max}, maximum plasma concentration; T_{max}, time to reach the maximum plasma concentration; $t_{1/2}$, elimination half-life; AUC, area under the concentration-time curve; CL, total body clearance; Vz, volume of distribution

4.(ii).A.(4).2) Rifampicin (5.3.3.4-2, Study 1199.162 [January to March 2013])

Non-Japanese healthy adults (n = 26) received a single dose of nintedanib orally at 150 mg (monotherapy), or rifampicin, a P-gp inducer, orally at 600 mg once daily for 7 days, followed by a single dose of oral nintedanib 150 mg on the following day of the last dose of rifampicin (combination therapy). The pharmacokinetics of unchanged nintedanib following the nintedanib monotherapy and the combination therapy with rifampicin was investigated. The pharmacokinetic parameters of unchanged nintedanib following the nintedanib monotherapy and the combination therapy of nintedanib with rifampicin are shown in Table 8. The ratios (combination therapy/monotherapy) of the adjusted geometric mean pharmacokinetic parameters [90% CI] was 0.60 [0.54, 0.66] for C_{max} and 0.50 [0.47, 0.53] for $AUC_{0-\infty}$.

[12] The covariates investigated for F1 were sex, alcohol use, creatinine clearance, ALT, AST, serum bilirubin, LDH, plasma total protein, hepatic impairment (based on liver function tests), UGT1A1 genetic polymorphism, concomitant use of P-gp inhibitor, concomitant use of P-gp inducer, concomitant use of cathartic, and individual study. The covariates investigated for CL/F were sex, race, alcohol use, creatinine clearance, ALT, AST, serum bilirubin, LDH, plasma total protein, hepatic impairment (based on liver function tests), individual study, UGT1A1 genetic polymorphism, concomitant use of P-gp inhibitor, and concomitant use of P-gp inducer. The covariates investigated for V2/F were sex, race, BMI, alcohol consumption, LDH, and individual study; and those investigated for KA were sex, race, individual study, concomitant use of P-gp inhibitor, concomitant use of P-gp inducer, and concomitant use of cathartic.

Table 8. Pharmacokinetic parameters of unchanged nintedanib following the nintedanib monotherapy and the combination therapy of nintedanib with rifampicin

Dose (mg)	No. of subjects	Route of administration	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)	CL (mL/min)	Vz (L)
Nintedanib 150	26	p.o.	24.8 ± 12.8	3.00 (0.50-6.00)	23.1 ± 5.3	194 ± 69	14,500 ± 5170	29,200 ± 12,500
Nintedanib 150 + rifampicin	25	p.o.	13.9 ± 6.2	4.00 (1.00-6.00)	24.0 ± 6.0	94.8 ± 32.7	29,800 ± 11,700	63,100 ± 31,400

Mean ± SD; T_{max} is expressed in median (range).
C_{max}, maximum plasma concentration; T_{max}, time to reach the maximum plasma concentration; $t_{1/2}$, elimination half-life; AUC, area under the concentration-time curve; CL, total body clearance; Vz, volume of distribution

4.(ii).A.(5) Pharmacodynamic studies

4.(ii).A.(5).1) Investigation of the effect on QT interval (5.3.5.4-1, Study 1199.26 [June 2010 to February 2011]; 5.3.5.3-6)

The effects of nintedanib on QT interval were investigated in a clinical study in patients with solid cancer, because of safety concerns with the long-term use of nintedanib in healthy adults.

Multiple doses of nintedanib was administered orally at 200 mg twice daily to patients with renal cell cancer (n = 96) to investigate the effects of nintedanib on heart rate-corrected QT interval (QTcF interval). Changes from baseline in QTcF interval at T_{max} of nintedanib were -2.8 ± 10.6 ms on Day 1 and -3.2 ± 12.8 ms on Day 15. Changes from baseline in QTcF interval at 1 to 12 hours post-dose were -2.2 ± 6.6 ms on Day 1 and 0.5 ± 8.8 ms on Day 15. No clinically relevant prolongation of QTcF interval was observed. No relationship was observed between plasma nintedanib concentrations and QTcF interval. The maximum plasma concentrations of unchanged nintedanib, m1, and m2 at steady state in this study were 54.1 ± 41.6, 122 ± 303, and 629 ± 918 ng/mL, respectively.

In global phase III studies (Study 1199.32, Study 1199.34), nintedanib was orally administered twice daily at 150 mg to Japanese patients with IPF to investigate the effect on QTcF interval. QTcF interval was 410.2 ± 20.3 before the start of administration or at baseline, 413.3 ± 23.0 ms on Day 29, and 414.2 ± 22.6 ms on Day 169 in the placebo group, and 406.1 ± 19.6 ms before the start of administration or at baseline, 406.3 ± 19.1 ms on Day 29, and 410.5 ± 23.4 ms on Day 169 in the nintedanib group. No clinically relevant prolongation of QTcF interval was observed. No relationship was observed between plasma nintedanib concentrations and QTcF interval.

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) Ethnic differences in pharmacokinetics

The applicant's explanation on ethnic differences in pharmacokinetics of nintedanib:
Nintedanib is metabolized to m1 mostly by carboxylesterase, and m1 is then metabolized to m2 by glucuronidation enzyme. The genotype distribution of UGT1A1 is known to differ by ethnic group (Stingl JC et al., *Pharmacol Ther.* 2014;141:92-116). The meta-analysis of data from Study 1199.6,[13] Study 1199.10,[14] and Study 1199.75 showed that $AUC_{0\text{-}12,\ norm}$[15] (geometric mean [coefficient of variation (CV) %]) of unchanged nintedanib in 8 subjects with the normal genotype of UGT1A1 was 1.33 (96.9%), and the those in heterozygous-dominant and in homozygous-dominant subjects (4 each) with a genotype causing decreased enzyme activity were 1.37 (50.5%) and 1.67 (27.3%) ng·h/mL/mg, respectively, suggesting no significant difference among 3 genotypes. The difference in the distribution of UGT1A1 genotypes is considered unlikely to affect the exposure to unchanged nintedanib. As nintedanib is a substrate of P-gp, any difference in P-gp expression may affect exposure to nintedanib, but ethnic differences involving P-gp remain unclear.

In Study 1199.31 in Japanese patients with IPF and Study 1199.26 in non-Japanese patients with renal cell cancer, plasma concentrations of unchanged nintedanib at steady state were investigated. $AUC_{0\text{-}12,\ norm}$[15] values (geometric mean [CV%]) were 1.45 (58.3%) in Study 1199.31 and 1.35 (67.5%) ng·h/mL/mg in Study 1199.26. $C_{max,\ norm}$[16] values (geometric mean [CV%]) were 0.264 (68.1%) in Study 1199.31 and 0.216 (72.7%) ng·h/mL/mg in Study 1199.26. The differences between the studies were not

[13] The combination therapy study of paclitaxel and carboplatin in patients with gynecologic malignant tumor
[14] A phase II study in patients with non-small cell lung cancer
[15] Dose-corrected $AUC_{0\text{-}12}$
[16] Dose-corrected C_{max}

significant. The population pharmacokinetic analysis of data from Study 1199.30, Study 1199.32, and Study 1199.34 showed that AUC of unchanged nintedanib at steady state corrected for the impact factors such as body weight in Japanese patients was estimated to be about 16% higher than that in Caucasian patients. Nevertheless, the ethnic difference fell within a range of inter-individual variability and thus is considered unlikely to have a clinically significant effect.

PMDA accepted the applicant's explanation. From the viewpoint of pharmacokinetics, the use of the data from the global studies including Japanese patients with IPF is generally acceptable as evidence of the efficacy and safety of nintedanib in Japanese IPF patients.

4.(ii).B.(2) Pharmacokinetic interactions

The applicant' explanation on explained the pharmacokinetic interactions of nintedanib:

CYP isoforms play limited roles in the metabolism of nintedanib. The inhibitory effect of nintedanib on CYP isoforms was shown to be weakest on CYP3A4 with IC_{50} of 70.1 μmol/L, which was approximately 947 times C_{max} of unchanged nintedanib at steady state in Japanese patients with IPF treated with nintedanib 150 mg (39.7 ng/mL [0.074 μmol/L], geometric mean). The *in vitro* study using human liver microsome showed that nintedanib did not induce enzymatic activities or mRNA expression of various CYP isoforms. These findings indicate that the clinical dose of nintedanib is unlikely to induce CYP-mediated pharmacokinetic interactions.

Glucuronidation of m1, a major metabolite of nintedanib, d by UGT isoforms (UGT1A1, UGT1A7, UGT1A8, UGT1A10) was suggested. In subjects with a UGT1A1 genotype who exhibit decreased enzyme activity, plasma concentration of m2, a glucuronate conjugate of m1, was low, while plasma concentrations of unchanged nintedanib and m1 were not affected by the genotype. The study using human liver microsome showed that the IC_{50} of nintedanib against UGT1A1-mediated glucuronidation was 24.5 μmol/mL, which was approximately 331 times C_{max} of unchanged nintedanib at steady state in the subjects treated with nintedanib 150 mg (39.7 ng/mL [0.074 μmol/L], geometric mean). It is therefore unlikely that the UGT1A1 genotype affects blood concentration of nintedanib and that nintedanib affects the glucuronidation of other drugs.

At the same time, nintedanib is considered to be a substrate of P-gp. $AUC_{0-\infty}$ (geometric mean) of unchanged nintedanib increased by approximately 70% when used with a P-gp inhibitor ketoconazole and decreased by approximately 50% when used with a P-gp inducer rifampicin. Precautionary statements on the P-gp-related pharmacokinetic interactions will be added in the package insert.

PMDA accepted the applicant's explanation. However, the clinical studies investigated only limited concomitant drugs. Safety and efficacy information for use of nintedanib in combination with other drugs should be further collected through post-marketing surveillance, etc.

4.(ii).B.(3) Effects of hepatic and renal impairment

The applicant's explanation on the effects of decreased hepatic or renal function on the pharmacokinetics of nintedanib:

The urinary excretion rate up to 72 hours after dosing of nintedanib was 0.67% [see "4.(ii).A.(2).1) Mass balance study"] and the decreased renal function is considered to have little effect on the pharmacokinetics of nintedanib. The population pharmacokinetic analysis on data from studies in patients with IPF [see "4.(ii).A.(3) Population pharmacokinetic analysis"] suggested that mild to moderate renal impairment does not affect the pharmacokinetics of nintedanib.

The limited number of patients with moderate to severe hepatic impairment who received nintedanib precludes a determination on the impact of hepatic impairment on nintedanib. Data of patients with IPF from Study 1199.32 and Study 1199.34 showed that the geometric mean of plasma trough concentrations in the patients with mild abnormalities in liver function test[17] (23 subjects) was 1.38 times higher than

[17] Patients with normal hepatic function; below the upper limit of normal (ULN) for ALT, AST, and total bilirubin.
Patients with mild abnormalities in liver function tests; ALT or AST > ULN and ≤2.5 × ULN, or total bilirubin > ULN and ≤1.5 × ULN.
Patients with moderate abnormalities in liver function tests; ALT or AST >2.5 × ULN and ≤5 × ULN, or total bilirubin >1.5 × ULN and ≤3 × ULN.
Patients with severe abnormalities in liver function tests; ALT or AST >5 × ULN, or total bilirubin >3 × ULN.

that in the patients with normal hepatic function (516 subjects), but there was no definite relationship between plasma concentrations of nintedanib and the adverse events (aspartate aminotransferase [AST] increased, alanine aminotransferase [ALT] increased, diarrhea). Data from Study 1199.32 and Study 1199.34 showed that the incidence of the adverse events including diarrhea in the patients with liver function test abnormal (mild) was comparable to that in the patients with normal hepatic function, indicating no safety difference between the two patient subgroups. Based on these findings, the increased exposure to nintedanib in the patients with liver function test abnormal (mild) is considered to have no clinical significance. Nevertheless, the safety and efficacy of nintedanib in patients with hepatic impairment have not been established, and liver function test increased was noted following treatment with nintedanib. Advice on the careful administration of nintedanib to patients with hepatic impairment will be included in the package insert. Results from the ongoing clinical pharmacology study in subjects with hepatic impairment will be available by the end of 2015, and relevant information including the study data will be provided to healthcare professionals.

PMDA's view:
The pharmacokinetics of nintedanib in patients with hepatic or renal impairment has not been investigated in details, and the effects of hepatic and renal functions on the pharmacokinetics of nintedanib remain unclear. However, because of a possible relationship between increased liver function test and the pharmacokinetics of nintedanib and increased liver function test noted following treatment with nintedanib, nintedanib should be carefully administered to patients with hepatic impairment. Information on the safety of nintedanib in patients with hepatic or renal impairment should be further collected.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

As efficacy and safety evaluation data, the results from the foreign phase II study for the dose-response relationship in patients with IPF (Study 1199.30 [5.3.5.1-1]), global phase III studies for the efficacy and safety of nintedanib in patients with IPF involving Japan (Study 1199.32 [5.3.5.1-2], Study 1199.34 [5.3.5.1-3]), and long-term treatment studies (Study 1199.33 [5.3.5.2-1], Study 1199.35 [5.3.5.2-2], Study 1199.40 [5.3.5.2-3]) were submitted. In this section, the doses of nintedanib are expressed in the amount of the free base.

4.(iii).A.(1) Foreign phase II study (5.3.5.1-1, Study 1199.30 [September 2007 to June 2010])

A placebo controlled, randomized, double-blind, parallel-group study was conducted to investigate the efficacy and safety of nintedanib in patients with IPF[18] (target sample size; 400 [80 patients per group]) in 25 foreign countries.

This study consisted of Period 1 (until Week 52) and Period 2 (from Week 52 to Month 36). Period 1 consisted of Cohort 1 to Cohort 4. In Period 1, nintedanib was orally administered once daily (QD) at 50 mg (the other dose in the twice-daily regimen was placebo), or twice daily (BID) at 50 mg, 100 mg, 150 mg, or placebo for 52 weeks.[19] In case of intolerance to the study drug, the dose was allowed to be reduced only by 50 mg. Subjects who completed Period 1 were allowed to receive the subsequent treatment in a blinded manner; the subjects assigned to the placebo group received nintedanib 50 mg QD, and those assigned to the nintedanib group entered in Period 2 in which they were treated at the ending dose of Period 1. A summary of the data from Period 2 in this study is not provided.

All of the 432 randomized subjects were included in the intent-to-treat (ITT) population for the efficacy analysis [Note by PMDA: data of the placebo group as the control group were collected across the

[18] Patients with (a) IPF which was diagnosed by an institutional physician within the past 5 years according to the criteria of the American Thoracic Society (ATS)/European Respiratory Society (ERS), and which was confirmed by the central assessment based on high resolution computed tomography (HRCT) image obtained within 52 weeks prior to randomization or biopsy; (b) forced vital capacity (FVC) ≥50% predicted; (c) carbon monoxide diffusing capacity (DLco) of the lungs 30% to 79% predicted; and (d) arterial O_2 pressure (PaO_2) (room air) ≥55 mm Hg.

[19] The patients were divided into 4 cohorts prior to randomization to the dose groups. In Cohort 1, the subjects were randomized to either the placebo group or nintedanib 50 mg QD group at the ratio of 1:2; in Cohort 2, to the placebo group, nintedanib 50mg QD group, or nintedanib 50 mg BID group at the ratio of 1:1:4; in Cohort 3, to the placebo group, nintedanib 50 mg QD group, 50 mg BID group, or 100 mg BID group at the ratio of 1:1:1:4; and in Cohort 4, to the placebo group, nintedanib 50 mg QD group, 50 mg BID group, 100 mg BID group, or 150 mg BID group at the ratio of 1:1:1:1:4. The entry into the next cohort was implemented based on the evaluation of the independent data monitoring committee.

cohorts, and data of each nintedanib dosing group were combined across the cohorts as follows; 87 subjects in the nintedanib 50 mg QD group, 86 subjects in the 50 mg BID group, 86 subjects in the 100 mg BID group, 86 subjects in the 150 mg BID group, 87 subjects in the placebo group]. Of these, 428 subjects who received the study drug (86 subjects in the nintedanib 50 mg QD group, 86 subjects in the 50 mg BID group, 86 subjects in the 100 mg BID group, 85 subjects in the 150 mg BID group, 85 subjects in the placebo group) were included in the safety analysis. In Period 1, treatment was discontinued in 27.9% (24 of 86) of subjects in the 50 mg QD group, 20.9% (18 of 86) of subjects in the 50 mg BID group, 16.3% (14 of 86) of subjects in the 100 mg BID group, 37.6% (32 of 85) of subjects in the 150 mg BID group, and 28.2% (24 of 85) of subjects in the placebo group.

The annual rates of decline in the forced vital capacity (FVC) from baseline to Week 52 (L/year), the primary endpoint of this study, are shown in Table 9.

