CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

205832Orig1s012

Trade Name:	OFEV
Generic or Proper Name:	nintedanib
Sponsor:	Boehringer Ingelheim Pharmaceuticals Inc.
Approval Date:	September 6, 2019
Indication:	OFEV is a kinase inhibitor indicated for: • Treatment of idiopathic pulmonary fibrosis (IPF). • Slowing the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD).

CENTER FOR DRUG EVALUATION AND RESEARCH

205832Orig1s012

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Officer/Employee List	
Multidiscipline Review(s) • **Summary Review** • **Office Director** • **Cross Discipline Team Leader** • **Clinical** • **Non-Clinical** • **Statistical** • **Clinical Pharmacology**	**X**
Product Quality Review(s)	**X**
Clinical Microbiology / Virology Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

NDA 205832/S-012

SUPPLEMENT APPROVAL

Boehringer Ingelheim Pharmaceuticals Inc.
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, CT 06877-0368

Attention: Ingeborg Arny-Cornejo, MD
Senior Associate Director
Regulatory Affairs

Dear Dr. Arny-Cornejo:

Please refer to your supplemental new drug application (sNDA) dated March 7, 2019, received March 7, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ofev (nintedanib) Capsules.

This Prior Approval supplemental new drug application provides for a new indication to slow the rate of decline in pulmonary function in patients with Systemic Sclerosis-associated Interstitial Lung Disease.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert,), with the addition of any labeling

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of decreased effectiveness of oral contraceptives (OC) due to a drug-drug interaction between nintedanib and OC. If coadministration of nintedanib resulted in a lower OC exposure, it will lead to compromised OC efficacy.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3706-1 A drug-drug interaction trial to assess the pharmacokinetics, safety, and tolerability for the coadministration of a combined oral contraceptive (containing ethinyl estradiol and levonorgestrel) with Ofev 150 mg twice daily.

The timetable you submitted on August 21, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	Submitted
Study Completion:	12/2019
Final Report Submission:	04/2020

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Sincerely,

{See appended electronic signature page}

Sally M. Seymour, MD
Director
Division of Pulmonary, Allergy, and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NIKOLAY P NIKOLOV
09/06/2019 01:58:31 PM
Signed under the authority, delegated by Dr. Sally Seymour, Division Director, DPARP.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205832Orig1s012

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OFEV safely and effectively. See full prescribing information for OFEV.

OFEV® (nintedanib) capsules, for oral use
Initial U.S. Approval: 2014

----------RECENT MAJOR CHANGES----------

Indications and Usage,	
Systemic Sclerosis-Associated Interstitial Lung Disease (1.2)	9/2019
Dosage and Administration,	
Testing Prior to OFEV Administration (2.1)	9/2019
Warnings and Precautions (5)	9/2019

----------INDICATIONS AND USAGE----------

OFEV is a kinase inhibitor indicated for:

- Treatment of idiopathic pulmonary fibrosis (IPF). (1.1)
- Slowing the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD). (1.2)

----------DOSAGE AND ADMINISTRATION----------

- Recommended dosage: 150 mg twice daily approximately 12 hours apart taken with food. (2.2)
- Recommended dosage in patients with mild hepatic impairment (Child Pugh A): 100 mg twice daily approximately 12 hours apart taken with food. (2.2, 8.6)
- Consider temporary dose reduction to 100 mg, treatment interruption, or discontinuation for management of adverse reactions. (2.3, 5.2, 5.3, 6)
- Prior to treatment initiation, conduct liver function tests in all patients and a pregnancy test in females of reproductive potential. (2.1, 5.2, 5.4)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 150 mg and 100 mg (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Hepatic impairment: OFEV is not recommended for use in patients with moderate or severe hepatic impairment. In patients with mild hepatic impairment (Child Pugh A), the recommended dosage is 100 mg twice daily approximately 12 hours apart taken with food. Consider treatment interruption, or discontinuation for management of adverse reactions in these patients. (2.2, 2.3, 5.1, 8.6, 12.3)
- Elevated liver enzymes and drug-induced liver injury: ALT, AST, and bilirubin elevations have occurred with OFEV, including cases of drug-induced liver injury. In the postmarketing period, non-serious and serious cases of drug-induced liver injury, including severe liver injury with fatal outcome, have been reported. The majority of hepatic events occur within the first three months of treatment. Liver enzyme and bilirubin increases were reversible with dose modification or interruption in the majority of cases. Monitor ALT, AST, and bilirubin prior to initiation of treatment, at regular intervals during the first three months of treatment, and periodically thereafter or as clinically indicated. Temporary dosage reductions or discontinuations may be required. (2.1, 2.3, 5.2)
- Gastrointestinal disorders: Diarrhea, nausea, and vomiting have occurred with OFEV. Treat patients at first signs with adequate hydration and antidiarrheal medicine (e.g., loperamide) or anti-emetics. Discontinue OFEV if severe diarrhea, nausea, or vomiting persists despite symptomatic treatment. (5.3)
- Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use highly effective contraception. As the impact of nintedanib on the effectiveness of hormonal contraception is unknown, advise women using hormonal contraceptives to add a barrier method. (5.4, 8.1, 8.3)
- Arterial thromboembolic events have been reported. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. (5.5)
- Bleeding events have been reported. Use OFEV in patients with known bleeding risk only if anticipated benefit outweighs the potential risk. (5.6)
- Gastrointestinal perforation has been reported. Use OFEV with caution when treating patients with recent abdominal surgery, previous history of diverticular disease or receiving concomitant corticosteroids or NSAIDs. Discontinue OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk. (5.7)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥5%) are: diarrhea, nausea, abdominal pain, vomiting, liver enzyme elevation, decreased appetite, headache, weight decreased, and hypertension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Coadministration of P-gp and CYP3A4 inhibitors may increase nintedanib exposure. Monitor patients closely for tolerability of OFEV. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Breastfeeding is not recommended. (8.2)
- Renal impairment: The safety and efficacy of OFEV have not been studied in patients with severe renal impairment and end-stage renal disease. (8.7, 12.3)
- Smokers: Decreased exposure has been noted in smokers which may alter the efficacy profile of OFEV. (8.8)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 9/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Idiopathic Pulmonary Fibrosis