Table 9. Annual rates of decline in FVC from baseline to Week 52 (L/year) (ITT population, OC)

	Nintedanib 50 mg QD group	Nintedanib 50 mg BID group	Nintedanib 100 mg BID group	Nintedanib 150 mg BID group	Placebo group
Baseline (L)	2.8 ± 0.8 (87)	2.7 ± 0.7 (86)	2.9 ± 0.8 (86)	2.7 ± 0.8 (86)	2.8 ± 0.8 (87)
Week 52 (L)	2.7 ± 0.9 (61)	2.5 ± 0.7 (71)	2.8 ± 0.8 (67)	2.7 ± 0.9 (57)	2.6 ± 0.8 (61)
Change (L)	−0.2 ± 0.3 (61)	−0.2 ± 0.3 (71)	−0.1 ± 0.3 (67)	−0.1 ± 0.3 (57)	−0.2 ± 0.4 (61)
Annual rate of decline in FVC [95% CI][a)]	−0.174 [−0.247, −0.102] (85)	−0.210 [−0.279, −0.141] (86)	−0.162 [−0.231, −0.093] (85)	−0.060 [−0.135, 0.016] (84)	−0.190 [−0.262, −0.119] (83)
Difference from the placebo group [95% CI][a)] *P* value[a) b)]	0.016 [−0.086, 0.118] *P* = 0.8530	−0.020 [−0.119, 0.080] *P* = 0.7920	0.028 [−0.071, 0.128] *P* = 0.8530	0.131 [0.027, 0.235] *P* = 0.0639	

Mean ± SD (number of subjects)

a) Linear mixed-effects model using interaction between the dose group and time (numerical variable), sex, age, and height as the fixed effects and intercept and time (numerical variable) as the random effects.

b) Adjusted *P* value according to the closed testing principle (the maximum among crude *P* value and *P* values of all the product hypotheses deriving the concerned hypothesis, the product hypothesis was tested based on the contrast).

In Period 1, adverse events occurred in 90.7% (78 of 86) of subjects in the nintedanib 50 mg QD group, 90.7% (78 of 86) of subjects in the 50 mg BID group, 95.3% (82 of 86) of subjects in the 100 mg BID group, 94.1% (80 of 85) of subjects in the 150 mg BID group, and 90.6% (77 of 85) of subjects in the placebo group. The major events are as shown in Table 10. Deaths occurred in 11.6% (10 subjects) in the nintedanib 50 mg QD group, 4.7% (4 subjects) in the 50 mg BID group, 5.8% (5 subjects) in the 100 mg BID group, 1.2% (1 subject) in the 150 mg BID group, and 14.1% (12 subjects) in the placebo group. The causes of deaths reported by ≥2 subjects in any group included IPF (1.2% [1 subject] in the nintedanib 50 mg QD group, 1.2% [1 subject] in the 50 mg BID group, 1.2% [1 subject] in the 100 mg BID group, 0% in the 150 mg BID group, 5.9% [5 subjects] in the placebo group) and respiratory failure (4.7% [4 subjects] in the 50 mg QD group, 0% in the 50 mg BID group, 0% in the 100 mg BID group, 0% in the 150 mg BID group, 0% of the placebo group), and a causal relationship to the study drug was ruled out for all events.

Serious adverse events occurred in 30.2% (26 subjects) in the nintedanib 50 mg QD group, 26.7% (23 subjects) in the 50 mg BID group, 20.9% (18 subjects) in the 100 mg BID group, 27.1% (23 subjects) in the 150 mg BID group, and 30.6% (26 subjects) in the placebo group. Serious adverse events reported by ≥3% of subjects in any group included diarrhoea (1.2% [1 subject] in the nintedanib 50 mg QD group, 1.2% [1 subject] in the 50 mg BID group, 0% in the 100 mg BID group, 3.5% [3 subjects] in the 150 mg BID group, 0% in the placebo group), pneumonia (1.2% [1 subject] in the nintedanib 50 mg QD group, 2.3% [2 subjects] in the 50 mg BID group, 2.3% [2 subjects] in the 100 mg BID group, 1.2% [1 subject] in the 150 mg BID group, 5.9% [5 subjects] in the placebo group), dyspnoea (1.2% [1 subject] in the nintedanib 50 mg QD group, 3.5% [3 subjects] in the 50 mg BID group, 2.3% [2 subjects] in the 100 mg BID group, 1.2% [1 subject] in the 150 mg BID group, 3.5% [3 subjects] in the placebo group), and IPF (5.8% [5 subjects] in the nintedanib 50 mg QD group, 7.0% [6 subjects] in the 50 mg BID group, 4.7% [4 subjects] in the 100 mg BID group, 3.5% [3 subjects] in the 150 mg BID group, 10.6% [9 subjects] in the placebo group).

Adverse events leading to the discontinuation of treatment occurred in 23.3% (20 subjects) in the nintedanib 50 mg QD group, 16.3% (14 subjects) in the 50 mg BID group, 14.0% (12 subjects) in the

100 mg BID group, 30.6% (26 subjects) in the 150 mg BID group, and 25.9% (22 subjects) in the placebo group. Adverse events reported by ≥4% of subjects in any group included diarrhoea (1.2% [1 subject] in the nintedanib 50 mg QD group, 1.2% [1 subject] of the 50 mg BID group, 0% in the 100 mg BID group, 11.8% [10 subjects] in the 150 mg BID group, 0% in the placebo group), nausea (0% in the nintedanib 50 mg QD group, 1.2% [1 subject] of the 50 mg BID group, 0% in the 100 mg BID group, 4.7% [4 subjects] in the 150 mg BID group, 0% in the placebo group), IPF (2.3% [2 subjects] in the nintedanib 50 mg QD group, 2.3% [2 subjects] in the 50 mg BID group, 1.2% [1 subject] in the 100 mg BID group, 2.4% [2 subjects] in the 150 mg BID group, 7.1% [6 subjects] in the placebo group), pneumonia (0% in the nintedanib 50 mg QD group, 1.2% [1 subject] in the 50 mg BID group, 1.2% [1 subject] in the 100 mg BID group, 0% in the 150 mg BID group, 4.7% [4 subjects] in the placebo group).

Adverse events for which a causal relationship to the study drug could not be ruled out (adverse drug reactions) occurred in 27.9% (24 subjects) in the nintedanib 50 mg QD group, 34.9% (30 subjects) in the 50 mg BID group, 47.7% (41 subjects) in the 100 mg BID group, 64.7% (55 subjects) in the 150 mg BID group, and 29.4% (25 subjects) in the placebo group.

Table 10. Adverse events reported by ≥5% of subjects in any group (safety analysis set)

	Nintedanib 50 mg QD(N = 86)	Nintedanib 50 mg BID (N = 86)	Nintedanib 100 mg BID (N = 86)	Nintedanib 150 mg BID (N = 85)	Placebo(N = 85)
Abdominal discomfort	2 (2.3)	3 (3.5)	3 (3.5)	5 (5.9)	1 (1.2)
Abdominal pain	3 (3.5)	5 (5.8)	4 (4.7)	6 (7.1)	3 (3.5)
Abdominal pain upper	6 (7.0)	10 (11.6)	2 (2.3)	10 (11.8)	3 (3.5)
Arthralgia	2 (2.3)	4 (4.7)	5 (5.8)	5 (5.9)	2 (2.4)
Back pain	2 (2.3)	2 (2.3)	3 (3.5)	7 (8.2)	7 (8.2)
Bronchitis	11 (12.8)	16 (18.6)	7 (8.1)	9 (10.6)	11 (12.9)
Chest pain	2 (2.3)	3 (3.5)	4 (4.7)	5 (5.9)	4 (4.7)
Cough	11 (12.8)	17 (19.8)	20 (23.3)	8 (9.4)	17 (20.0)
Decreased appetite	3 (3.5)	4 (4.7)	4 (4.7)	13 (15.3)	0
Diarrhoea	9 (10.5)	17 (19.8)	32 (37.2)	47 (55.3)	13 (15.3)
Dizziness	1 (1.2)	6 (7.0)	7 (8.1)	6 (7.1)	3 (3.5)
Dyspnoea	7 (7.8)	14 (16.3)	13 (15.1)	6 (7.1)	11 (12.9)
Fatigue	4 (4.7)	5 (5.8)	8 (9.3)	9 (10.6)	7 (8.2)
γ-GT increased	0	0	2 (2.3)	6 (7.1)	0
Headache	7 (8.1)	9 (10.5)	8 (9.3)	11 (12.9)	5 (5.9)
IPF	11 (12.8)	7 (8.1)	9 (10.5)	4 (4.7)	11 (12.9)
Influenza	1 (1.2)	3 (3.5)	1 (1.2)	6 (7.1)	4 (4.7)
Lower respiratory tract infection	2 (2.3)	4 (4.7)	6 (7.0)	6 (7.1)	6 (7.1)
Muscle cramp	1 (1.2)	2 (2.3)	5 (5.8)	2 (2.4)	3 (3.5)
Nasopharyngitis	11 (12.8)	8 (9.3)	15 (17.4)	6 (7.1)	11 (12.9)
Nausea	9 (10.5)	8 (9.3)	17 (19.8)	20 (23.5)	8 (9.4)
Pneumonia	2 (2.3)	2 (2.3)	3 (3.5)	1 (1.2)	6 (7.1)
Pruritus	2 (2.3)	2 (2.3)	0	1 (1.2)	7 (8.2)
Pyrexia	1 (1.2)	2 (2.3)	5 (5.8)	5 (5.9)	2 (2.4)
Rash	2 (2.3)	5 (5.8)	5 (5.8)	2 (2.4)	4 (4.7)
Respiratory failure	5 (5.8)	1 (1.2)	0	1 (1.2)	0
Respiratory tract infection	5 (5.8)	5 (5.8)	1 (1.2)	5 (5.9)	4 (4.7)
Sinusitis	1 (1.2)	7 (8.1)	4 (4.7)	2 (2.4)	1 (1.2)
Upper respiratory tract infection	7 (8.1)	10 (11.6)	13 (15.1)	7 (8.2)	13 (15.3)
Urinary tract infection	1 (1.2)	6 (7.0)	5 (5.8)	2 (2.4)	3 (3.5)
Vomiting	1 (1.2)	6 (7.0)	11 (12.8)	11 (12.9)	4 (4.7)
Weight decreased	4 (4.7)	1 (1.2)	3 (3.5)	8 (9.4)	0

Number of subjects (%)
γ-GT: γ-gamma-glutamyltransferase

4.(iii).A.(2) Global phase III study (5.3.5.1-2, Study 1199.32 [May 2011 to October 2013])

A placebo controlled, randomized, double-blind, parallel-group study was conducted to investigate the efficacy and safety of nintedanib in IPF patients[20] (target sample size; 485 subjects [290 in the nintedanib group, 195 in the placebo group]) in 13 countries including Japan, China, France, Germany, India, the UK, and the US.

Nintedanib 150 mg or placebo was orally administered twice daily for 52 weeks. In case of intolerance to the study drug, dose reduction to 100 mg twice daily or treatment interruption[21] was allowed. Of 515 randomized subjects, 513 subjects who received the study drug (309 subjects in the nintedanib group, 204 subjects in the placebo group) were included in the full analysis set (FAS) and the FAS was used for the safety and efficacy analyses. Treatment was discontinued in 25.2% (78 of 309) of subjects in the nintedanib group and 17.6% (36 of 204) of subjects in the placebo group. In the FAS, the Japanese subpopulation consisted of 55 subjects (35 subjects in the nintedanib group, 20 subjects in the placebo group). In this subspopulation, treatment was discontinued in 42.9% (15 of 35) of subjects in the nintedanib group and 25.0% (5 of 20) of subjects in the placebo group.

The annual rates of decline in FVC from baseline to Week 52 (mL/year), the primary endpoint of this study, are shown in Table 11. A statistically significant difference was observed in pair-wise comparison between the nintedanib group and the placebo group, verifying the superiority of nintedanib to placebo. Changes in FVC from baseline to Week 52 were as shown in Figure 2.

Table 11. Annual rates of decline in FVC from baseline to Week 52 (mL/year) (FAS, OC)

	Nintedanib	Placebo
Baseline (mL)	2756.8 ± 735.1 (309)	2844.5 ± 820.1 (204)
Week 52 (mL)	2669.0 ± 772.0 (250)	2664.4 ± 834.0 (165)
Change (mL)	−90.93 ± 242.7 (250)	−201.8 ± 305.9 (165)
Annual rate of decline in FVC [95% CI][a)]	−114.65 [−144.78, −84.53] (309)	−239.91 [−276.68, −203.14] (204)
Difference from the placebo [95% CI][a)] *P* value[a)]	125.26 [77.68, 172.84] *P* < 0.0001	

Mean ± SD (number of subjects)

a) Linear mixed-effects model using the dose group, sex, age, and height as the fixed effects and intercept and time (numerical variable) as the random effects

[20] Patients with (a) IPF which was diagnosed within the past 5 years by an institutional physician according to the criteria of the latest versions of the ATS/ERS/the Japanese Respiratory Society (JRS)/the Latin American Thoracic Association (ALAT) guidelines, and which was confirmed by the central assessment based on the HRCT image (including surgical lung biopsy, if available) obtained within the past 12 months; (b) DLco 30% to 79% of the predicted normal value; and (c) FVC ≥50% of the predicted normal value.

[21] When a subject experienced an adverse event requiring treatment interruption and the event was assessed to be related to the study drug by the investigator (sub-investigator), the subject was allowed to be temporarily withdraw from the study drug for up to 4 weeks. The resumption of the study drug at 100 mg BID was recommended, and, when well tolerated, the dose was increased to 150 mg BID again within 4 weeks. In the event of occurrence of an adverse event being assessed to be unrelated to the study drug by the investigator (sub-investigator) or acute exacerbation of IPF, the subject was allowed to temporarily withdraw from the study drug for up to 8 weeks, then the study drug was to be resumed at the dose used before interruption.

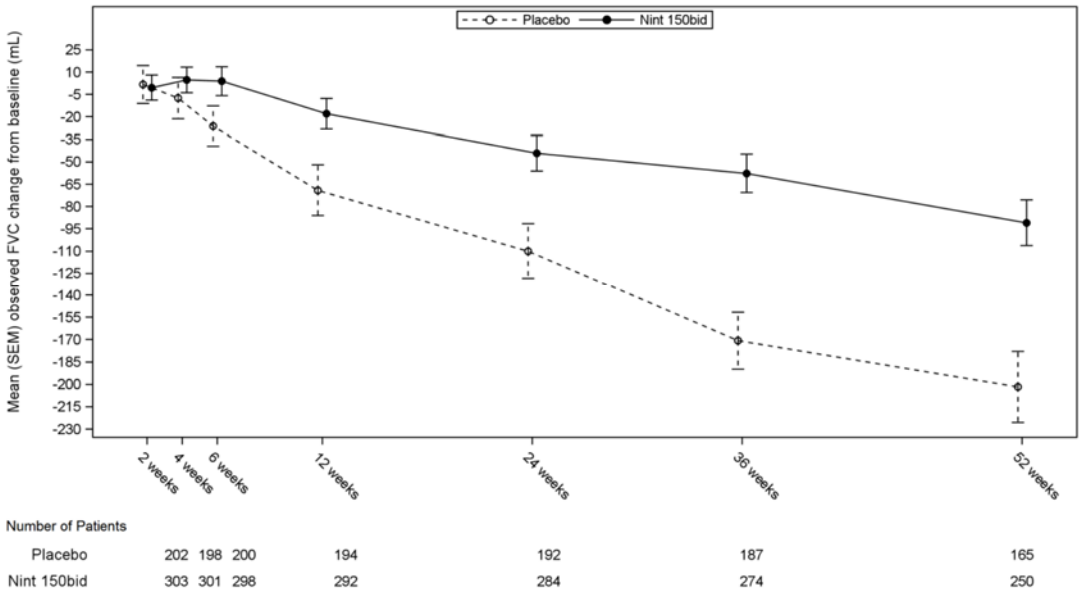

Figure 2. Time-course changes in FVC from baseline to Week 52 (mean ± standard error [SE])

The annual rates of decline in FVC from baseline to Week 52 (mL/year) in the Japanese subset is as shown in Table 12.

Table 12. Annual rates of decline in FVC from baseline to Week 52 (mL/year) in the Japanese subset (FAS, OC)

	Nintedanib	Placebo
Baseline (mL)	2333.1 ± 629.6 (35)	2825.5 ± 568.9 (20)
Week 52 (mL)	2334.5 ± 678.7 (26)	2698.5 ± 683.5 (17)
Change (mL)	−99.7 ± 191.0 (26)	−222.8 ± 284.8 (17)
Annual rate of decline in FVC [95% CI][a)]	−142.20 [−234.62, −49.78] (35)	−282.81 [−395.74, −169.87] (20)
Difference from the placebo group [95% CI][a)]	140.61 [−6.14, 287.35]	

Mean ± SD (number of subjects)

a) Linear mixed-effects model using the dose group, sex, age, and height as the fixed effects and intercept and time (numerical variable) as the random effects.

The incidence of adverse events occurred in 96.4% (298 of 309) of subjects in the nintedanib group and 88.7% (181 of 204 subjects) in the placebo group. Major events are shown in Table 13. Deaths occurred in 3.9% (12 subjects) in the nintedanib group and 4.9% (10 subjects) in the placebo group. The causes of deaths reported by ≥2 subjects in any group included IPF (2.3% [7 subjects] in the nintedanib group, 2.0% [4 subjects] in the placebo group) and lung neoplasm malignant (0.6% [2 subjects] in the nintedanib group, 0% in the placebo group). A causal relationship to the study drug could not be ruled out for a death in 1 subject (sepsis/angina pectoris) of the placebo group.

Serious adverse events occurred in 31.1% (96 subjects) in the nintedanib group and 27.0% (55 subjects) in the placebo group. Serious adverse events reported by ≥2% of subjects in any group included IPF (6.5% [20 subjects] in the nintedanib group, 5.4% [11 subjects] in the placebo group), pulmonary hypertension (1.6% [5 subjects] in the nintedanib group, 2.9% [6 subjects] in the placebo group), pneumonia (1.6% [5 subjects] in the nintedanib group, 2.5% [5 subjects] in the placebo group), and squamous cell carcinoma (0.3% [1 subject] in the nintedanib group, 2.0% [4 subjects] in the placebo group).

Adverse events leading to the discontinuation of treatment occurred in 21.0% (65 subjects) in the nintedanib group and 10.8% (22 subjects) in the placebo group. Adverse events reported by ≥2% of subjects in any group included diarrhoea (4.5% [14 subjects] in the nintedanib group, 0% in the placebo group), IPF (2.3% [7 subjects] in the nintedanib group, 3.4% [7 subjects] in the placebo group), and nausea (2.3% [7 subjects] in the nintedanib group, 0% in the placebo group).

Adverse drug reactions occurred in 73.8% (228 subjects) in the nintedanib group and 31.4% (64 subjects) in the placebo group.

Table 13. Adverse events reported by ≥5% of subjects in any group (safety analysis set)

	Nintedanib (N = 309)	Placebo (N = 204)
Nasopharyngitis	39 (12.6)	34 (16.7)
Bronchitis	36 (11.7)	28 (13.7)
Upper respiratory tract infection	28 (9.1)	18 (8.8)
Lower respiratory tract infection	16 (5.2)	14 (6.9)
Decreased appetite	26 (8.4)	14 (6.9)
Headache	21 (6.8)	12 (5.9)
Cough	47 (15.2)	26 (12.7)
IPF	31 (10.0)	21 (10.3)
Dyspnoea	22 (7.1)	23 (11.3)
Diarrhoea	190 (61.5)	38 (18.6)
Nausea	70 (22.7)	12 (5.9)
Vomiting	40 (12.9)	4 (2.0)
Abdominal pain	26 (8.4)	3 (1.5)
Abdominal pain upper	23 (7.4)	9 (4.4)
Constipation	18 (5.8)	7 (3.4)
Meteorism	18 (5.8)	1 (0.5)
Rash	16 (5.2)	6 (2.9)
Back pain	17 (5.5)	16 (7.8)
Chest pain	18 (5.8)	10 (4.9)
Fatigue	14 (4.5)	13 (6.4)
Weight decreased	25 (8.1)	13 (6.4)

Number of subjects (%)

In the Japanese subset, adverse events occurred in 97.1% (34 of 35) of subjects in the nintedanib group and 90.0% (18 of 20) of subjects in the placebo group. Major events are shown in Table 14. Deaths occurred in 1 subject (IPF) in the nintedanib group and 2 subjects (IPF and pneumothorax in 1 subject each) in the placebo group, but a causal relationship to the study drug was ruled out for all events. Serious adverse events occurred in 51.4% (18 subjects) in the nintedanib group and 30.0% (6 subjects) in the placebo group. Serious adverse events reported by ≥2 subjects in any group included bronchitis (2.9% [1 subject] in the nintedanib group, 10.0% [2 subjects] in the placebo group), lung neoplasm malignant (5.7% [2 subjects] in the nintedanib group, 0% in the placebo group), IPF (11.4% [4 subjects] in the nintedanib group, 15.0% [3 subjects] in the placebo group), pneumothorax (0% in the nintedanib group, 15.0% [3 subjects] in the placebo group), and hepatic enzyme increased (5.7% [2 subjects] in the nintedanib group, 0% in the placebo group).

Adverse events leading to the discontinuation of treatment occurred in 40.0% (14 subjects) in the nintedanib group and 15.0% (3 subjects) in the placebo group. These events reported by ≥2 subjects in any group included decreased appetite (5.7% [2 subjects] in the nintedanib group, 0% in the placebo group), diarrhoea (5.7% [2 subjects] in the nintedanib group, 0% in the placebo group), and hepatic enzyme increased (5.7% [2 subjects] in the nintedanib group, 0% in the placebo group).

Adverse drug reactions occurred in 85.7% (30 subjects) in the nintedanib group and 30.0% (6 subjects) in the placebo group.

Table 14. Adverse events reported by ≥3 subjects in any group (safety analysis set)

	Nintedanib (N = 35)	Placebo (N = 20)
Diarrhoea	25 (71.4)	4 (20.0)
Nasopharyngitis	11 (31.4)	8 (40.0)
Hepatic enzyme increased	9 (25.7)	1 (5.0)
IPF	6 (17.1)	4 (20.0)
Vomiting	6 (17.1)	0
Constipation	5 (14.3)	1 (5.0)
Hepatic function abnormal	5 (14.3)	0
Decreased appetite	4 (11.4)	2 (10.0)
Rash	4 (11.4)	1 (5.0)
Nausea	4 (11.4)	0
Bronchitis	3 (8.6)	4 (20.0)
Pneumothorax	1 (2.9)	3 (15.0)
Insomnia	3 (8.6)	1 (5.0)
Weight decreased	3 (8.6)	1 (5.0)
Abdominal pain upper	3 (8.6)	0

Number of subjects (%)

4.(iii).A.(3) Global phase III study (5.3.5.1-3, Study 1199.34 [May 2011 to October 2013])

A placebo controlled, randomized, double-blind, parallel-group study was conducted to investigate the efficacy and safety of nintedanib in patients with IPF[22] (target sample size; 485 [290 subjects in the nintedanib group, 195 subjects in the placebo group]) in 17 countries including Japan, Canada, China, France, Germany, India, South Korea, and the US.

Nintedanib 150 mg or placebo was orally administered twice daily for 52 weeks. In the case of intolerance to the study drug, dose reduction to 100 mg twice daily or treatment interruption[23] was allowed. Of 551 randomized subjects, 548 subjects who received the study drug (329 subjects in the nintedanib group, 219 subjects in the placebo group) were included in the FAS as well as in the safety and efficacy analyses. Treatment was discontinued in 23.7% (78 of 329) of subjects in the nintedanib group and 20.1% (44 of 219) of subjects in the placebo group. In the FAS, the Japanese subpopulation consisted of 71 subjects (41 subjects in the nintedanib group, 30 subjects in the placebo group). In the Japanese subpopulation, treatment was discontinued in 17.1% (7 of 41) of subjects in the nintedanib group and 20.0% (6 of 30) of subjects in the placebo group.

The annual rates of decline in FVC from baseline to Week 52 (mL/year), the primary endpoint of this study, are shown in Table 15. A statistically significant difference was observed in pair-wise comparison between the nintedanib group and the placebo group, verifying the superiority of nintedanib to placebo. Changes in FVC from baseline to Week 52 were as shown in Figure 3.

[22] Patients who meet all of the following criteria: (a) Patients diagnosed with IPF according to the latest versions of the criteria of the ATS/ERS/JRS/ALAT guidelines within 5 years by an institutional physician, and IPF confirmed by a central laboratory of the HRCT image (including surgical lung biopsy, if available) obtained within 12 months; (b) patients with DLco 30% to 79% of predicted normal value; and (c) patients with FVC ≥50% of predicted normal value.

[23] When a subject experienced an adverse event requiring treatment interruption and the event was assessed to be related to the study drug by the investigator (sub-investigator), the subject could temporarily withdraw from the study drug for up to 4 weeks. The resumption of the study drug at 100 mg BID was recommended, and, when well tolerated, the dose was increased to 150 mg BID again within 4 weeks. In the event of occurrence of an adverse event being assessed to be unrelated to the study drug by the investigator (sub-investigator) or acute exacerbation of IPF, the subject was allowed to temporarily withdraw from the study drug for up to 8 weeks, and then the study drug was to be resumed at the dose used before interruption.

Table 15. Annual rates of decline in FVC from baseline to Week 52 (mL/year) (FAS, OC)

	Nintedanib	Placebo
Baseline (mL)	2672.8 ± 776.0 (329)	2619.0 ± 787.3 (219)
Week 52 (mL)	2637.3 ± 811.8 (269)	2512.5 ± 821.4 (180)
Change (mL)	−86.9 ± 283.4 (269)	−204.0 ± 280.5 (180)
Annual rate of decline in FVC [95% CI][a)]	−113.59 [−144.50, −82.69] (329)	−207.32 [−245.27, −169.38] (219)
Difference from the placebo group [95% CI][a)] *P* value[b)]	93.73 [44.78, 142.68] *P* = 0.0002	

Mean ± SD (number of subjects)

a) Linear mixed-effects model using the dose group, sex, age, and height as the fixed effects and intercept and time (numerical variable) as the random effects.

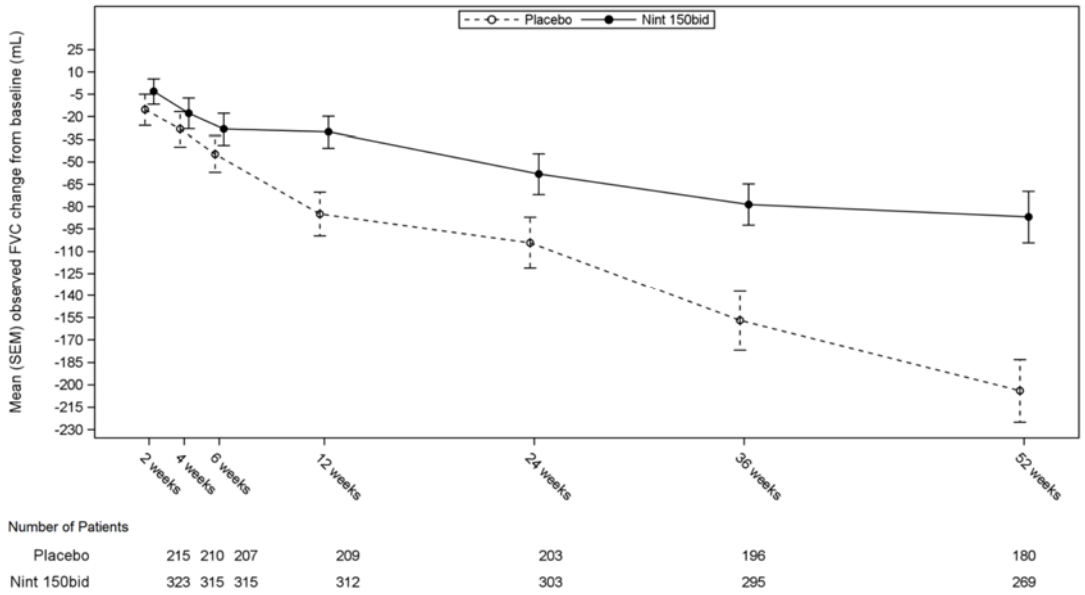

Figure 3. Time-course Changes in FVC from baseline to Week 52 (mean ± SE)

The annual rates of decline in FVC from baseline to Week 52 (mL/year) in the Japanese subset are shown in Table 16.

Table 16. Annual rates of decline in FVC from baseline to Week 52 (mL/year) in the Japanese subset (FAS, OC)

	Nintedanib	Placebo
Baseline (mL)	2497.1 ± 705.2 (41)	2273.8 ± 768.2 (30)
Week 52 (mL)	2378.3 ± 742.3 (38)	2134.7 ± 797.4 (25)
Change (mL)	−104.9 ± 232.0 (38)	−229.8 ± 164.6 (25)
Annual rate of decline in FVC [95% CI][a)]	−137.60 [−226.16, −49.03] (41)	−254.02 [−359.35, −148.69] (30)
Difference from the placebo group [95% CI][a)]	116.43 [−23.21, 256.06]	

Mean ± SD (number of subjects)

a) Linear mixed-effects model using the dose group, sex, age, and height as the fixed effects and intercept and time (numerical variable) as the random effects

Adverse events occurred in 94.5% (311 of 329) of subjects in the nintedanib group and 90.4% (198 of 219 subjects) in the placebo group, and the major events are shown in Table 17. Deaths occurred in 7.6% (25 subjects) in the nintedanib group and 9.6% (21 subjects) in the placebo group. The causes of deaths reported by ≥2 subjects in any group were IPF (3.3% [11 subjects] in the nintedanib group, 5.5% [12 subjects] in the placebo group), pneumonia (1.5% [5 subjects] in the nintedanib group, 0.5% [1 subject] in the placebo group), myocardial infarction (0.6% [2 subjects] in the nintedanib group, 0% in the placebo group), respiratory failure (0.6% [2 subjects] in the nintedanib group, 0.9% [2 subjects] in the placebo group), and cardiac arrest (0% in the nintedanib group, 0.9% [2 subjects] in the placebo group), and a causal relationship to the study drug was ruled out for all events.

Serious adverse events occurred in 29.8% (98 subjects) in the nintedanib group and 32.9% (72 subjects) in the placebo group. Serious adverse events reported by ≥2% of subjects in any group included IPF

(6.7% [22 subjects] in the nintedanib group, 12.8% [28 subjects] in the placebo group), pneumonia (5.5% [18 subjects] in the nintedanib group, 5.0% [11 subjects] in the placebo group), and respiratory failure (0.6% [2 subjects] in the nintedanib group, 2.3% [5 subjects] in the placebo group).

Adverse events leading to the discontinuation of treatment occurred in 17.6% (58 subjects) in the nintedanib group and 15.1% (33 subjects) in the placebo group. These events reported by ≥1% of subjects in any group included diarrhoea (4.3% [14 subjects] in the nintedanib group, 0.5% [1 subject] in the placebo group), nausea (1.8% [6 subjects] in the nintedanib group, 0% in the placebo group), IPF (1.8% [6 subjects] in the nintedanib group, 6.4% [14 subjects] in the placebo group), pneumonia (1.5% [5 subjects] in the nintedanib group, 0.5% [1 subject] in the placebo group), and decreased appetite (1.2% [4 subjects] in the nintedanib group, 0% in the placebo group).

Adverse drug reactions occurred in 69.0% (227 subjects) in the nintedanib group and 25.6% (56 subjects) in the placebo group.

Table 17. Adverse events reported by ≥5% of subjects in any group (safety analysis set)

	Nintedanib (N = 329)	Placebo (N = 219)
Nasopharyngitis	48 (14.6)	34 (15.5)
Bronchitis	31 (9.4)	17 (7.8)
Upper respiratory tract infection	30 (9.1)	24 (11.0)
Pneumonia	21 (6.4)	18 (8.2)
Respiratory tract infection	19 (5.8)	15 (6.8)
Influenza	17 (5.2)	8 (3.7)
Decreased appetite	42 (12.8)	10 (4.6)
Headache	22 (6.7)	7 (3.2)
Hypertension	13 (4.0)	11 (5.0)
Cough	38 (11.6)	31 (14.2)
IPF	33 (10.0)	40 (18.3)
Dyspnoea	27 (8.2)	25 (11.4)
Diarrhoea	208 (63.2)	40 (18.3)
Nausea	86 (26.1)	16 (7.3)
Vomiting	34 (10.3)	7 (3.2)
Abdominal pain	30 (9.1)	7 (3.2)
Constipation	20 (6.1)	10 (4.6)
Abdominal pain upper	18 (5.5)	6 (2.7)
Back pain	20 (6.1)	13 (5.9)
Arthralgia	8 (2.4)	12 (5.5)
Fatigue	26 (7.9)	20 (9.1)
Chest pain	16 (4.9)	12 (5.5)
Weight decreased	37 (11.2)	2 (0.9)

Number of subjects (%)

In the Japanese subset, adverse events occurred in 100% (41 of 41) of subjects in the nintedanib group and 96.7% (29 of 30) subjects in the placebo group. Major events are shown in Table 18. Death occurred in 1 subject (IPF) of the placebo group, and a causal relationship to the study drug was ruled out for the death. Serious adverse events occurred in 36.6% (15 subjects) in the nintedanib group and 50.0% (15 subjects) in the placebo group. Serious adverse events reported by ≥4% of subjects in any group included pneumonia (7.3% [3 subjects] in the nintedanib group, 6.7% [2 subjects] in the placebo group), bronchitis (4.9% [2 subjects] in the nintedanib group, 0% in the placebo group), deep vein thrombosis (0% in the nintedanib group, 6.7% [2subjects] in the placebo group), hypoxia (7.3% [3 subjects] in the nintedanib group, 3.3% [1 subject] in the placebo group), IPF (7.3% [3 subjects] in the nintedanib group, 30.0% [9 subjects] in the placebo group).