OFEV is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

1.2 Systemic Sclerosis-Associated Interstitial Lung Disease

OFEV is indicated to slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD).

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to OFEV Administration

Conduct liver function tests in all patients and a pregnancy test in females of reproductive potential prior to initiating treatment with OFEV *[see Warnings and Precautions (5.2, 5.4)]*.

2.2 Recommended Dosage

The recommended dosage of OFEV is 150 mg twice daily administered approximately 12 hours apart.

OFEV capsules should be taken with food *[see Clinical Pharmacology (12.3)]* and swallowed whole with liquid. OFEV capsules should not be chewed or crushed because of a bitter taste. The effect of chewing or crushing of the capsule on the pharmacokinetics of nintedanib is not known.

If a dose of OFEV is missed, the next dose should be taken at the next scheduled time. Advise the patient to not make up for a missed dose. Do not exceed the recommended maximum daily dosage of 300 mg.

In patients with mild hepatic impairment (Child Pugh A), the recommended dosage of OFEV is 100 mg twice daily approximately 12 hours apart taken with food.

2.3 Dosage Modification due to Adverse Reactions

In addition to symptomatic treatment, if applicable, the management of adverse reactions of OFEV may require dose reduction or temporary interruption until the specific adverse reaction resolves to levels that allow continuation of therapy. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If a patient does not tolerate 100 mg twice daily, discontinue treatment with OFEV *[see Warnings and Precautions (5.2, 5.3, 5.5, 5.7) and Adverse Reactions (6.1)]*.

Dose modifications or interruptions may be necessary for liver enzyme elevations. Conduct liver function tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin) prior to initiation of treatment with OFEV, at regular intervals during the first three months of treatment, and periodically thereafter or as clinically indicated. Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. Discontinue OFEV in patients with AST or ALT greater than 3 times the upper limit of normal (ULN) with signs or symptoms of liver injury and for AST or ALT elevations greater than 5 times the upper limit of normal. For AST or ALT greater than 3 times to less than 5 times the ULN without signs of liver damage, interrupt treatment or reduce OFEV to 100 mg twice daily. Once liver enzymes have returned to baseline values, treatment with OFEV may be reintroduced at a reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage (150 mg twice daily) *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

In patients with mild hepatic impairment (Child Pugh A), consider treatment interruption, or discontinuation for management of adverse reactions.

3 DOSAGE FORMS AND STRENGTHS

150 mg capsules: brown, opaque, oblong, soft capsules imprinted in black with the Boehringer Ingelheim company symbol and "150".

100 mg capsules: peach, opaque, oblong, soft capsules imprinted in black with the Boehringer Ingelheim company symbol and "100".

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Hepatic Impairment

Treatment with OFEV is not recommended in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*. Patients with mild hepatic impairment (Child Pugh A) can be treated with a reduced dose of OFEV *[see Dosage and Administration (2.2)]*.

5.2 Elevated Liver Enzymes and Drug-Induced Liver Injury

Cases of drug-induced liver injury (DILI) have been observed with OFEV treatment. In the clinical trials and postmarketing period, non-serious and serious cases of DILI were reported. Cases of severe liver injury with fatal outcome have been reported in the postmarketing period. The majority of hepatic events occur within the first three months of treatment. In clinical trials, administration of OFEV was associated with elevations of liver enzymes (ALT, AST, ALKP, GGT) and bilirubin. Liver enzyme and bilirubin increases were reversible with dose modification or interruption in the majority of cases. In IPF studies (Studies 1, 2, and 3), the majority (94%) of patients with ALT and/or AST elevations had elevations less than 5 times ULN and the majority (95%) of patients with bilirubin elevations had elevations less than 2 times ULN. In the SSc-ILD study (Study 4), a maximum ALT and/or AST greater than or equal to 3 times ULN was observed for 4.9% of patients in the OFEV group and for 0.7% of patients in the placebo group *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*. Patients with a low body weight (less than 65 kg), Asian, and female patients may have a higher risk of elevations in liver enzymes. Nintedanib exposure increased with patient age, which may also result in a higher risk of increased liver enzymes *[see Clinical Pharmacology (12.3)]*.