Adverse events leading to the discontinuation of treatment occurred in 12.2% (5 subjects; decreased appetite in 2 subjects, bladder cancer, IPF, erectile dysfunction, and fatigue in 1 subject each) in the nintedanib group and 20.0% (6 subjects; IPF in 5 subjects, deep vein thrombosis in 1 subject) in the placebo group. Adverse drug reactions occurred in 87.8% (36 subjects) in the nintedanib group and 40.0% (12 subjects) in the placebo group.

Table 18. Adverse events reported by ≥3 subjects in any group (safety analysis set)

	Nintedanib (N = 41)	Placebo (N = 30)
Diarrhoea	32 (78.0)	5 (16.7)
Nasopharyngitis	16 (39.0)	11 (36.7)
Nausea	11 (26.8)	0
Decreased appetite	10 (24.4)	2 (6.7)
Hepatic function abnormal	9 (22.0)	1 (3.3)
Bronchitis	8 (19.5)	3 (10.0)
Weight decreased	8 (19.5)	2 (6.7)
Constipation	5 (12.2)	1 (3.3)
IPF	4 (9.8)	9 (30.0)
Vomiting	4 (9.8)	0
Abdominal discomfort	3 (7.3)	6 (20.0)
Pneumonia	3 (7.3)	3 (10.0)
Upper respiratory tract inflammation	3 (7.3)	3 (10.0)
Back pain	3 (7.3)	3 (10.0)
Hepatic enzyme increased	3 (7.3)	1 (3.3)
Fatigue	2 (4.9)	3 (10.0)
Gastritis	3 (7.3)	1 (3.3)
Hypoxia	3 (7.3)	1 (3.3)
Herpes zoster	1 (2.4)	3 (10.0)
Insomnia	1 (2.4)	3 (10.0)
Eczema	1 (2.4)	3 (10.0)
Diabetes mellitus	0	6 (20.0)
Dermatitis contact	0	3 (10.0)
Arthralgia	0	3 (10.0)

Number of subjects (%)

4.(iii).A.(4) Long-term treatment study (5.3.5.2-1, Study 1199.33 [July 2012 to ongoing, [redacted] 20[redacted] data cut-off])

An open-label, uncontrolled study was conducted to investigate the long-term safety of nintedanib in patients with IPF (target sample size, 750 subjects) who completed Study 1199.32 or Study 1199.34 (including the follow-up period after 52 weeks of treatment).

The ending dose of Study 1199.32 or Study 1199.34 was used as the starting dose of this study. Nintedanib was orally administered at 150 mg twice daily to the subjects who had orally received the study drug (nintedanib 150 mg or placebo) twice daily in the preceding study, while nintedanib was orally administered at 100 mg twice daily to subjects who had orally received the study drug (nintedanib 100 mg or placebo) twice daily in the preceding study. After the data-lock and key opening of Study 1199.32 or Study 1199.34, the subjects who had received nintedanib 100 mg or placebo in the preceding study were allowed to receive nintedanib 150 mg twice daily. In case of intolerance to nintedanib, dose reduction to 100 mg twice daily or treatment interruption[24] was allowed.

Of 825 subjects who completed the treatment in the preceding study, 734 subjects (360 subjects participating in Study 1199.32 and 374 subjects participating in Study 1199.34 prior to entry to this study) who received the study drug were all included in the FAS. The FAS was used for the safety and efficacy analyses. The discontinuation of treatment occurred in 238 of 734 subjects (32.4%). The median treatment period (range) as of the data cut-off was 18.4 months (1 day to 28.8 months). In the FAS, the Japanese subpopulation consisted of 84 subjects. Of these, 29 subjects (34.5%) discontinued treatment.

Adverse events occurred in 94.4% (693 of 734) of subjects. Major events are shown in Table 19. Deaths occurred in 10.2% (75 subjects). The causes of deaths reported by ≥3 subjects included IPF (3.3% [24 subjects]), respiratory failure (1.1% [8 subjects]), pneumonia (0.7% [5 subjects]), lung infection (0.5%

[24] When a subject experiences an adverse event requiring treatment interruption and the event was assessed to be related to the study drug by the investigator (sub-investigator), the subject was allowed to temporarily withdraw from the study drug for up to 4 weeks. The resumption of the study drug at 100 mg BID was recommended, and, when well tolerated, the dose was increased to 150 mg BID again within 4 weeks. Following acute exacerbation of IPF, the subject was allowed to temporarily withdraw from the study drug for up to 8 weeks, and then the study drug was to be resumed at the dose used before interruption. In the event of occurrence of an adverse event being assessed to be unrelated to the study drug by the investigator (sub-investigator), the subject was allowed to temporarily withdraw from the study drug for up to 12 weeks, then treatment was to be resumed at the dose used before interruption.

[4 subjects]), acute respiratory failure, dyspnoea, hypoxia, pulmonary embolism, and multi-organ failure (0.4% each [3 subjects each]), and a causal relationship to the study drug could not be ruled out for IPF in 1 subject. Serious adverse events occurred in 40.9% (300 subjects). Serious adverse events reported by ≥2% of subjects included IPF (10.2% [75 subjects]), pneumonia (5.6% [41 subjects]), pulmonary hypertension (4.1% [30 subjects]), dyspnoea (3.4% [25 subjects]), lung infection (2.9% [21 subjects]), and respiratory failure (2.0% [15 subjects]). Adverse events leading to the discontinuation of treatment occurred in 23.6% (173 subjects). These events reported by ≥1% of subjects included IPF (6.0% [44 subjects]), diarrhoea (5.3% [39 subjects]), and weight decreased (1.0% [7 subjects]).

Adverse drug reactions occurred in 68.4% (502 subjects).

Table 19. Adverse events reported by ≥5% of subjects (safety analysis set)

Diarrhoea	467 (63.6)
Cough	122 (16.6)
Nausea	119 (16.2)
IPF	118 (16.1)
Nasopharyngitis	103 (14.0)
Bronchitis	102 (13.9)
Dyspnoea	98 (13.4)
Weight decreased	84 (11.4)
Decreased appetite	77 (10.5)
Upper respiratory tract infection	74 (10.1)
Vomiting	68 (9.3)
Fatigue	55 (7.5)
Abdominal pain	52 (7.1)
Pneumonia	51 (6.9)
Constipation	40 (5.4)
Abdominal pain upper	38 (5.2)

Number of subjects (%)

Adverse events occurred in 98.8% (83 of 84) of subjects in the Japanese subpopulation. The events reported by ≥6% of subjects included diarrhoea (76.2% [64 subjects]), nasopharyngitis (35.7% [30 subjects]), IPF (26.2% [22 subjects]), decreased appetite and weight decreased (20.2% each [17 subjects each]), pneumonia (14.3% [12 subjects]), pulmonary hypertension and bronchitis (13.1% each [11 subjects each]), nausea (11.9% [10 subjects]), hepatic enzyme increased and vomiting (9.5% each [8 subjects each]), hepatic function abnormal (7.1% [6 subjects]), and insomnia and back pain (6.0% each [5 subjects each]). Deaths occurred in 11.9% (10 subjects). The causes of deaths reported by ≥2 subjects included IPF (3.6% [3 subjects]) and pneumonia (2.4% [2 subjects]), but a causal relationship to the study drug was ruled out for all events. Serious adverse events occurred in 57.1% (48 subjects). Serious adverse events reported by ≥2 subjects included IPF (19.0% [16 subjects]), pneumonia and pulmonary hypertension (13.1% each [11 subjects each]), dyspnoea exertional (3.6% [3 subjects]), and acute respiratory failure, dyspnoea, hypoxia, pneumothorax, bronchitis, pneumonia bacterial, pneumonia influenza, and cataract (2.4% each [2 subjects each]). Adverse events leading to the discontinuation of treatment occurred in 29.8% (25 subjects). These events reported by ≥2% of subjects included IPF (8.3% [7 subjects]), diarrhoea (3.6% [3 subjects]), and decreased appetite and weight decreased (2.4% each [2 subjects each]).

Adverse drug reactions occurred in 82.1% (69 subjects).

4.(iii).A.(5) Long-term treatment study (5.3.5.2-3, Study 1199.40 [September 2011 to ongoing, [redacted] 20[redacted] data cut-off])

An open-label, uncontrolled study was conducted to investigate the long-term safety of nintedanib used concomitantly with pirfenidone in patients with IPF (target sample size, 20) who completed the Japanese phase II study (Study 1199.31) [see “4.(ii).A.(1) Studies in Japanese patients”].

Pirfenidone[25] (at a constant dose throughout the study period) and nintedanib 150 mg were orally administered twice daily. In case of intolerance to nintedanib, dose reduction to 100 mg twice daily or the interruption and subsequent resumption[26] of the treatment were allowed.

Of 46 subjects who completed Study 1199.31, 20 subjects participated in Study 1199.40 and received the study drug. The 20 subjects were all included in the safety and efficacy analyses. The discontinuation of treatment occurred in 65.0% (13 subjects). As of the data cut-off, the median treatment period (range) was 28.6 months (1.8-37.4 months).

Adverse events occurred in 100.0% (20 subjects). Major events are shown in Table 20. Death occurred in 35.0% (7 subjects IPF), and a causal relationship to the study drug was ruled out for all events. Serious adverse events occurred in 80.0% (16 subjects). Serious adverse events reported by ≥2 subjects included IPF (60.0% [12 subjects]), dyspnoea exertional (20.0% [4 subjects]), and pneumothorax, pneumonia, respiratory tract infection, decreased appetite, cholecystitis, and deep vein thrombosis (10.0% each [2 subjects each]). A causal relationship to the study drug could not be ruled out for cholecystitis/decreased appetite (1 subject). Adverse events leading to the discontinuation of treatment occurred in 45.0% (9 subjects; IPF in 7 subjects, squamous cell carcinoma of lung in 1 subject, decreased appetite in 1 subject). A causal relationship to the study drug could not be ruled out for decreased appetite (1 subject).

Adverse drug reactions occurred in 75.0% (15 subjects).

Table 20. Adverse events reported by ≥3 subjects (safety analysis set)

Diarrhoea	13 (65.0)
IPF	12 (60.0)
Nausea	10 (50.0)
Decreased appetite	8 (40.0)
Constipation	7 (35.0)
Nasopharyngitis	7 (35.0)
Weight decreased	5 (25.0)
Vomiting	5 (25.0)
Hypertension	5 (25.0)
Abdominal pain	4 (20.0)
Dyspnoea exertional	4 (20.0)
Oral candidiasis	4 (20.0)
Pneumonia	4 (20.0)
Hepatic enzyme increased	3 (15.0)
Respiratory tract infection	3 (15.0)
Pyrexia	3 (15.0)
Back pain	3 (15.0)
Insomnia	3 (15.0)
Pneumothorax	3 (15.0)
Haemorrhoids	3 (15.0)

Number of subjects (%)

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Data for review

The applicant's explanation on the drug therapy system for IPF:
A set of the clinical practice guidelines (Raghu G et al., *Am J Respir Crit Care Med.* 2011;183:788-824) was established by cooperation of 4 academic societies, namely the Japanese Respiratory Society, American Thoracic Society, European Respiratory Society, and Latin American Thoracic Association. It explains that IPF is diagnosed by the following: (a) exclusion of interstitial pneumonia with an apparent cause other than IPF; (b) identifying the presence or absence of findings indicative of usual interstitial pneumonia (UIP) on high-resolution computed tomography (HRCT) image; and (c)

[25] Pirfenidone was administered at 1800 mg/day to 17 of 20 subjects (85.0%) and at 1200 mg/day to 3 of 20 subjects (15.0%).

[26] When a subject experienced an adverse event requiring treatment interruption and the event was assessed to be related to the study drug by the investigator (sub-investigator), the subject was allowed to temporarily withdraw from the study drug for up to 4 weeks. The resumption of treatment with nintedanib100 mg BID was recommended, and, when well tolerated, the dose of nintedanib was increased to 150 mg BID again within 4 weeks. In the event of occurrence of an adverse event being assessed to be unrelated to the study drugs by the investigator (sub-investigator) or acute exacerbation of IPF, the subject were allowed to temporarily withdraw from the study drugs for up to 8 weeks, then treatment was to be resumed at the dose used before interruption (nintedanib 150 mg BID).

confirmed findings by HRCT and surgical biopsy. This method is common in clinical practice in Japan. There have been no reports suggesting ethnic differences in pathology or symptoms of IPF. The clinical practice guidelines describes that the standard drug therapy for IPF has not been established. The clinical guidelines in Japan (Guidelines for diagnosis and treatment of idiopathic interstitial pneumonia [2nd ed.], 2011) also explain that the treatment goal is "at least prevention of disease progression, if not improvement."

Because of the similarities between Japan and other countries in the diagnosis, pathology, treatment system, etc. of IPF and of no obvious ethnic differences in the pharmacokinetic profile of nintedanib [see "4.(ii).B.(1) Ethnic differences in pharmacokinetics"], the applicant considered the data from the global phase III studies (Study 1199.32, Study 1199.34) involving Japan were able to be used as the pivotal study data to construct a data package for the purpose of the application in Japan.

Considering the applicant's explanation, PMDA has concluded that the efficacy and safety of nintedanib in patients with IPF can be evaluated primarily based on the data from the global phase III studies involving Japan, and thus decided to evaluate the efficacy and safety in Japanese patients with IPF based on the results of the subgroup analysis of data from Japanese patients included in the mentioned studies.

4.(iii).B.(2) Efficacy

4.(iii).B.(2).1) Endpoint

The applicant's explanation on the primary endpoint in the global phase III studies (Study 1199.32, Study 1199.34):

In medical settings, FVC is used as one of the standard indices for the assessment of pathology and treatment-related decision making on IPF (du Bois RM et al., *Am J Respir Crit Care Med*. 2012;186:712-715.). Several reports also indicate that over-time change in FVC is related to prognosis (Latsi PI et al., *Am J Respir Crit Care Med*. 2003;168:531-537, Collard HR et al., *Am J Respir Crit Care Med*. 2003;168:538-542, Flaherty KR et al., *Am J Respir Crit Care Med*. 2003;168:543-548.). Reflecting such characteristics information, change in FVC from baseline to Month 6 to Month 12 has been used as the efficacy endpoint in recent clinical studies in patients with IPF (du Bois RM et al., *Am J Respir Crit Care Med*. 2011;184:459-466, Collard HR et al., *Am J Respir Crit Care Med*. 2003;168:538-542, Latsi PI et al., *Am J Respir Crit Care Med*. 2003;168:531-537.). Therefore, the annual rate of decline in FVC (mL/year) was selected as the primary endpoint of the global phase III studies (Study 1199.32, Study 1199.34).

PMDA's view:

Considering the treatment goal of IPF described as "at least prevention of disease progression, if not improvement" in the clinical guideline available in Japan (Guidelines for diagnosis and treatment of idiopathic interstitial pneumonia [2nd ed.], 2011) and the life-threatening nature of IPF, the aim of the drug therapy for IPF is life prolongation. Nevertheless, considering the published several reports suggesting a relationship between change in FVC and life prognoses of patients with IPF and the possibility that the prevention of decline in FVC leads to delayed worsening of the patient's QOL accompanied by worsening respiratory function, the annual rate of decline in FVC (mL/year) is acceptable as the primary endpoint in the global phase III studies.

4.(iii).B.(2).2) Study data

The applicant's explanation on the efficacy of nintedanib:

As shown in Table 21, the annual rates of decline in FVC in Study 1199.32 and Study 1199.34 were -115 and -114 mL/year in the nintedanib group and -240 and -207 mL/year in the placebo group, respectively. The difference between the nintedanib group and the placebo group [95% CI] was 125.26 [77.68, 172.84] mL/year in Study 1199.32 and was 93.73 [44.78, 142.68] mL/year in Study 1199.34. In both studies, statistically significant differences ($P < 0.001$, suppressed annual rate of decline in FVC by approximately 50%) were consistently observed.

According to a report on other clinical studies in patients with IPF, the annual rate of decline in FVC was approximately 200 mL/year (Ley B et al., *Am J Respir Crit Care Med.* 2011;183:431-440). Other reports point out that a comparison in the annual rates of decline in FVC revealed accelerated deterioration of lung function in patients with IPF as compared with the healthy elderly (30-40 mL/year)

(Knudson RJ et al., *Am Rev Respir Dis.* 1976;113:587-600) and that prolonged survival was demonstrated in the patients who had had ≤5% or ≤10% absolute decline in %FVC after 6-to-12-month treatment (du Bois RM et al., *Am J Respir Crit Care Med*. 2011;184:459-466, du Bois RM et al., *Am J Respir Crit Care Med*. 2011;184:1382-1389, Collard HR et al., *Am J Respir Crit Care Med*. 2003;168:538-542, Zappala CJ et al., *Eur Respir J*. 2010;35:830-835, Flaherty KR et al., *Am J Respir Crit Care Med*. 2003;168:543-548, Richeldi L et al., *Thorax*. 2012;67:407-411, Schmidt SL et al., *Eur Respir J*. 2011;38:176-183, Schmidt SL et al., *Chest*. 2014;145:579-585.). The odds ratio [95% CI] of the percentage of patients with a ≤5% or ≤10% absolute decline in %FVC (FVC responders) from baseline to Week 52 in the nintedanib group relative to the placebo group was 1.85 [1.28, 2.66] and 1.91 [1.32, 2.79], respectively, in Study 1199.32 and 1.79 [1.26, 2.55] and 1.29 [0.89, 1.86], respectively, in Study 1199.34, indicating higher percentages of FVC responders in the nintedanib groups than in the placebo groups. Both studies suggested that nintedanib showed clinically significant reduction in the annual rate of decline in FVC (mL/year).