Conduct liver function tests (ALT, AST, and bilirubin) prior to initiation of treatment with OFEV, at regular intervals during the first three months of treatment, and periodically thereafter or as clinically indicated. Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. Dosage modifications or interruption may be necessary for liver enzyme elevations *[see Dosage and Administration (2.1, 2.3)]*.

5.3 Gastrointestinal Disorders

Diarrhea

In clinical trials, diarrhea was the most frequent gastrointestinal event reported. In most patients, the event was of mild to moderate intensity and occurred within the first 3 months of treatment. In IPF studies (Studies 1, 2, and 3), diarrhea was reported in 62% versus 18% of patients treated with OFEV and placebo, respectively *[see Adverse Reactions (6.1)]*. Diarrhea led to permanent dose reduction in 11% of patients treated with OFEV compared to 0 placebo-treated patients. Diarrhea led to discontinuation of OFEV in 5% of the patients

compared to less than 1% of placebo-treated patients. In the SSc-ILD study (Study 4), diarrhea was reported in 76% versus 32% of patients treated with OFEV and placebo, respectively *[see Adverse Reactions (6.1)]*. Diarrhea led to permanent dose reduction in 22% of patients treated with OFEV compared to 1% of placebo-treated patients. Diarrhea led to discontinuation of OFEV in 7% of the patients compared 0.3% of placebo-treated patients.

Dosage modifications or treatment interruptions may be necessary in patients with adverse reactions of diarrhea. Treat diarrhea at first signs with adequate hydration and antidiarrheal medication (e.g., loperamide), and consider treatment interruption if diarrhea continues *[see Dosage and Administration (2.3)]*. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe diarrhea persists despite symptomatic treatment, discontinue treatment with OFEV.

Nausea and Vomiting

In IPF studies (Studies 1, 2, and 3), nausea was reported in 24% versus 7% and vomiting was reported in 12% versus 3% of patients treated with OFEV and placebo, respectively. In the SSc-ILD study (Study 4), nausea was reported in 32% versus 14% and vomiting was reported in 25% versus 10% of patients treated with OFEV and placebo, respectively *[see Adverse Reactions (6.1)]*. In most patients, these events were of mild to moderate intensity. In IPF studies (Studies 1, 2, and 3), nausea led to discontinuation of OFEV in 2% of patients and vomiting led to discontinuation of OFEV in 1% of the patients. In the SSc-ILD study (Study 4), nausea led to discontinuation of OFEV in 2% of patients and vomiting led to discontinuation of OFEV in 1% of the patients.

For nausea or vomiting that persists despite appropriate supportive care including anti-emetic therapy, dose reduction or treatment interruption may be required *[see Dosage and Administration (2.3)]*. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe nausea or vomiting does not resolve, discontinue treatment with OFEV.

5.4 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, OFEV can cause fetal harm when administered to a pregnant woman. Nintedanib caused embryo-fetal deaths and structural abnormalities in rats and rabbits when administered during organogenesis at less than (rats) and approximately 5 times (rabbits) the maximum recommended human dose (MRHD) in adults. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to avoid becoming pregnant while receiving treatment with OFEV and to use highly effective contraception during treatment and at least 3 months after the last dose of OFEV. It is currently unknown whether nintedanib may reduce the effectiveness of hormonal contraceptives, therefore advise women using hormonal contraceptives to add a barrier method. Verify pregnancy status prior to treatment with OFEV and during treatment as appropriate *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)]*.

5.5 Arterial Thromboembolic Events

Arterial thromboembolic events have been reported in patients taking OFEV. In IPF studies (Studies 1, 2, and 3), arterial thromboembolic events were reported in 2.5% of patients treated with OFEV and 0.8% of placebo-treated patients. Myocardial infarction was the most common adverse reaction under arterial thromboembolic events, occurring in 1.5% of OFEV-treated patients compared to 0.4% of placebo-treated patients. In the SSc-ILD study (Study 4), arterial thromboembolic events were reported in 0.7% of patients in both treatment arms. There were 0 cases of myocardial infarction in OFEV-treated patients compared to 0.7% of placebo-treated patients.

Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia.

5.6 Risk of Bleeding

Based on the mechanism of action (VEGFR inhibition), OFEV may increase the risk of bleeding. In IPF studies (Studies 1, 2, and 3), bleeding events were reported in 10% of patients treated with OFEV and in 7% of patients treated with placebo. In the SSc-ILD study (Study 4), bleeding events were reported in 11% of patients treated with OFEV and in 8% of patients treated with placebo. In the postmarketing period non-serious and serious bleeding events, some of which were fatal, have been observed.

Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk.

5.7 Gastrointestinal Perforation

Based on the mechanism of action, OFEV may increase the risk of gastrointestinal perforation. In IPF studies (Studies 1, 2, and 3), gastrointestinal perforation was reported in 0.3% of patients treated with OFEV, compared to 0 cases in the placebo-treated patients. In the SSc-ILD study (Study 4), no cases of gastrointestinal perforation were reported in patients treated with OFEV or in placebo-treated patients. In the postmarketing period, cases of gastrointestinal perforations have been reported, some of which were fatal. Use caution when treating patients who have had recent abdominal surgery, previous history of diverticular disease or receiving concomitant corticosteroids or NSAIDs.

Discontinue therapy with OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Elevated Liver Enzymes and Drug-Induced Liver Injury *[see Warnings and Precautions (5.2)]*
- Gastrointestinal Disorders *[see Warnings and Precautions (5.3)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.4)]*
- Arterial Thromboembolic Events *[see Warnings and Precautions (5.5)]*
- Risk of Bleeding *[see Warnings and Precautions (5.6)]*
- Gastrointestinal Perforation *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of OFEV was evaluated in over 1000 IPF patients and over 280 patients with SSc-ILD. Over 200 IPF patients were exposed to OFEV for more than 2 years in clinical trials.

Idiopathic Pulmonary Fibrosis

OFEV was studied in three randomized, double-blind, placebo-controlled, 52-week trials. In the phase 2 (Study 1) and phase 3 (Studies 2 and 3) trials, 723 patients with IPF received OFEV 150 mg twice daily and 508 patients received placebo. The median duration of exposure was 10 months for patients treated with OFEV and 11 months for patients treated with placebo. Subjects ranged in age from 42 to 89 years (median age of 67 years). Most patients were male (79%) and Caucasian (60%).

The most frequent serious adverse reactions reported in patients treated with OFEV, more than placebo, were bronchitis (1.2% vs. 0.8%) and myocardial infarction (1.5% vs. 0.4%). The most common adverse events leading to death in patients treated with OFEV, more than placebo, were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV-treated patients and 1.8% of placebo-treated patients.

Adverse reactions leading to permanent dose reductions were reported in 16% of OFEV-treated patients and 1% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (11%).

Adverse reactions leading to discontinuation were reported in 21% of OFEV-treated patients and 15% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (5%), nausea (2%), and decreased appetite (2%).

The most common adverse reactions with an incidence of greater than or equal to 5% and more frequent in the OFEV than placebo treatment group are listed in Table 1.

Table 1 Adverse Reactions Occurring in ≥5% of OFEV-treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3

Adverse Reaction	OFEV, 150 mg n=723	Placebo n=508
Gastrointestinal disorders		
Diarrhea	62%	18%
Nausea	24%	7%
Abdominal pain[a]	15%	6%
Vomiting	12%	3%
Hepatobiliary disorders		
Liver enzyme elevation[b]	14%	3%
Metabolism and nutrition disorders		
Decreased appetite	11%	5%
Nervous system disorders		
Headache	8%	5%
Investigations		
Weight decreased	10%	3%
Vascular disorders		
Hypertension[c]	5%	4%

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain and abdominal tenderness.
[b] Includes gamma-glutamyltransferase increased, hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic function abnormal, liver function test abnormal, transaminase increased, blood alkaline phosphatase-increased, alanine aminotransferase abnormal, aspartate aminotransferase abnormal, and gamma-glutamyltransferase abnormal.
[c] Includes hypertension, blood pressure increased, hypertensive crisis, and hypertensive cardiomyopathy.

In addition, hypothyroidism was reported in patients treated with OFEV, more than placebo (1.1% vs. 0.6%).

Combination with Pirfenidone
Concomitant treatment with nintedanib and pirfenidone was investigated in an exploratory open-label, randomized (1:1) trial of nintedanib 150 mg twice daily with add-on pirfenidone (titrated to 801 mg three times a day) compared to nintedanib 150 mg twice daily alone in 105 randomized patients for 12 weeks. The primary endpoint was the percentage of patients with gastrointestinal adverse events from baseline to Week 12. Gastrointestinal adverse events were in line with the established safety profile of each component and were

experienced in 37 (70%) patients treated with pirfenidone added to nintedanib versus 27 (53%) patients treated with nintedanib alone.

Diarrhea, nausea, vomiting, and abdominal pain (includes upper abdominal pain, abdominal discomfort, and abdominal pain) were the most frequent adverse events reported in 20 (38%) versus 16 (31%), in 22 (42%) versus 6 (12%), in 15 (28%) versus 6 (12%) patients, and in 15 (28%) versus 7 (14%) treated with pirfenidone added to nintedanib versus nintedanib alone, respectively. More subjects reported AST or ALT elevations (greater than or equal to 3x the upper limit of normal) when using pirfenidone in combination with nintedanib (n=3 (6%)) compared to nintedanib alone (n=0) *[see Warnings and Precautions (5.2, 5.3)]*.

Systemic Sclerosis-Associated Interstitial Lung Disease

OFEV was studied in a phase 3, randomized, double-blind, placebo-controlled trial (Study 4) in which 576 patients with SSc-ILD received OFEV 150 mg twice daily (n=288) or placebo (n=288). Patients were to receive treatment for at least 52 weeks; individual patients were treated for up to 100 weeks. The median duration of exposure was 15 months for patients treated with OFEV and 16 months for patients treated with placebo. Subjects ranged in age from 20 to 79 years (median age of 55 years). Most patients were female (75%). Patients were mostly Caucasian (67%), Asian (25%), or Black (6%). At baseline, 49% of patients were on stable therapy with mycophenolate.