The results of the secondary endpoints used in Study 1199.32 and 1199.34 are shown in Table 21. The changes in Saint George's Respiratory Questionnaire (SGRQ) total score[27] and time to first acute IPF exacerbation[28] showed no differences between the nintedanib group and the placebo group in Study 1199.32. On the other hand, the nintedanib group was superior to the placebo group in these parameters in Study 1199.34. The mortality tended to be lower in the nintedanib group than in the placebo group in both studies.

These data showed that nintedanib had clinically significant reduction in the progression of the pathological conditions, which may contribute to improved prognosis of patients with IPF.

Table 21. Results from the FAS in Study 1199.32 and Study 1199.34 (FAS, OC)

	Study 1199.32			Study 1199.34		
	Nintedanib	Placebo	Difference from the placebo [95% CI] *P* value	Nintedanib	Placebo	Difference from the placebo [95% CI] *P* value
Annual rate of decline in FVC (mL/year)[a)]	−114.65 ± 15.33 (309)	−239.91 ± 18.71 (204)	125.26 [77.68, 172.84] *P* < 0.0001	−113.59 ± 15.73 (329)	−207.32 ± 19.31 (219)	93.73 [44.78, 142.68] *P* = 0.0002
Change in SGRQ[b)] total score	4.34 ± 0.80 (289)	4.39 ± 0.96 (200)	−0.05 [−2.50, 2.40]	2.80 ± 0.73 (320)	5.48 ± 0.89 (213)	−2.69 [−4.95, −0.43]
Percentage of the subjects with acute exacerbation	6.1% (19/309)	5.4% (11/204)	1.15[c)] [0.54, 2.42]	3.6% (12/329)	9.6% (21/219)	0.38[c)] [0.19, 0.77]
Mortality	4.2% (13/309)	6.4% (13/204)	0.63[d)] [0.29, 1.36]	6.7% (22/329)	9.1% (20/219)	0.74[d)] [0.40, 1.35]
FVC responders (≤5%)	52.8% (163/309)	38.2% (78/204)	1.85[e)] [1.28, 2.66]	53.2% (175/329)	39.3% (86/219)	1.79[e)] [1.26, 2.55]
FVC responders (≤10%)	70.6% (218/309)	56.9% (116/204)	1.91[e)] [1.32, 2.79]	69.6% (229/329)	63.9% (140/219)	1.29[e)] [0.89, 1.86]

Least squares mean ± SE (number of subjects) or % (number of subjects)

a) Linear mixed-effects model using the dose group, sex, age, and height as fixed effects and intercept and time (numerical variable) as random effects

b) Repeated measure mixed-effects model on the hypothesis of compound symmetry covariance structure in the subjects using the dose group, time (Visit), interaction between the dose group and time (Visit), baseline, and interaction between baseline and time (Visit) as fixed effects and the intercept as random effects

c) Cox regression model using the dose group, sex, age, and height as explanatory variables for time to first acute exacerbation

d) Cox regression model using the dose group, sex, age, and height as explanatory variables

e) Logistic regression model using the dose group, sex, age, height, and %FVC at baseline as explanatory variables

[27] QOL indicator: The questionnaire consists of 3 parts including symptoms, activity, and impact. It is calculated based on the total score of all questions. The total score ranges from 0 (completely healthy) to 100 (worst possible condition).

[28] In Study 1199.32 and Study 1199.34, acute exacerbation of IPF was defined as an adverse event meeting all of the following conditions: (a) unexplained worsening or onset of dyspnea within 30 days; (b) new diffuse pulmonary infiltrates on chest X-ray or new HRCT parenchymal abnormalities other than pneumothorax or pleural effusion (new ground-glass opacities) since the last visit; and (c) the exclusion of infections, left heart failure, pulmonary embolism, and acute lung disorder with an identifiable cause in routine clinical practice or by microbiology tests.

PMDA's view:
The superiority of nintedanib to placebo in the annual rate of decline in FVC (mL/year) was demonstrated in both Study 1199.32 and Study 1199.34. The FVC response rate (percentages of the patients with a ≤5% or ≤10% decline in %FVC), which is reported to have certain clinical significance, was higher in the nintedanib group than in the placebo group. Taking into account of these facts, nintedanib is expected to be effective in patients with IPF

Data of Study 1199.32 and Study 1199.34 are shown in Table 21. In Study 1199.32, the hazard ratio [95% CI] of time to first acute exacerbation in the 150 mg BID group relative to the placebo group was 1.15 [0.54, 2.42], indicating similar results in the 2 groups. However, the hazard ratio [95% CI] was 0.38 [0.19, 0.77] in Study 1199.34 and was 0.158 [0.035, 0.711] in Study 1199.30 (foreign phase II study), indicating the superiority of nintedanib to placebo. The hazard ratios [95% CI] of mortality also indicated superiority of nintedanib over placebo in all of the above studies including Study 1199.30 (hazard ratio [95% CI], 0.732 [0.271, 1.977]). The results of Study 1199.32 and Study 1199.34 need to be carefully interpreted considering the protocols. However, time to first acute exacerbation[29] and mortality rates are likely to affect the prognosis of patients with IPF, and these data are expected to supplement the outcome of the primary endpoint. Because it is difficult to determine the impact of nintedanib on prognosis based on these study data, information about prognoses of patients with IPF treated with nintedanib should be further collected.

4.(iii).B.(2).3) Efficacy in the Japanese subpopulation

The applicant's explanation on the efficacy of nintedanib in Japanese patients with IPF:
The results of the primary endpoint in the Japanese subpopulation were similar to those in the FAS in both Study 1199.32 and Study 1199.34, as shown in Table 21 and Table 22.

Table 22. Results in the Japanese subpopulation in Study 1199.32 and Study 1199.34 (FAS, OC)

	Study 1199.32			Study 1199.34		
	Nintedanib	Placebo	Difference from placebo[95% CI]	Nintedanib	Placebo	Difference from placebo [95% CI]
Annual rate of decline in FVC (mL/year)[a)]	−142.20 ± 45.81 (N = 35)	−282.81 ± 55.99 (N = 20)	140.61 [−6.14, 287.35]	−137.60 ± 45.09 (N = 41)	−254.02 ± 53.62 (N = 30)	116.43 [−23.21, 256.06]
Change in SGRQ[b)] total score	6.63 ± 2.45 (N = 32)	10.28 ± 3.16 (N = 20)	−3.64 [−11.57, 4.28]	5.25 ± 1.87 (N = 41)	9.50 ± 2.20 (N = 30)	−4.25 [−9.97, 1.47]
Percentage of the subjects with acute exacerbation	8.6% (3/35)	10.0% (2/20)	0.86[c)] [0.13, 5.54]	0% (0/41)	13.3% (4/30)	-
Mortality	8.6% (3/35)	15.0% (3/20)	0.66[d)] [0.13, 3.38]	2.4% (1/41)	6.7% (2/30)	0.43[d)] [0.04, 5.03]
FVC responders (≤5%)	48.6% (17/35)	40.0% (8/20)	2.81[e)] [0.74, 10.71]	61.0% (25/41)	23.3% (7/30)	5.60[e)] [1.80, 17.41]
FVC responders (≤10%)	62.9% (22/35)	60.0% (12/20)	3.11[e)] [0.68, 14.19]	75.6% (31/41)	60.0% (18/30)	1.75[e)] [0.56, 5.44]

Least squares mean ± SE (number of subjects) or % (number of subjects)
a) Linear mixed-effects model using the dose group, sex, age, and height as fixed effects and intercept and time (numerical variable) as random effects
b) Repeated measure mixed-effects model on the hypothesis of compound symmetry covariance structure in the subjects using the dose group, time (Visit), interaction between the dose group and time (Visit), baseline, and interaction between baseline and time (Visit) as fixed effects and the intercept as random effect.
c) Cox regression model using the dose group, sex, age, and height as explanatory variables for time to first acute exacerbation
d) Cox regression model using the dose group, sex, age, and height as explanatory variables
e) Logistic regression model using the dose group, sex, age, height, and %FVC at baseline as explanatory variables

Patient characteristics were compared between the FAS and the Japanese subpopulation using the pooled data from the 2 studies. Differences were observed in the mean body weight (FAS, 79.0 kg; Japanese

[29] In Study 1199.30, acute exacerbation of IPF was defined as an adverse event meeting all of the following conditions: (a) unexplained worsening or onset of dyspnea within 30 days; (b) new diffuse pulmonary infiltrates on chest X-ray or HRCT new parenchymal abnormalities other than pneumothorax or pleural effusion (new ground-glass opacities) since the last visit; (c) the exclusion of infections, left heart failure, pulmonary embolism, and acute lung disorder with an identifiable cause, in routine clinical practice or by microbiology tests; and (d) decreased arterial oxygen partial pressure/oxygen fraction in inspired air (PaO_2/FiO_2) to <225 or decreased PaO_2 by ≥10 mm Hg since the last visit.

subpopulation, 63.8 kg) and smoking history (percentage of the subjects without smoking history: FAS, 27.9%; Japanese subset, 15.9%). Baseline FVC was lower in the Japanese subpopulation than in the FAS (FAS [placebo group, 2727.7 ± 810.2 mL; nintedanib group, 2713.5 ± 757.0 mL], Japanese subpopulation [placebo group, 2494.5 ± 741.1 mL; nintedanib group, 2421.6 ± 672.1 mL]). The results of subgroup analysis by body weight, smoking history, and baseline FVC are shown in Table 23. No clear differences were observed between the FAS and the Japanese subpopulation, and the differences observed in these factors were considered unlikely to affect the efficacy evaluation.

Accordingly, the efficacy of nintedanib in Japanese patients with IPF may be evaluated based on data from the global phase III studies.

Table 23. Subgroup analysis on the annual rates of decline in FVC (mL/year) in the pooled data from Study 1199.32 and Study 1199.34

		Nintedanib	Placebo	Difference from placebo [95% CI]
Body weight	≥65 kg	−131.20 (512)	−246.40 (347)	115.20 [77.11, 153.29]
	<65 kg	−102.37 (126)	−194.54 (76)	92.17 [17.85, 166.50]
Smoking history	Absent	−134.55 (174)	−224.35 (122)	89.80 [32.82, 146.77]
	Present	−105.41 (464)	−223.61 (301)	118.20 [76.22, 160.18]
Baseline FVC	>70%	−91.32 (431)	−200.36 (269)	109.04 [68.16, 149.91]
	≤70%	−133.16 (207)	−242.20 (154)	113.48 [51.25, 175.71]

Mean (number of subjects)

a) Linear mixed-effects model using the dose group, sex, age, and height as fixed effects and intercept and time (numerical variable) as random effects

PMDA's view:
Similarities were seen in the data between the Japanese subpopulation and the FAS in both studies. The subgroup analysis results by patient demographic factor which revealed difference between the FAS and the Japanese subpopulation were almost comparable to those from the primary analysis in the FAS. PMDA therefore considers that nintedanib is expected to be effective in Japanese patients with IPF as is in the entire population.

4.(iii).B.(3) Safety

The applicant's explanation on the safety of nintedanib based on the pooled data from 2 global phase III studies (Study 1199.32, Study 1199.34) in patients with IPF:
The incidence of adverse events in the pooled data from Study 1199.32 and Study 1199.34 is shown in Table 24. Adverse events occurring more frequently in the nintedanib group than in the placebo group included diarrhoea (62.4% [398 of 638] of subjects in the nintedanib group versus 18.4% [78 of 423] of subjects in the placebo group), nausea (24.5% [156 subjects] versus 6.6% [28 subjects]), vomiting (11.6% [74 subjects] versus 2.6% [11 subjects]), abdominal pain (8.8% [56 subjects] versus 2.4% [10 subjects]), abdominal pain upper (6.4% [41 subjects] versus 3.5% [15 subjects]), weight decreased (9.7% [62 subjects] versus 3.5% [15 subjects]), and decreased appetite (10.7% [68 subjects] versus 5.7% [24 subjects]).

Adverse events leading to death were reported by 37 subjects (5.8%) in the nintedanib group and 31 subjects (7.3%) in the placebo group. The most commonly reported system organ class (SOC) of adverse event was "Respiratory, thoracic and mediastinal disorders" (23 subjects [3.6%] in the nintedanib group versus 22 subjects [5.2%] in the placebo group). The causes (preferred term [PT]) of deaths reported by ≥2 subjects of the nintedanib group included IPF (18 subjects versus 16 subjects), respiratory failure (2 subjects versus 2 subjects), pneumonia (5 subjects versus 2 subjects), lung neoplasm malignant (2 subjects versus 0 subjects), and myocardial infarction (2 subjects versus 1 subject). Events (PT) observed more frequently in the placebo group than in the nintedanib group included IPF (18 subjects versus 16 subjects) and respiratory failure (2 subjects versus 2 subjects). Adverse events classified as "Neoplasms benign, malignant and unspecified" (SOC) resulting in deaths were reported by 5 subjects (lung neoplasm malignant/metastatic neoplasm, lung neoplasm malignant, B-cell lymphoma, chloroma, and non-small cell lung cancer in 1 subject each) in the nintedanib group but did not occur in the placebo group. Studies using epidemiological database report that the incidence of malignant tumor, especially lung cancer, is significantly high in patients with IPF (Jeune L I et al., *Respir Med*. 2007;101:2534-2540, Hubbard R et al., *Am J Respir Crit Care Med.* 2000;161:5-8.). Given the natural course of lung cancer,

it is highly likely that 3 subjects with lung cancer in the nintedanib group had the disease at the time of randomization. The mechanism of action of nintedanib is unlikely to promote tumor growth. The frequencies of deaths with other causes were generally similar between the dose groups.

The incidences of serious adverse events were 30.4% (194 subjects) in the nintedanib group and 30.0% (127) of subjects in the placebo group, which were not largely different. The incidences of adverse events classified under the SOCs of "Gastrointestinal disorders" (3.0% [19] of subjects in the nintedanib group versus 1.7% [7 subjects] in the placebo group), "Investigations" (1.3% [8 subjects] versus 0.5% [2 subjects]), "Hepatobiliary disorders" (1.1% [7 subjects] versus 0.2% [1 subject]), and "Musculoskeletal and connective tissue disorders" (1.3% [8 subjects] versus, 0.9% [4 subjects]) were higher in the nintedanib group than in the placebo group. Those classified under the PTs reported by ≥2% of subjects in the nintedanib group included IPF (6.6% [42 subjects] versus 9.2% [39 subjects]) and pneumonia (3.6% [23 subjects] versus 3.8% [16 subjects]). The incidences of bronchitis (1.3% [8 subjects] versus 0.5% [2 subjects]) and myocardial infarction (1.1% [7 subjects] versus 0.5% [2 subjects]) were slightly higher in the nintedanib group than in the placebo group.

The incidences of adverse events leading to the discontinuation of treatment were 19.3% (123 subjects) in the nintedanib group and 13.0% (55 subjects) in the placebo group, and the incidences in the nintedanib group tended to be higher than those in the placebo group. The SOCs of adverse events with an incidence in the nintedanib group ≥1% higher than that in the placebo group were "Gastrointestinal disorders" (7.4% [47 subjects] in the nintedanib group versus 1.2% [5 subjects] in the placebo group) and "Investigations" (2.8% [18 subjects] versus 0.5% [2 subjects]).

The incidences of adverse events leading to dose reduction (without re-administration at the starting dose) were 15.8% (101 subjects) in the nintedanib group and 0.5% (2 subjects) in the placebo group, showing higher incidence in the nintedanib group than in the placebo group. Adverse events classified under the SOC of "Gastrointestinal disorders" (12.9% [82 subjects] in the nintedanib group versus 0% in the placebo group) occurred most frequently in the nintedanib group, and those under "Investigations" (1.9% [12 subjects] versus 0.5% [2 subjects]), "Hepatobiliary disorders" (0.9% [6 subjects] versus 0%), and "Metabolism and nutrition disorders" (0.8% [5 subjects] versus 0%) occurred more frequently in the nintedanib group than in the placebo group. Adverse event classified under PT, "diarrhoea" (10.7% [68 subjects] versus 0%) occurred most frequently.

In the nintedanib group, major adverse events and serious adverse events occurred most frequently during a period from baseline to Day 90. Some of the events such as IPF and acute kidney injury constantly occurred throughout the study period, and these events also occurred in the placebo as frequently as in the nintedanib group. These findings did not suggest that the prolonged treatment with nintedanib increases the risk of adverse events.