The most frequent serious adverse events reported in patients treated with OFEV, more than placebo, were interstitial lung disease (2.4% nintedanib vs. 1.7% placebo) and pneumonia (2.8% nintedanib vs. 0.3% placebo). Within 52 weeks, 5 patients treated with OFEV (1.7%) and 4 patients treated with placebo (1.4%) died. There was no pattern among adverse events leading to death in either treatment arm.

Adverse reactions leading to permanent dose reductions were reported in 34% of OFEV-treated patients and 4% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (22%).

Adverse reactions leading to discontinuation were reported in 16% of OFEV-treated patients and 9% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (7%), nausea (2%), vomiting (1%), abdominal pain (1%), and interstitial lung disease (1%).

The safety profile in patients treated with OFEV with or without mycophenolate at baseline was comparable.

The most common adverse reactions with an incidence of greater than or equal to 5% in OFEV-treated patients and more commonly than in placebo are listed in Table 2.

Table 2 Adverse Reactions Occurring in ≥5% of OFEV-treated Patients and More Commonly Than Placebo in Study 4

Adverse Reaction	OFEV, 150 mg n=288	Placebo n=288
Diarrhea	76%	32%
Nausea	32%	14%
Vomiting	25%	10%
Skin ulcer	18%	17%
Abdominal pain[a]	18%	11%
Liver enzyme elevation[b]	13%	3%
Weight decreased	12%	4%
Fatigue	11%	7%
Decreased appetite	9%	4%
Headache	9%	8%
Pyrexia	6%	5%
Back pain	6%	4%
Dizziness	6%	4%
Hypertension[c]	5%	2%

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, and esophageal pain.
[b] Includes alanine aminotransferase increased, gamma-glutamyltransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, blood alkaline phosphatase increased, transaminase increased, and hepatic function abnormal.
[c] Includes hypertension, blood pressure increased, and hypertensive crisis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of OFEV. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following adverse reactions have been identified during postapproval use of OFEV: drug-induced liver injury *[see Warnings and Precautions (5.2)]*, non-serious and serious bleeding events, some of which were fatal *[see Warnings and Precautions (5.6)]*, pancreatitis, thrombocytopenia, rash, pruritus.

7 DRUG INTERACTIONS

7.1 P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers

Nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4 *[see Clinical Pharmacology (12.3)]*. Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib by 60%. Concomitant use of P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib *[see Clinical Pharmacology (12.3)]*. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV *[see Dosage and Administration (2.3)]*.

Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exposure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John's wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib *[see Clinical Pharmacology (12.3)]*.

7.2 Anticoagulants

Nintedanib is a VEGFR inhibitor and may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary *[see Warnings and Precautions (5.6)]*.

7.3 Pirfenidone
In a multiple-dose study conducted to assess the pharmacokinetic effects of concomitant treatment with nintedanib and pirfenidone, the coadministration of nintedanib with pirfenidone did not alter the exposure of either agent *[see Clinical Pharmacology (12.3)]*. Therefore, no dose adjustment is necessary during concomitant administration of nintedanib with pirfenidone.

7.4 Bosentan
Coadministration of nintedanib with bosentan did not alter the pharmacokinetics of nintedanib *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary

Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, OFEV can cause fetal harm when administered to a pregnant woman. There are no data on the use of OFEV during pregnancy. In animal studies of pregnant rats and rabbits treated during organogenesis, nintedanib caused embryo-fetal deaths and structural abnormalities at less than (rats) and approximately 5 times (rabbits) the maximum recommended human dose *[see Data]*. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects is 2% to 4% and miscarriage in clinically recognized pregnancies is 15% to 20%.

Data

Animal Data

In animal reproduction toxicity studies, nintedanib caused embryo-fetal deaths and structural abnormalities in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults (on a plasma AUC basis at maternal oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). Malformations included abnormalities in the vasculature, urogenital, and skeletal systems. Vasculature anomalies included missing or additional major blood vessels. Skeletal anomalies included abnormalities in the thoracic, lumbar, and caudal vertebrae (e.g., hemivertebra, missing, or asymmetrically ossified), ribs (bifid or fused), and sternebrae (fused, split, or unilaterally ossified). In some fetuses, organs in the urogenital system were missing. In rabbits, a significant change in sex ratio was observed in fetuses (female:male ratio of approximately 71%:29%) at approximately 15 times the MRHD in adults (on an AUC basis at a maternal oral dose of 60 mg/kg/day). Nintedanib decreased post-natal viability of rat pups during the first 4 post-natal days when dams were exposed to less than the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day).

8.2 Lactation
Risk Summary

There is no information on the presence of nintedanib in human milk, the effects on the breast-fed infant or the effects on milk production. Nintedanib and/or its metabolites are present in the milk of lactating rats *[see Data]*. Because of the potential for serious adverse reactions in nursing infants from OFEV, advise women that breastfeeding is not recommended during treatment with OFEV.

Data

Milk and plasma of lactating rats have similar concentrations of nintedanib and its metabolites.

8.3 Females and Males of Reproductive Potential

Based on findings from animal studies and its mechanism of action, OFEV can cause fetal harm when administered to a pregnant woman and may reduce fertility in females of reproductive potential *[see Use in Specific Populations (8.1), Clinical Pharmacology (12.1), and Nonclinical Toxicology (13.1)]*. Counsel patients on pregnancy prevention and planning.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to treatment with OFEV and during treatment as appropriate *[see Dosage and Administration (2.1), Warnings and Precautions (5.4), and Use in Specific Populations (8.1)]*.

Contraception

OFEV can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to avoid becoming pregnant while receiving treatment with OFEV. Advise females of reproductive potential to use highly effective contraception during treatment, and for at least 3 months after taking the last dose of OFEV. It is currently unknown whether nintedanib may reduce the effectiveness of hormonal contraceptives, therefore advise women using hormonal contraceptives to add a barrier method.

Infertility

Based on animal data, OFEV may reduce fertility in females of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in phase 2 and 3 clinical studies of OFEV in IPF, 60.8% were 65 and over, while 16.3% were 75 and over. In SSc-ILD, 21.4% were 65 and over, while 1.9% were 75 and older. In phase 3 studies, no overall differences in effectiveness were observed between subjects who were 65 and over and younger subjects; no overall differences in safety were observed between subjects who were 65 and over or 75 and over and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

Nintedanib is predominantly eliminated via biliary/fecal excretion (greater than 90%). In a PK study performed in patients with hepatic impairment (Child Pugh A, Child Pugh B), exposure to nintedanib was increased *[see Clinical Pharmacology (12.3)]*. In patients with mild hepatic impairment (Child Pugh A), the recommended dosage of OFEV is 100 mg twice daily *[see Dosage and Administration (2.2)]*. Monitor for adverse reactions and consider treatment interruption, or discontinuation for management of adverse reactions in these patients *[see Dosage and Administration (2.3)]*. Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with OFEV is not recommended *[see Warnings and Precautions (5.1)]*.

8.7 Renal Impairment

Based on a single-dose study, less than 1% of the total dose of nintedanib is excreted via the kidney *[see Clinical Pharmacology (12.3)]*. Adjustment of the starting dose in patients with mild to moderate renal impairment is not required. The safety, efficacy, and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment (less than 30 mL/min CrCl) and end-stage renal disease.

8.8 Smokers

Smoking was associated with decreased exposure to OFEV *[see Clinical Pharmacology (12.3)],* which may alter the efficacy profile of OFEV. Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using OFEV.

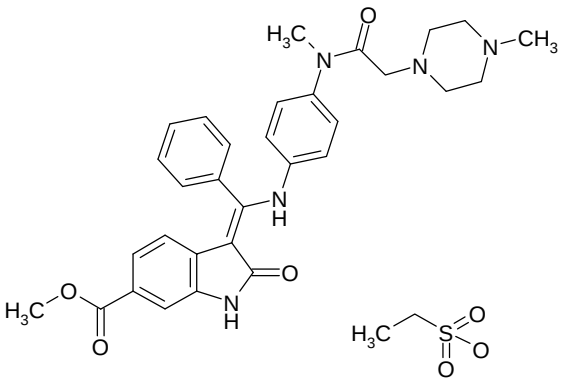
10 OVERDOSAGE

In IPF trials, one patient was inadvertently exposed to a dose of 600 mg daily for a total of 21 days. A non-serious adverse event (nasopharyngitis) occurred and resolved during the period of incorrect dosing, with no onset of other reported events. Overdose was also reported in two patients in oncology studies who were exposed to a maximum of 600 mg twice daily for up to 8 days. Adverse events reported were consistent with the existing safety profile of OFEV. Both patients recovered. In case of overdose, interrupt treatment and initiate general supportive measures as appropriate.

11 DESCRIPTION

OFEV capsules contain nintedanib, a kinase inhibitor *[see Mechanism of Action (12.1)]*. Nintedanib is presented as the ethanesulfonate salt (esylate), with the chemical name 1*H*-Indole-6-carboxylic acid, 2,3-dihydro-3-[[[4-[methyl[(4-methyl-1-piperazinyl)acetyl]amino]phenyl]amino]phenylmethylene]-2-oxo-,methyl ester, (3*Z*)-, ethanesulfonate (1:1).

Its structural formula is:



Nintedanib esylate is a bright yellow powder with an empirical formula of $C_{31}H_{33}N_5O_4 \cdot C_2H_6O_3S$ and a molecular weight of 649.76 g/mol.

OFEV capsules for oral administration are available in 2 dose strengths containing 100 mg or 150 mg of nintedanib (equivalent to 120.40 mg or 180.60 mg nintedanib ethanesulfonate, respectively). The inactive ingredients of OFEV are the following: Fill Material: triglycerides, hard fat, lecithin. Capsule Shell: gelatin, glycerol, titanium dioxide, red ferric oxide, yellow ferric oxide, black ink.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nintedanib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs). Nintedanib inhibits the following RTKs: platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, vascular endothelial growth factor receptor (VEGFR) 1-3, colony stimulating factor 1 receptor (CSF1R), and Fms-like tyrosine kinase-3 (FLT-3). These kinases except for FLT-3 have been implicated in pathogenesis of interstitial lung diseases (ILD). Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these kinases and blocks the intracellular signaling

cascades, which have been demonstrated to be involved in the pathogenesis of fibrotic tissue remodeling in ILD. Nintedanib also inhibits the following nRTKs: Lck, Lyn and Src kinases. The contribution of FLT3 and nRTK inhibition to nintedanib efficacy in ILD is unknown.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a study in renal cell cancer patients, QT/QTc measurements were recorded and showed that a single oral dose of 200 mg nintedanib as well as multiple oral doses of 200 mg nintedanib administered twice daily for 15 days did not prolong the QTcF interval.