The applicant further explained the safety in the Japanese subset as follows:
Adverse events in the Japanese subset in the pooled data from Study 1199.32 and Study 1199.34 are shown in Table 24. The incidences of these events were comparable to those in the FAS. There were no great differences in the types of events between the Japanese subpopulation and the FAS. However, the incidences of hepatic enzyme increased (15.8% [12 of 76 subjects]) and hepatic function abnormal (18.4% [14 of 76 subjects]) in the nintedanib group in the Japanese subpopulation were higher than those in the nintedanib group in the FAS (3.3% [21 of 638 subjects], 2.7% [17 of 638 subjects]), and the incidences of diarrhoea (75.0% [57 of 76 subjects]), constipation (13.2% [10 of 76 subjects]), and nasopharyngitis (35.5% [27 of 76 subjects]) also tended to be slightly higher than those in the FAS. The results from subgroup analyses are shown in Table 25. In the patients who were Asian females weighing <65 kg, the incidences of events related to gastrointestinal tract and increased hepatic enzyme values tended to be higher in the nintedanib group than in the placebo group. However, the incidence of AST or ALT increased (≥3 × ULN) in the nintedanib group in the Japanese subpopulation (6.6% [5 of 76 subjects]) was comparable to that in the FAS (5.0% [32 of 638 subjects]); the differences found in the subgroup analysis were not large; most of the events were moderate to mild in severity; and the incidence of nasopharyngitis in the nintedanib group was comparable to that in the placebo group in the Japanese subpopulation. Thus, these differences were considered to have little clinical significance.

The incidences of adverse events leading to deaths, serious adverse events, and adverse events leading to dose reduction in the Japanese subpopulation were not significantly different from those in the FAS. The incidence of adverse events leading to the discontinuation of treatment tended to be higher in the nintedanib group in the Japanese subpopulation, and decreased appetite (5.3% [4 of 19 subjects]) occurred frequently in the Japanese subpopulation.

Table 24. Adverse events in the pooled data from Study 1199.32 and Study 1199.34

	FAS		Japanese subpopulation	
	Nintedanib (N = 638)	Placebo (N = 423)	Nintedanib (N = 76)	Placebo (N = 50)
Adverse events	609 (95.5)	379 (89.6)	75 (98.7)	47 (94.0)
Adverse events leading to deaths	37 (5.8)	31 (7.3)	1 (1.3)	3 (6.0)
Serious adverse events	194 (30.4)	127 (30.0)	33 (43.4)	21 (42.0)
Adverse events leading to discontinuation	123 (19.3)	55 (13.0)	19 (25.0)	9 (18.0)
Adverse events leading to dose reduction	101 (15.8)	2 (0.5)	10 (13.2)	0
Adverse drug reactions	455 (71.3)	120 (28.4)	66 (86.8)	18 (36.0)
Adverse events reported by ≥10% of subjects in any group				
Diarrhoea	398 (62.4)	78 (18.4)	57 (75.0)	9 (18.0)
Nausea	156 (24.5)	28 (6.6)	15 (19.7)	0
Nasopharyngitis	87 (13.6)	68 (16.1)	27 (35.5)	19 (38.0)
Cough	85 (13.3)	57 (13.5)	2 (2.6)	1 (2.0)
Vomiting	74 (11.6)	11 (2.6)	10 (13.2)	0
Decreased appetite	68 (10.7)	24 (5.7)	14 (18.4)	4 (8.0)
Bronchitis	67 (10.5)	45 (10.6)	11 (14.5)	7 (14.0)
IPF	64 (10.0)	61 (14.4)	10 (13.2)	13 (26.0)
Weight decreased	62 (9.7)	15 (3.5)	11 (14.5)	3 (6.0)
Dyspnoea	49 (7.7)	48 (11.3)	0	1 (2.0)
Constipation	38 (6.0)	17 (4.0)	10 (13.2)	2 (4.0)
Back pain	37 (5.8)	29 (6.9)	3 (3.9)	5 (10.0)
Hepatic function abnormal	17 (2.7)	1 (0.2)	14 (18.4)	1 (2.0)
Hepatic enzyme increased	21 (3.3)	2 (0.5)	12 (15.8)	2 (4.0)
Abdominal discomfort	15 (2.4)	8 (1.9)	3 (3.9)	6 (12.0)
Diabetes mellitus	4 (0.6)	12 (2.8)	2 (2.6)	7 (14.0)

Number of subjects (%)

Table 25. Subgroup analysis on major adverse events in the pooled data from Study 1199.32 and Study 1199.34

	Male		Female		Caucasian		Asian		<65 kg		≥65 kg	
	Nintedanib (N = 507)	Placebo (N = 334)	Nintedanib (N = 131)	Placebo (N = 89)	Nintedanib (N = 360)	Placebo (N = 248)	Nintedanib (N = 194)	Placebo (N = 128)	Nintedanib (N = 126)	Placebo (N = 76)	Nintedanib (N = 512)	Placebo (N = 347)
Diarrhoea	61.9%	16.5%	64.1%	25.8%	63.6%	20.6%	56.2%	15.6%	59.5%	18.4%	63.1%	18.4%
Nausea	20.7%	6.0%	38.9%	9.0%	26.9%	9.3%	18.0%	1.6%	24.6%	3.9%	24.4%	7.2%
Vomiting	7.1%	2.4%	29.0%	3.4%	13.9%	2.4%	8.2%	3.1%	19.8%	3.9%	9.6%	2.3%
Weight decreased	9.5%	3.0%	10.7%	5.6%	8.9%	4.0%	7.7%	3.1%	13.5%	5.3%	8.8%	3.2%
Decreased appetite	9.3%	6.9%	16.0%	1.1%	9.7%	4.8%	12.4%	7.8%	15.1%	3.9%	9.6%	6.1%
Dehydration	0.6%	0.3%	1.5%	0%	1.1%	0.4%	0.5%	0%	0.8%	0%	0.8%	0.3%
Abdominal pain	7.3%	2.7%	14.5%	1.1%	8.3%	1.6%	4.1%	1.6%	8.7%	1.3%	8.8%	2.6%
ALT increased	2.2%	0.3%	6.9%	0%	1.9%	0%	4.1%	0.8%	5.6%	1.3%	2.5%	0%
AST increased	1.6%	0.3%	6.1%	0%	1.4%	0%	3.1%	0.8%	4.8%	1.3%	2.0%	0%
γ-GT increased	3.4%	1.8%	5.3%	0%	2.8%	1.2%	4.1%	1.6%	3.2%	1.3%	3.9%	1.4%
Hepatic enzyme increased	3.2%	0.3%	3.8%	1.1%	2.2%	0%	6.7%	1.6%	5.6%	0%	2.7%	0.6%
Hepatic function abnormal	2.4%	0.3%	3.8%	0%	0.3%	0%	8.2%	0.8%	7.1%	1.3%	1.6%	0%

%

In consideration of adverse events reported in clinical studies of nintedanib and the pharmacological action of nintedanib, PMDA mainly reviewed the following events.

4.(iii).B.(3).1) Gastrointestinal events

The applicant's explanation on gastrointestinal events:

The mechanism whereby a gastrointestinal disorder is induced by a vascular endothelial growth factor receptor (VEGFR) inhibitor in humans and animals has been unknown. In a safety pharmacology study in rats, gastrointestinal motility was affected at a dose of ≥30 mg/kg, and the effect is considered attributable to inhibition of the platelet-derived growth factor receptor (PDGFR) α.

In Study 1199.32 and Study 1199.34, gastrointestinal events such as diarrhoea, nausea, vomiting, weight decreased, decreased appetite, and dehydration occurred more frequently in the nintedanib group than in the placebo group when nintedanib was administered twice daily at 150 mg. The incidences of adverse events by severity in the pooled data from Study 1199.32 and Study 1199.34 are shown in Table 26. Most of the events are mild to moderate in severity and their outcomes were either "resolved" or "improved" except for weight decreased (1 subject in the nintedanib group) which did not resolve. Not many serious adverse events were reported (diarrhoea [2 subjects in the nintedanib group versus 1 subject in the placebo group], vomiting [1 subject versus 0 subjects], weight decreased [1 subject versus 0 subjects], decreased appetite [1 subject versus 1 subject]). Adverse events in the Japanese subpopulation included diarrhoea (75.0% [57 of 76] of subjects in the nintedanib group versus 18.0% [9 of 50] of subjects in the placebo group), nausea (19.7% [15 subjects] versus 0%), vomiting (13.2% [10 subjects] versus 0%), weight decreased (14.5% [11 subjects] versus 6.0% [3 subjects]), decreased appetite (18.4% [14 subjects] versus 8.0% [4 subjects]), and dehydration (14.5% [11 subjects] versus 0%). These events occurred more frequently in the nintedanib group than in the placebo group but were neither severe nor serious.

The incidences of gastrointestinal events in Study 1199.30 were 38.4% (33 of 86 subjects) in the nintedanib 50 mg QD group, 36.0% (31 of 86 subjects) in the 50 mg BID group, 57.0% (49 of 86 subjects) in the 100 mg BID group, 74.1% (63 of 85 subjects) in the 150 mg BID group, and 31.8% (27 of 85 subjects) in the placebo group, showing a dose-dependent increase. In the global phase III studies (Study 1199.32, Study 1199.34), dose reduction and treatment interruption were allowed[30] in case of intolerance to the study drug. In 101 subjects who experienced adverse events leading to dose reduction in the nintedanib group, diarrhoea (68 subjects), nausea (11 subjects), vomiting (7 subjects), and weight decreased and decreased appetite (4 subjects each), and dehydration (1 subject) were observed. The gastrointestinal events accounted for a major part of the adverse events leading to dose reduction. Adverse events leading to the discontinuation of treatment included diarrhoea (28 subjects), nausea (13 subjects), vomiting (5 subjects), weight decreased (6 subjects), decreased appetite (9 subjects), and dehydration (2 subjects). Most of the events were manageable with symptomatic treatment or treatment interruption or dose reduction of nintedanib.

[30] When a subject experienced an adverse event requiring treatment interruption and the event was assessed to be related to the study drug by the investigator (sub-investigator), the subject was allowed to temporarily withdraw from the study drug for up to 4 weeks. The resumption of the study drug at 100 mg BID was recommended, and, when well tolerated, the dose was increased to 150 mg BID again within 4 weeks.In the event of occurrence of an adverse event being assessed to be unrelated to the study drug by the investigator (sub-investigator) or acute exacerbation of IPF, the subject was allowed to temporarily withdraw from the study drug for up to 8 weeks, and then the study drug was to be resumed at the dose used before interruption.

Table 26. Gastrointestinal events in the pooled data from Study 1199.32 and Study 1199.34

		Nintedanib (N = 638)	Placebo (N = 423)
Diarrhoea	Mild	226 (35.4)	60 (14.2)
	Moderate	150 (23.5)	16 (3.8)
	Severe	21 (3.3)	2 (0.5)
Nausea	Mild	116 (18.2)	26 (6.1)
	Moderate	38 (6.0)	2 (0.5)
	Severe	2 (0.3)	0 (0)
Vomiting	Mild	49 (7.7)	9 (2.1)
	Moderate	21 (3.3)	2 (0.5)
	Severe	4 (0.6)	0 (0)
Weight decreased	Mild	39 (6.1)	8 (1.9)
	Moderate	22 (3.4)	7 (1.7)
	Severe	1 (0.2)	0 (0)
Decreased appetite	Mild	47 (7.4)	20 (4.7)
	Moderate	21 (3.3)	3 (0.7)
	Severe	0 (0)	1 (0.2)
Dehydration	Mild	3 (0.5)	0 (0)
	Moderate	1 (0.2)	0 (0)
	Severe	1 (0.2)	1 (0.2)

Number of subjects (%)

As reported above, the gastrointestinal events were considered manageable with appropriate measures, which include dose reduction, interruption or discontinuation of treatment and treatment with nintedanib may be resumed at 100 mg BID in patients with improved symptoms.

PMDA's view:
In clinical studies, most gastrointestinal events following the administration of nintedanib were non-serious. In most cases, these events are manageable with dose reduction or interruption or discontinuation of treatment. Nevertheless, these events are the major contributory factors of dose reduction and the interruption or discontinuation of treatment and are influential to a decision on whether or not to continue nintedanib. Attention should be paid to the events because the incidences of such events tended to be higher in Japanese patients than in non-Japanese patients. The criteria for dose reduction and treatment interruption and the actions taken to cope with the events in clinical studies should be shared with healthcare professionals in an appropriate manner. The incidences of the events in routine clinical use of the drug product should be further investigated through post-marketing surveillance.

4.(iii).B.(3).2) Increases in hepatic enzyme and serum bilirubin values
The applicant's explanation on the increases in hepatic enzyme and serum bilirubin levels:
In the pooled data from Study 1199.32 and Study 1199.34, hepatic enzyme increased[31] and events classified under liver related investigations, signs and symptoms (MedDRA SMQ) occurred more frequently in the nintedanib group (13.6% [87 of 638 subjects], 14.9% [95 subjects]) than in the placebo group (2.6% [11 of 423 subjects], 2.8% [12 subjects]). Major events (PTs) included γ-glutamyltransferase (γ-GT) increased (3.8% [24 subjects] in the nintedanib group versus 1.4% [6 subjects] in the placebo group), hepatic enzyme increased (3.3% [21 subjects] versus 0.5% [2 subjects]), ALT increased (3.1% [20 subjects] versus 0.2% [1 subject]), hepatic function abnormal (2.7% [17 subjects] versus 0.2% [1 subject]), AST increased (2.5% [16 subjects] versus 0.2% [1 subject]), and blood bilirubin increased (1.3% [8 subjects] versus 0.2% [1 subject]), which occurred more frequently in the nintedanib group than in the placebo group. Serious events of hepatic enzyme increased occurred in 0.6% (4 subjects) in the nintedanib group and 0.2% (1 subject) in the placebo group, and serious events classified under liver related investigations, signs and symptoms (MedDRA SMQ) occurred in 0.6% (4 subjects) in the nintedanib group and 0.2% (1 subject) in the placebo group.

An analysis was performed on changes from the normal range at baseline to values exceeding the reference range for ALT, AST, γ-GT, alkaline phosphatase, and total bilirubin levels. The percentages of patients who had normal baseline value and the maximum on-treatment value outside of the reference

[31] PTs classified under liver related investigations, signs and symptoms (MedDRA SMQ)

range were 27.3% (169 of 620 subjects), 21.4% (134 of 625 subjects), 39.2% (225 of 574 subjects), 15.3% (94 of 615 subjects), and 7.7% (48 of 621 subjects) in the nintedanib group, respectively, and 7.2% (30 of 416 subjects), 5.3% (22 of 418 subjects), 10.4% (40 of 386 subjects), 6.8% (28 of 412 subjects), and 5.3% (22 of 413 subjects) in the placebo group, respectively, showing higher percentages in the nintedanib group than in the placebo group. The percentages of patients with ALT or AST ≥3 × ULN and ≥5 × ULN were 5.0% (32 of 638 subjects) and 2.2% (14 of 638 subjects) in the nintedanib group, respectively, and 0.7% (3 of 423 subjects) and 0.2% (1 of 423 subjects) in the placebo group, respectively. The percentages of patients with total bilirubin ≥2 × ULN were 0.5% (3 of 638 subjects) in the nintedanib group and 0.5% (2 of 423 subjects) in the placebo group.

In the Japanese subpopulation, hepatic enzyme increased occurred in 39.5% (30 of 76) of subjects in the nintedanib group and in 8.0% (4 of 50) of subjects in the placebo group, and events classified under liver related investigations, signs and symptoms (SMQ) occurred in 39.5% (30 subjects) versus 8.0% (4 subjects), respectively, showing the higher incidences in the nintedanib group than in the placebo group. Major events (PTs) included hepatic function abnormal (18.4% [14 of 76] of subjects versus 2.0% [1 of 50] of subjects), hepatic enzyme increased (15.8% [12 subjects] versus 4.0% [2 subjects]), liver function test abnormal (2.6% [2 subjects] versus 0%), γ-GT increased (1.3% [1 subject] versus 2.0% [1 subject]), ALT increased (1.3% [1 subject] versus 0%), and blood bilirubin increased (1.3% [1 subject] versus 0%), tending to occur more frequently in the nintedanib group than in the placebo group. Although the incidences of hepatic function abnormal and hepatic enzyme increased in the nintedanib group were higher in the Japanese subpopulation than in the FAS, the percentage of the patients with AST or ALT increased (≥3 × ULN) in the Japanese subpopulation (6.6% [5 subjects]) of the nintedanib group was comparable to that of the FAS (5.0% [32 subjects]), and most of the events were mild to moderate in severity. Therefore, the difference between the Japanese subpopulation and the FAS is considered to have little clinical significance.