12.3 Pharmacokinetics

The PK properties of nintedanib were similar in healthy volunteers, patients with IPF, patients with SSc-ILD, and cancer patients. The PK of nintedanib is linear. Dose proportionality was shown by an increase of nintedanib exposure with increasing doses (dose range 50 to 450 mg once daily and 150 to 300 mg twice daily). Accumulation upon multiple administrations in patients with IPF was 1.76-fold for AUC. Steady-state plasma concentrations were achieved within one week of dosing. Nintedanib trough concentrations remained stable for more than one year. The inter-individual variability in the PK of nintedanib was moderate to high (coefficient of variation of standard PK parameters in the range of 30% to 70%), intra-individual variability low to moderate (coefficients of variation below 40%).

Absorption

Nintedanib reached maximum plasma concentrations approximately 2 to 4 hours after oral administration as a soft gelatin capsule under fed conditions. The absolute bioavailability of a 100 mg dose was 4.7% (90% CI: 3.62 to 6.08) in healthy volunteers. Absorption and bioavailability are decreased by transporter effects and substantial first-pass metabolism.

After food intake, nintedanib exposure increased by approximately 20% compared to administration under fasted conditions (90% CI: 95.3% to 152.5%) and absorption was delayed (median t_{max} fasted: 2.00 hours; fed: 3.98 hours), irrespective of the food type.

Distribution

Nintedanib follows bi-phasic disposition kinetics. After intravenous infusion, a high volume of distribution which was larger than total body volume (V_{ss}: 1050 L) was observed.

The *in vitro* protein binding of nintedanib in human plasma was high, with a bound fraction of 97.8%. Serum albumin is considered to be the major binding protein. Nintedanib is preferentially distributed in plasma with a blood to plasma ratio of 0.87.

Elimination

The effective half-life of nintedanib in patients with IPF was 9.5 hours (gCV 31.9%). Total plasma clearance after intravenous infusion was high (CL: 1390 mL/min; gCV 28.8%). Urinary excretion of unchanged drug within 48 hours was about 0.05% of the dose after oral and about 1.4% of the dose after intravenous administration; the renal clearance was 20 mL/min.

Metabolism

The prevalent metabolic reaction for nintedanib is hydrolytic cleavage by esterases resulting in the free acid moiety BIBF 1202. BIBF 1202 is subsequently glucuronidated by UGT enzymes, namely UGT 1A1, UGT 1A7, UGT 1A8, and UGT 1A10 to BIBF 1202 glucuronide. Only a minor extent of the biotransformation of nintedanib consisted of CYP pathways, with CYP 3A4 being the predominant enzyme involved. The major CYP-dependent metabolite could not be detected in plasma in the human absorption, distribution, metabolism,

and elimination study. *In vitro*, CYP-dependent metabolism accounted for about 5% compared to about 25% ester cleavage.

Excretion
The major route of elimination of drug-related radioactivity after oral administration of [^{14}C] nintedanib was via fecal/biliary excretion (93.4% of dose), and the majority of OFEV was excreted as BIBF 1202. The contribution of renal excretion to the total clearance was low (0.65% of dose). The overall recovery was considered complete (above 90%) within 4 days after dosing.

Specific Populations
Age, Body Weight, and Sex
Based on population PK analysis, age and body weight were correlated with nintedanib exposure. However, the effects on exposure are not sufficient to warrant a dose adjustment. There was no influence of sex on the exposure of nintedanib.

Renal Impairment
Based on a population PK analysis of data from 933 patients with IPF, exposure to nintedanib was not influenced by mild (CrCl: 60 to 90 mL/min; n=399) or moderate (CrCl: 30 to 60 mL/min; n=116) renal impairment. Data in severe renal impairment (CrCl below 30 mL/min) was limited.

Hepatic Impairment
A dedicated single-dose phase I pharmacokinetics study of OFEV compared 8 subjects with mild hepatic impairment (Child Pugh A) and 8 subjects with moderate hepatic impairment (Child Pugh B) to 17 subjects with normal hepatic function. In subjects with mild hepatic impairment, the mean exposure to nintedanib was 2.4-fold higher based on C_{max} (90% CI 1.6 to 3.6) and 2.2-fold higher based on $AUC_{0\text{-}inf}$ (90% CI 1.4 to 3.5). In subjects with moderate hepatic impairment, exposure was 6.9-fold higher based on C_{max} (90% CI 4.4 to 11.0) and 7.6-fold higher based on $AUC_{0\text{-}inf}$ (90% CI 5.1 to 11.3). Subjects with severe hepatic impairment (Child Pugh C) have not been studied.

Smokers
In the population PK analysis, the exposure of nintedanib was 21% lower in current smokers compared to ex- and never-smokers. The effect is not sufficient to warrant a dose adjustment.