In Study 1199.30, the incidences of hepatic enzyme increased were 1.2% (1 of 86 subjects) in the nintedanib 50 mg QD group, 2.3% (2 of 86 subjects) in the 50 mg BID group, 0% in the 100 mg BID group, 4.7% (4 of 85 subjects) in the 150 mg BID group, and 1.2% (1 of 85 subjects) in the placebo group. The incidences of the events classified under hepatobiliary disorders (SOC) were 0% in the nintedanib 50 mg QD group, 1.2% (1 of 86 subjects) in the 50 mg BID group, 1.2% (1 of 86 subjects) in the 100 mg BID group, 7.1% (6 of 85 subjects) in the 150 mg BID group, and 3.5% (3 of 85 subjects) in the placebo group. The incidences tended to increase in a dose-dependent manner. In the global phase III studies (Study 1199.32, Study 1199.34) in which dose reduction and treatment interruption of the study drug were allowed,[32] 101 subjects in the nintedanib group experienced adverse events leading to dose reduction. In the 101 subjects, hepatobiliary disorders (6 subjects), hepatic enzyme increased (2 subjects), and ALT increased (1 subject) were observed. These events accounted for a substantial percentage of the adverse events leading to dose reduction. Adverse events leading to the discontinuation of study drug included hepatobiliary disorders (7 subjects), ALT increased (4 subjects), γ-GT increased (1 subject), AST increased (3 subjects), blood bilirubin increased (3 subjects), and hepatic enzyme increased (3 subjects).

As reported above, liver function tests should be performed before the start of treatment and regularly during treatment. The interruption or discontinuation of treatment should be determined according to the criteria used in clinical studies when any abnormality is detected, and treatment should be resumed at the reduced dose of 100 mg BID when the abnormal liver test value returns to normal. By following this procedure, hepatic adverse events should be manageable. The patients with ALT, AST, or bilirubin ≥1.5 × ULN were excluded from the clinical studies, and thus the efficacy and safety of nintedanib in these patients have not been evaluated. This information will be provided to healthcare professionals to ensure that nintedanib is carefully used in patients with hepatic impairment.

[32] (a) If AST or ALT increases to 3 to 5 × ULN without any sign of severe hepatic disease, the dose is reduced to 100 mg BID or treatment is interrupted according to the condition of the patient. Nintedanib treatment is resumed at100 mg or 150 mg BID or is discontinued according to the condition of the patient. (b) If AST or ALT increases to 5 to 8 × ULN without any sign of severe hepatic disease, treatment is interrupted, then nintedanib treatment is resumed at the reduced dose of 100 mg BID or is discontinued according to the condition of the patient. (c) If AST or ALT increases to 8 × ULN or a sign of severe hepatic disease is present, treatment is discontinued. (severe hepatic disease is characterized by fatigue, nausea, vomiting, right upper quadrant pain or upper abdominal tenderness, pyrexia, eczema, or eosinophil count increased by >5%, total bilirubin >1.5 × ULN, or INR >1.5 × ULN).

PMDA's view:
In the clinical studies, serious cases of liver function test increased were limited, and serious events resulting from dose reduction, or treatment interruption or discontinuation were not reported. However, given the risk of serious hepatic impairment resulting from prolonged treatment with nintedanib in patients with liver function test increased and the incidences of these events tended to be higher in the Japanese patients than in non-Japanese patients, liver function tests should be performed regularly. Healthcare professionals should be advised to ensure early detection of abnormalities to prevent the progression of IPF, through the provision of information including the dose reduction and treatment interruption criteria and actions taken to cope with the events in the clinical studies. Given that liver function test increased may affect prolonged treatment with nintedanib, that the incidences of the events tended to be higher in the Japanese patients than in non-Japanese patients, and that limited safety information in patients with hepatic impairment in clinical studies, the incidences of the adverse events associated with nintedanib in clinical use should be further investigated through post-marketing surveillance.

4.(iii).B.(3).3) Thromboembolism
The applicant's explanation on thromboembolism:
Similarly to nintedanib, sunitinib malate, sorafenib tosilate, and an anti-VEGF humanized monoclonal antibody bevacizumab (genetical recombination) have an antiangiogenic effect. In clinical studies of these compounds in cancer patients, thromboembolism-related events were reported. According to a report, the inhibition of VEGFR-medicated intracellular signaling induces apoptosis of endothelial cells in stationary phase, which prevents blood coagulation cascade from being activated (Taraseviciene-Stewart L et al., *FASEB J*. 2001;15:427-438). The findings suggest that nintedanib may also promote blood coagulation.

In the clinical studies of nintedanib, patients with a history of myocardial infarction or stroke were excluded. In the pooled data from Study 1199.32 and Study 1199.34, the incidences of thromboembolism-related events were 3.8% (24 of 638 subjects) in the nintedanib group and 2.4% (10 of 423 subjects) in the placebo group, and most of the events were reported as serious (3.1% [20 subjects] in the nintedanib group, 2.4% [10 subjects] in the placebo group). The incidences of venous thromboembolism (1.1% [7 subjects] in the nintedanib group, 1.2% [5 subjects] in the placebo group) and serious venous thromboembolism (0.9% [6 subjects] in the nintedanib group, 1.2% [5 subjects] in the placebo group) were similar between the dose groups. The event leading to death was reported by 1 subject (pulmonary embolism) in the nintedanib group, but its causal relationship to the study drug was ruled out. On the other hand, the incidences of arterial thromboembolism (2.5% [15 subjects] in the nintedanib group, 0.7% [3 subjects] in the placebo group) and serious arterial thromboembolism (2.0% [12 subjects] in the nintedanib group, 0.7% [3 subjects] in the placebo group) were higher in the nintedanib group than in the placebo group. The commonly reported adverse events in the nintedanib group included myocardial infarction (1.1% [7 subjects] in the nintedanib group, 0.5% [2 subjects] in the placebo group) and acute myocardial infarction (0.5% [3 subjects] in the nintedanib group, 0% in the placebo group). Of 10 subjects who experienced myocardial infarction in the nintedanib group, 9 already had a related disease at baseline. Myocardial infarction occurring in 2 subjects of the nintedanib group and 1 subject of the placebo group resulted in death, and a causal relationship to the study drug could not be ruled out for the deaths in 2 subjects in the nintedanib group.

The incidences of adverse events of ischaemic heart disease were similar between the dose groups (4.2% [27 subjects] in the nintedanib group, 4.0% [17 subjects] in the placebo group). The incidence rate of ischaemic heart disease in the nintedanib group (myocardial infarction, 1.18/100 patient-years; acute myocardial infarction, 0.50/100 patient-years) was lower than that reported in a representative observation research cohort of IPF (21.7/1000 patient-years) (Collard HR et al., *J Med Econ*. 2012;15:829-835).

Nintedanib should be carefully administered to patients with a high cardiovascular risk such as a history of coronary artery disease. Once thromboembolism is identified, treatment with nintedanib should be interrupted or discontinued. This advice will be given to healthcare professionals.

PMDA's view:
Considering the pharmacological effect of nintedanib and the incidence of thromboembolism associated with the use of drugs with a similar mechanism of action, treatment with nintedanib may induce thromboembolism, leading to a serious outcome. The incidence of myocardial infarction tended to be slightly higher in the nintedanib group than in the placebo group. Therefore, healthcare professionals should be advised on the careful use of nintedanib in patients with high cardiovascular risk such as a history of cardiac disease. Thromboembolism associated with the administration of nintedanib should be further monitored, and investigation on the event, including a risk in long-term treatment and that in patients with a concurrent cardiovascular disease, should be continued through post-marketing surveillance.

4.(iii).B.(3).4) Haemorrhage
The applicant's explanation on haemorrhage-related adverse events:
As with nintedanib, VEGFR-mediated intracellular signaling inhibitors (bevacizumab [recombinant], sunitinib malate, sorafenib tosilate) are known to increase the hemorrhage risk, and the inhibition of VEGFR-mediated intracellular signaling is considered to break the homeostasis between platelets and endothelial cells, leading to haemorrhage (Verheul HMW et al., *Nat Rev Cancer.* 2007;7:475-485).

Patients at risk of haemorrhage were excluded from the clinical studies of nintedanib. In the pooled data from Study 1199.32 and Study 1199.34, the incidence of haemorrhage-related events was higher in the nintedanib group than in the placebo group (10.3% [66 of 638 subjects] in the nintedanib group, 7.8% [33 of 423 subjects] in the placebo group). Major events that occurred more frequently in the nintedanib group than in the placebo group included non-serious epistaxis (3.9% [25 subjects] in the nintedanib group, 2.8% [12 subjects] in the placebo group) and contusion (1.4% [9 subjects] in the nintedanib group, 0.9% [4 subjects] in the placebo group). The incidences of serious hemorrhage were similar between the groups (1.3% [8 subjects] in the nintedanib group, 1.4% [6 subjects] in the placebo group). Haemorrhage resulted in death of 1 subject of the nintedanib group, but its causal relationship to the study drug was ruled out. The subject was a British woman in her 60s with no history of neoplasm. The study drug was discontinued due to abdominal pain on Day 55, and liver metastasis was diagnosed later. The subject died from lung cancer, liver metastasis, severe hematemesis, gastrointestinal hemorrhage, and duodenal ulcer 9 days after the discontinuation of the study drug. The primary cause of death was reported as massive gastrointestinal haemorrhage.

Nintedanib should be carefully administered to patients at risk of haemorrhage including those with a genetic predisposing factor for haemorrhage or those on anticoagulant therapy, and this advice will be given to healthcare professionals.

PMDA's view:
Increased risk of haemorrhage is predicted from the pharmacological effect of nintedanib, and it has been seen with the drugs with a similar mechanism of action. The incidence of haemorrhage tended to be slightly higher in the nintedanib group than in the placebo group in the clinical studies. Therefore, healthcare professionals should be advised to ensure careful administration of nintedanib to patients at risk of haemorrhage, and the occurrence of the events in the clinical use of nintedanib should be investigated through post-marketing surveillance.

4.(iii).B.(3).5) Delayed wound healing
The applicant's explanation on delayed wound healing:
VEGFR-mediated intracellular signaling inhibitors acting similarly to nintedanib (bevacizumab [recombinant], sunitinib malate, sorafenib tosilate) are known to increase the risk of delayed wound healing, and the inhibition of VEGFR-mediated intracellular signaling is considered to break the homeostasis between platelets and endothelial cells, leading to the event (Verheul HMW et al., *Nat Rev Cancer.* 2007;7:475-485). In the clinical studies of nintedanib in patients with IPF, none of 15 subjects who received nintedanib and underwent lung transplantation experienced an event suggestive of delayed wound healing. Despite that, precautions about the use of nintedanib in perioperative patients will be provided.

PMDA's view:
Delayed wound healing is predicted from the pharmacological effect of nintedanib, and patients with IPF may undergo lung transplantation or other surgical procedures. Treatment should therefore be discontinued prior to the operation and not be resumed until the surgical wound heals This advice should be given to healthcare professionals.

4.(iii).B.(3).6) Gastrointestinal perforation
The applicant's explanation on gastrointestinal perforation:
Gastrointestinal perforation was reported by patients with cancer who received VEGFR-mediated intracellular signaling inhibitors that act similarly to nintedanib (bevacizumab [recombinant], sunitinib malate, sorafenib tosilate). Although the pathogenesis of gastrointestinal perforation remains unknown, it is reported that the inhibition of VEGFR-mediated intracellular signaling breaks the homeostasis between platelets and endothelial cells, leading to the event (Walraven M et al., *Angiogenesis.* 2011;14:135-141.). Based on these findings, nintedanib may increase a risk of gastrointestinal perforation.

According to an analysis of the pooled data from Study 1199.32 and Study 1199.34, the incidence of gastrointestinal perforation was 0.3% (2 of 638 subjects, peritoneal abscess and duodenal ulcer perforation/peritonitis in 1 subject each) of the nintedanib group, and no event occurred in the placebo group. All the relevant events were serious.

If gastrointestinal perforation is identified, treatment with nintedanib should be interrupted or discontinued. This advice will be given to healthcare professionals.

PMDA's view:
Gastrointestinal perforation also occurred in patients treated with the other drugs with similar pharmacological effects to nintedanib. Patients treated with nintedanib who have abdominal pain should be monitored for the event. The incidence of gastrointestinal perforation associated with nintedanib in clinical use should be further investigated through post-marketing surveillance.

4.(iii).B.(3).7) Interstitial lung disease
Interstitial pneumonia was reported by patients receiving a tyrosine kinase inhibitor that acts similarly to nintedanib. PMDA asked the applicant to explain the risk of drug-induced interstitial lung disease in patients treated with nintedanib.

The applicant's explanation:
In the pooled data from Study 1199.32 and Study 1199.34, the incidence of events classified under interstitial lung disease (MedDRA SMQ) was 10.2% (65 of 638 subjects) in the nintedanib group and 14.4% (61 of 423 subjects) in the placebo group. However, no interstitial pneumonia (PT) occurred, and the major event was IPF (PT) (10.0% [64 of 638 subjects] in the nintedanib group, 14.4% [61 of 423 subjects] in the placebo group). Reported interstitial lung disease is considered related to the progression of IPF as the primary disease. In the other clinical studies in patients with IPF, interstitial lung disease (PT) was reported by 10 subjects who received nintedanib (including interstitial pneumonia and interstitial pneumonia aggravated), but a causal relationship to the study drug was ruled out for all events. No interstitial lung disease (PT) occurred in Japanese patients with IPF (Study 1199.32, Study 1199.34, Study 1199.31, Study 1199.33, Study 1199.40).

In clinical studies in patients with non-small cell lung cancer who received nintedanib 200 mg BID, the incidence of the events classified under interstitial lung disease (MedDRA SMQ) was 1.4% (9 of 652 subjects) in the nintedanib group and was 0.8% (5 of 655 subjects) in the placebo group. Interstitial lung disease (PT) was reported by 1 subject in the nintedanib group in Study 1199.13; the incidence of interstitial lung disease (MedDRA SMQ) was 0.6% (2 of 345 subjects) in the nintedanib group and was 0.9% (3 of 346 subjects) in the placebo group. Interstitial lung disease (PT) was reported by 1 subject in the placebo group in Study 1199.14.

PMDA's view:
In IPF patients, it is difficult to distinguish drug-induced interstitial lung disease from the primary disease, but interstitial lung disease was reported in the clinical studies of nintedanib in patients with IPF. Interstitial pneumonia was reported in the clinical studies in patients with non-small cell lung cancer, in which nintedanib was administered at high doses. Therefore, the possibility that nintedanib induces interstitial lung disease cannot be ruled out. Reports also revealed higher risks of interstitial pneumonia in Japanese patients using other tyrosine kinase inhibitors (Cohen MH et al., *Oncologist*. 2003;8:303-306, Nakagawa K et al., *J Thorac Oncol*. 2012;7:1296-1303.). Patients with IPF should be closely monitored during treatment with nintedanib, and the interruption or discontinuation of treatment should be considered when symptoms worsen. This advice should be given to healthcare professionals, and the occurrence of interstitial lung disease associated with nintedanib in clinical use should be further investigated through post-marketing surveillance.

4.(iii).B.(3).8) Skin disorder
Serious skin or subcutaneous tissue disorders were reported in the clinical studies in patients with cancer, which investigated some of the drugs having a similar antiangiogenic effect to that of nintedanib. Toxicity studies of nintedanib suggested phototoxicity. PMDA therefore asked the applicant to explain the risk of skin or subcutaneous tissue disorders.

The applicant's explanation:
In the pooled data from Study 1199.32 and Study 1199.34, the incidence of rash was 6.9% (44 of 638 subjects) in the nintedanib group and was 9.0% (38 of 423 subjects) in the placebo group. All of the events were non-serious, suggesting that nintedanib does not pose a risk of skin and subcutaneous tissue disorders.

PMDA's view:
The studies of other drugs with similar pharmacological effects to that of nintedanib revealed serious events involving skin and subcutaneous tissues and suggested the phototoxicity of nintedanib. Attention should be paid to skin disorders in patients treated with nintedanib. The occurrence of skin disorders associated with nintedanib in clinical use should be further investigated through post-marketing surveillance.

The above PMDA's conclusion on the safety of nintedanib and post-marketing safety measures will be discussed at the Expert Discussion.

4.(iii).B.(4) Dosage and administration
In the preceding clinical studies of nintedanib in patients with cancer, the maximum dose of nintedanib was 200 mg BID, and the dose was allowed to be reduced for the management of adverse events. In a phase II study in IPF patients (Study 1199.30), therefore, 4 regimens (50 mg QD, 50 mg BID, 100 mg BID, and 150 mg BID) were used for nintedanib, and dose reduction was allowed in patients intolerant to the study drug. The difference in annual rate of decline in FVC (the primary efficacy endpoint) from that in the placebo group was largest in the nintedanib 150 mg BID group (difference between the groups [95% CI]: 0.131 [0.027, 0.235] L/year). The safety analysis of Study 1199.30 revealed that the percentages of subjects experiencing dose reduction due to adverse events were 8.0% (7 of 87 subjects) in the placebo group, 5.7% (5 of 87 subjects) in the nintedanib 50 mg QD group, 8.1% (7 of 86 subjects) in the 50 mg BID group, 12.8% (11 of 86 subjects) in the 100 mg BID group, 23.3% (20 of 86 subjects) in the 150 mg BID group, showing the highest percentage in the 150 mg BID group. The incidences of gastrointestinal-related events (diarrhoea, nausea, vomiting, abdominal pain, weight decreased, decreased appetite, etc.) and hepatic enzyme increased increased dose-dependently [see "4.(iii).A.(1) Foreign phase II study"].

Accordingly, the dosage of nintedanib in the confirmatory global phase III studies (Study 1199.32, Study 1199.34) was determined as 150 mg BID, and dose reduction to 100 mg BID or treatment interruption was allowed in subjects with poor tolerance or acute exacerbation of IPF. However, subsequent dose increase to 150 mg BID was encouraged wherever possible. In both Study 1199.32 and Study 1199.34, superiority of nintedanib to placebo in the annual rate of decline in FVC (mL/year) as the primary efficacy endpoint was verified [see "4.(iii).B.(2) Efficacy"]. In the pooled data from both studies, the

dose intensity[33] of the study drug was 93.7% in the nintedanib group and was 98.9% in the placebo group. The dose intensity in patients who received the study drug at the reduced dosage was 79.6% (178 subjects) in the nintedanib group and was 83.9% (16 subjects) in the placebo group. Treatment was discontinued in 24.5% (156 of 638) of subjects in the nintedanib group and 18.9% (80 of 423) of subjects in the placebo group, showing no great difference between dose groups. Treatment was continued in many patients throughout the study period because dose reduction and interruption were allowed. The annual rate of decline in FVC in the patients with the dose intensity of nintedanib >90% (484 subjects) was -112.7 ± 12.8 and those with the dose intensity ≤90% (154 subjects) was -72.7 ± 24.3 mL/year, suggesting the potential efficacy of nintedanib even in the patients who experienced dose reduction or interruption.

Based on the above, the proposed dosage and administration of nintedanib below were considered appropriate for the proposal.

[Proposed dosage and administration]
The usual adult dosage is 150 mg as nintedanib administered orally twice daily after meal in the morning and evening at intervals of approximately 12 hours. The dose may be reduced to 100 mg of nintedanib twice daily for patients experiencing an adverse drug reaction.

PMDA's view:
As explained, the efficacy of nintedanib was demonstrated in the global phase III studies (Study 1199.32, Study 1199.34), with the dosage regimen of 150 mg BID and optional dose reduction to 100 mg BID or treatment interruption for patients who did not tolerate the study drug. The safety analysis identified a certain percentage of the patients who did not tolerate nintedanib 150 mg BID due to gastrointestinal events and increased liver function tests. Taking account of these findings, the proposed dosage and administration of nintedanib is acceptable. Although the dose intensity of nintedanib was >90% in the global phase III studies, a large percentage of the patients included in these studies had early-stage IPF characterized by mild impairment of lung function (patients with %FVC >70% accounted for 66.0% [700 of 1061 subjects] of the study population). In clinical use, nintedanib is expected to be administered to patients with severe IPF characterized by deterioration of respiratory function. The dose intensity of nintedanib should be further investigated through post-marketing surveillance.

Healthcare professionals should be appropriately informed of the criteria for dose reduction and treatment interruption used in the global phase III studies for the purpose to detect adverse events early so that worsening of the events can be prevented. Healthcare professionals should also be advised to consider dose reduction or treatment interruption in the event of occurrence of adverse events and to resume treatment or increase the dose carefully.

4.(iii).B.(5) Clinical positioning of nintedanib
PMDA asked the applicant to explain the clinical positioning of nintedanib and pirfenidone in the drug therapy for IPF and the safety of concomitant use of these drugs.

The applicant's explanation:
The clinical practice guidelines established by the Japanese Respiratory Society, American Thoracic Society, European Respiratory Society, and Latin American Thoracic Association (Raghu G et al., *Am J Respir Crit Care Med.* 2011;183:788-824) do not recommend the use of immunosuppressive agents such as azathioprine, cyclophosphamide, and cyclosporine as therapeutic options for patients with IPF because of their poor efficacy. The use of corticosteroid, either alone or in combination with an immunosuppressive agent, is also discouraged for the treatment of IPF. The guidelines do not recommend pirfenidone for most patients with IPF but explain that it may be a therapeutic option for some IPF patients. Given this situation, only nintedanib and pirfenidone are likely to serve as major drugs indicated for IPF. Data on FVC and VC have demonstrated that both nintedanib and pirfenidone slow disease progression. The 2 drugs have never been directly compared in clinical studies, and thus criteria for the choice of a drug remain unclear. Therefore, whether or not treatment with nintedanib or

[33] A value obtained by dividing the actual total dose of the study drug throughout the study period by the total dose of the study drug administered at 150 mg twice daily for 52 weeks as planned or until discontinuation

pirfenidone should be started is decided based on the pathological condition of individual patients with IPF.

Nintedanib and pirfenidone act through different mechanisms, and the 2 drugs may be used in combination in clinical practice. The safety of the nintedanib plus pirfenidone combination therapy was thus investigated in a Japanese phase II study (Study 1199.31) and its extension open-label study (Study 1199.40). In Study 1199.31, the safety of nintedanib monotherapy and the nintedanib plus pirfenidone combination therapy was evaluated in Japanese patients with IPF. Of 24 subjects assigned to the nintedanib 150 mg BID group, 13 subjects received concomitant pirfenidone at its recommended dose, and the remaining 11 subjects received nintedanib alone. Adverse events that occurred in the subjects receiving the nintedanib plus pirfenidone combination therapy and in those receiving the nintedanib monotherapy are shown in Table 27. Although the number of subjects was small (24 subjects) and the study duration was short (4 weeks), nausea and vomiting occurred more frequently in subjects receiving the combination therapy than in those receiving the nintedanib monotherapy, and the incidences of diarrhoea were similar between the 2 therapies. In Study 1199.40, 20 subjects received the nintedanib plus pirfenidone combination therapy. Adverse events reported by these patients are listed in Table 20 [see "4.(iii).A.(5) Long-term treatment study"], showing only slight differences as compared with the safety profile in subjects receiving nintedanib alone in the global phase III studies (Study 1199.32, Study 1199.34).

Table 27. Adverse events in nintedanib 150 mg BID group and placebo group in Study 1199.31

	Nintedanib 150 mg BID (N = 24)		Placebo (N = 12)	
	Nintedanib + pirfenidone (N = 13)	Nintedanib alone (N = 11)	Nintedanib + pirfenidone (N = 5)	Nintedanib alone (N = 7)
All adverse events	9 (69.2)	6 (54.5)	2 (40.0)	2 (28.6)
Serious adverse events	0	1 (9.1)	0	0
Adverse drug reactions	7 (53.8)	3 (27.3)	1 (20.0)	1 (14.3)
Major adverse events				
Vomiting	5 (38.5)	0 (0)	0	0
Nausea	4 (30.8)	1 (9.1)	0	0
Diarrhoea	2 (15.4)	2 (18.2)	0	0
Nasopharyngitis	2 (15.4)	0	0	0
ALT increased	0 (0)	2 (18.2)	0	0
AST increased	0 (0)	2 (18.2)	0	0
Adverse events leading to discontinuation	2 (15.4)	2 (18.2)	0	0
Transaminases increased	1 (7.7)	0	0	0
Vomiting	1 (7.7)	0	0	0
γ-GT increased	0	1 (9.1)	0	0
ALT increased	0	1 (9.1)	0	0
AST increased	0	1 (9.1)	0	0

Number of subjects (%)

PMDA's view:
Establishing precise guidelines for decision-making on whether to choose nintedanib, or pirfenidone, the sole approved drug indicated for IPF in Japan, is a task to be addressed. Given that both drugs have been demonstrated to slow disease progression, the choice of a drug should be made according to the patient's condition including tolerance to the drugs as explained by the applicant. However, currently available information about the efficacy and safety of the nintedanib plus pirfenidone combination therapy is limited, decisions on the use of the combination therapy should be made carefully. The safety of the nintedanib plus pirfenidone combination therapy should be further investigated through post-marketing surveillance, and obtained relevant information should be provided to healthcare professionals appropriately.

4.(iii).B.(6) Indication

The proposed indication is "Treatment of idiopathic pulmonary fibrosis and slowing of disease progression" based on the review in "4.(iii).B.(2) Efficacy" and "4.(iii).B.(3) Safety." However, PMDA considers it more appropriate to define the indication of nintedanib as "idiopathic pulmonary fibrosis," taking account of the objective of drug therapies for IPF and the indication of other drugsof the same class.

4.(iii).B.(7) Post-marketing surveillance etc.

The applicant plans to conduct post-marketing surveillance in patients with IPF after the market launch to confirm the safety and efficacy of nintedanib in routine clinical use, including those in long-term treatment. The surveillance will primarily focus on the incidence of gastrointestinal events such as diarrhoea and that of liver function tests increased. Safety in patients with hepatic impairment or renal impairment from whom only limited data were obtained in the clinical studies, those recovering from wounds, and those receiving anticoagulant agents will also be investigated in the surveillance.

PMDA's view:

The clinical study data demonstrated acceptable safety of nintedanib as explained in "4.(iii).B.(3) Safety." However, potential users of nintedanib in clinical settings may be patients with more severe IPF than those who participated in the clinical studies. Experience with long-term use of nintedanib and knowledge about the nintedanib plus pirfenidone combination therapy are limited. In addition, the known pharmacological effects of nintedanib leave a risk of nintedanib-induced serious gastrointestinal or cardiovascular adverse events, such as gastrointestinal perforation and myocardial infarction, and interstitial lung diseases that are common to VEGFR-mediated intracellular signaling inhibitors. On the basis of these findings, the safety and efficacy of nintedanib should be therefore further investigated closely through post-marketing surveillance.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

Document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. The area for improvement was the electronic data capture system being used by the sponsor, in which did not allow the investigators to view some of modified case report data. Despite this, the final case report data were checked and confirmed by the investigators after all, and PMDA concluded that there should be no problem with conducting the regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.3.2-1, 5.3.5.1-2, 5.3.5.2-1, 5.3.5.2-3). PMDA concluded that the clinical studies as a whole were performed in compliance with GCP and that there should be no problem with conducting a regulatory review based on the submitted application documents. Of note, the following issues were pointed out at some clinical study sites and the sponsor. Although the issues did not significantly affect the evaluation of the whole study, the heads of the study sites and the applicant (sponsor) were notified of the issues and were requested to take corrective actions.

Issues to be corrected:

Clinical study sites

- Defective contract on the extension of the study period

Sponsor

- Defective contract on the extension of the study period

IV. Overall Evaluation

Based on the submitted data, the efficacy of nintedanib in the treatment of patients with idiopathic pulmonary fibrosis has been demonstrated and the safety of nintedanib is acceptable in view of its observed benefits. Nintedanib is a new therapeutic option for idiopathic pulmonary fibrosis and thus is considered to have clinical significance. In the safety analyses, adverse events such as gastrointestinal events and hepatic enzyme increased were identified, and the risk of serious adverse events such as hepatic impairment, gastrointestinal perforation, and myocardial infarction were also noted. Healthcare professionals should be advised to closely monitor patients for adverse events during treatment with nintedanib and to cope with adverse events by taking appropriate actions, including the interruption of

treatment and dose reduction. The safety of nintedanib in clinical settings, including that in long-term treatment and in the combination use with pirfenidone, should be further investigated through post-marketing surveillance.

PMDA considers that Ofev (nintedanib) may be approved if it can be concluded based on the comments from the Expert Discussion that there are no particular problems.

Review Report (2)

May 18, 2015

I. Product Submitted for Registration

[Brand name] Ofev Capsules 100 mg, Ofev Capsules 150 mg
[Non-proprietary name] Nintedanib Ethanesulfonate
[Name of applicant] Nippon Boehringer Ingelheim Co., Ltd.
[Date of application] October 14, 2014

II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for registration, 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) Efficacy, indication, and dosage and administration

The conclusion of PMDA on the efficacy, indication, and dosage and administration of the "Ofev Capsules 100 mg and Ofev Capsules 150 mg" (hereinafter referred to as "Ofev" or "nintedanib") as described in the Review Report (1) was supported by the expert advisors.

(2) Safety and the draft risk management plan

The conclusion of PMDA on the safety of nintedanib as described in the Review Report (1) was supported by the expert advisors. The following comments were made by the expert advisors: Drugs that inhibit intracellular signaling mediated by platelet-derived growth factor receptor, fibroblast growth factor receptor, and vascular endothelial growth factor receptor are known to induce adverse events that are likely to lead to a serious outcome. To prepare for the launch of nintedanib, the safety concerns of nintedanib including risks of hepatic impairment, gastrointestinal events, and thromboembolism should be highlighted in the package insert. The occurrence of these events and the risk of drug-induced interstitial pneumonia should be carefully monitored through post-marketing surveillance.

Taking account of "4.(iii).B.(3) Safety and 4.(iii).B.(7) Post-marketing surveillance, etc." of the Review Report (1) and the comments from the expert advisors at the Expert Discussion, PMDA has concluded that the safety and efficacy specifications listed in Table 28 should be included in the draft risk management plan and that additional pharmacovigilance activities and risk minimization actions listed in Table 29 should be implemented.

Table 28. Safety specification and efficacy specifications in the draft risk management plan

Safety specifications		
Important identified risks	Important potential risks	Important missing information
- Gastrointestinal symptoms such as diarrhoea and nausea - Hepatic impairment - Gastrointestinal perforation - Thromboembolism	- Interstitial pneumonia - Serious skin disorder - Haemorrhage - Osteonecrosis of jaw - Delayed wound healing	- None
Efficacy specifications		
- Efficacy in clinical use		

Table 29. Summary of additional pharmacovigilance activities and risk minimization actions in the draft risk management plan

Additional pharmacovigilance activities	Additional risk minimization actions
- Early post-marketing phase vigilance - Specified drug use-results survey (all patient survey) - Specified drug use-results survey (follow-up survey)	- Early post-marketing phase vigilance - Preparation and distribution of materials for healthcare professionals - Preparation and distribution of materials for patients

The Japanese clinical studies of nintedanib enrolled only a limited number of eligible patients with idiopathic pulmonary fibrosis. PMDA instructed the applicant to conduct post-marketing surveillance targeting all patients receiving nintedanib until data from a specified number of patients are collected, to have sufficient information as early as possible to investigate the above-listed matters.

The applicant's explanation:
As shown in Table 30, the specified drug use-results survey with a 1-year observation period will be conducted targeting all patients receiving nintedanib, until data are collected from the target number of 1000 patients (safety analysis set). The investigation of the safety and efficacy of nintedanib in clinical use will focus on the priority investigation items including gastrointestinal symptoms such as diarrhea and nausea, hepatic impairment, gastrointestinal perforation, thromboembolism, hemorrhage, drug-induced interstitial pneumonia. Information to be collected from patients with an experience of the interruption or discontinuation of treatment includes the dose level of nintedanib before the interruption or discontinuation, the resumption dose, and the safety of nintedanib after resumption of treatment and the safety in the nintedanib plus pirfenidone combination therapy. Although the safety analysis will be performed when data of 1000 patients become available, the survey will be continued until the final evaluation results are received from the regulatory authority. To collect safety data on treatment for a longer period, relevant patients will undergo an additional 1-year follow-up survey when possible.

Table 30. Outline of specified drug use-results survey plan (draft)

Objective	To identify safety and efficacy of nintedanib in clinical use
Survey method	All-case surveillance system
Patient population	Patients with idiopathic pulmonary fibrosis
Observation period	1 year
Target sample size	1000 patients (safety analysis set)
Priority investigation items	Gastrointestinal symptoms such as diarrhoea and nausea, hepatic impairment, gastrointestinal perforation, thromboembolism, haemorrhage, drug-induced interstitial pneumonia
Main investigation items	- Patient characteristics (disease duration, severity, prior treatment history, medical history, complications, etc.) - Use status of nintedanib - Concomitant drugs or therapy - Adverse events - Efficacy evaluation

PMDA considers the survey should be started immediately and obtained results should be provided to healthcare professionals in an appropriate manner.

III. Overall Evaluation

PMDA has concluded that Ofev (nintedanib) may be approved after modifying the indication and the dosage and administration as shown below, with the following conditions for approval. Since this product is an orphan drug, the re-examination period is 10 years. Both drug substance and drug product are classified as powerful drugs, and the product is not classified as a biological product or a specified biological product.

[Indication] Idiopathic pulmonary fibrosis

[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.

[Conditions for approval] The applicant is required to:

1. Develop a risk management plan and ensure that the plan is implemented appropriately.
2. Conduct a post-marketing drug use-results survey targeting all patients treated with the product until data from a specified number of the patients are gathered for better understanding of the characteristics of patients using the product, because of the limited

number of patients enrolled in the Japanese clinical studies; and ensure that safety and efficacy data of the product are collected early, thereby taking necessary measures for the proper use of the product.