Drug Interaction Studies
Potential for Nintedanib to Affect Other Drugs
Effect of nintedanib coadministration on pirfenidone AUC and C_{max} was evaluated in a multiple-dose study. Nintedanib did not have an effect on the exposure of pirfenidone.

In *in vitro* studies, nintedanib was shown not to be an inhibitor of OATP-1B1, OATP-1B3, OATP-2B1, OCT-2, or MRP-2. *In vitro* studies also showed that nintedanib has weak inhibitory potential on OCT-1, BCRP, and P-gp; these findings are considered to be of low clinical relevance. Nintedanib and its metabolites, BIBF 1202 and BIBF 1202 glucuronide, did not inhibit or induce CYP enzymes *in vitro*.

Potential for Other Drugs to Affect Nintedanib
Nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4. Coadministration with the P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib 1.61-fold based on AUC and 1.83-fold based on C_{max} in a dedicated drug-drug interaction study. In a drug-drug interaction study with the P-gp and CYP3A4 inducer, rifampicin, exposure to nintedanib decreased to 50.3% based on AUC and to 60.3% based on C_{max} upon coadministration with rifampicin compared to administration of nintedanib alone.

Effect of pirfenidone coadministration on nintedanib AUC and C_{max} was evaluated in a multiple-dose drug-drug interaction study. Pirfenidone did not have an effect on the exposure of nintedanib. Concomitant treatment with nintedanib and pirfenidone was also investigated in a separate trial, which was an exploratory open-label, randomized (1:1) trial of nintedanib 150 mg twice daily with add-on pirfenidone (titrated to 801 mg three times a day) compared to nintedanib 150 mg twice daily alone in 105 randomized patients for 12 weeks. Similar nintedanib trough plasma concentrations were observed when comparing patients receiving nintedanib alone with patients receiving nintedanib with add-on pirfenidone.

Healthy volunteers received a single dose of 150 mg nintedanib before and after multiple dosing of 125 mg bosentan twice daily at steady state. Coadministration of nintedanib with bosentan did not alter the pharmacokinetics of nintedanib.

Nintedanib displays a pH-dependent solubility profile with increased solubility at acidic pH less than 3. However, in the clinical trials, coadministration with proton pump inhibitors or histamine H2 antagonists did not influence the exposure (trough concentrations) of nintedanib.

In *in vitro* studies, nintedanib was shown not to be a substrate of OATP-1B1, OATP-1B3, OATP-2B1, OCT-2, MRP-2, or BCRP. *In vitro* studies also showed that nintedanib was a substrate of OCT-1; these findings are considered to be of low clinical relevance.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year oral carcinogenicity studies of nintedanib in rats and mice have not revealed any evidence of carcinogenic potential. Nintedanib was dosed up to 10 and 30 mg/kg/day in rats and mice, respectively. These doses were less than and approximately 4 times the MRHD on a plasma drug AUC basis.

Nintedanib was negative for genotoxicity in the *in vitro* bacterial reverse mutation assay, the mouse lymphoma cell forward mutation assay, and the *in vivo* rat micronucleus assay.

In rats, nintedanib reduced female fertility at exposure levels approximately 3 times the MRHD (on an AUC basis at an oral dose of 100 mg/kg/day). Effects included increases in resorption and post-implantation loss, and a decrease in gestation index. Changes in the number and size of corpora lutea in the ovaries were observed in chronic toxicity studies in rats and mice. An increase in the number of females with resorptions only was observed at exposures approximately equal to the MRHD (on an AUC basis at an oral dose of 20 mg/kg/day). Nintedanib had no effects on male fertility in rats at exposure levels approximately 3 times the MRHD (on an AUC basis at an oral dose of 100 mg/kg/day).

14 CLINICAL STUDIES

14.1 Idiopathic Pulmonary Fibrosis

The clinical efficacy of OFEV has been studied in 1231 patients with IPF in one phase 2 (Study 1) and two phase 3 (Studies 2 and 3). These were randomized, double-blind, placebo-controlled studies comparing treatment with OFEV 150 mg twice daily to placebo for 52 weeks.

Studies 2 and 3 were identical in design. Study 1 was very similar in design. Patients were randomized in a 3:2 ratio (1:1 for Study 1) to either OFEV 150 mg or placebo twice daily for 52 weeks. Study 1 also included other treatment arms (50 mg daily, 50 mg twice daily, and 100 mg twice daily) that are not further discussed. The primary endpoint was the annual rate of decline in Forced Vital Capacity (FVC). Time to first acute IPF exacerbation was a key secondary endpoint in Studies 2 and 3 and a secondary endpoint in Study 1. Change from baseline in FVC percent predicted and survival were additional secondary endpoints in all studies.

Patients were required to have a diagnosis of IPF (ATS/ERS/JRS/ALAT criteria) for less than 5 years. Diagnoses were centrally adjudicated based on radiologic and, if applicable, histopathologic confirmation. Patients were required to be greater than or equal to 40 years of age with an FVC greater than or equal to 50% of predicted and a carbon monoxide diffusing capacity (DLCO, corrected for hemoglobin) 30% to 79% of predicted. Patients with relevant airways obstruction (i.e., pre-bronchodilator FEV_1/FVC less than 0.7) or, in the opinion of the investigator, likely to receive a lung transplant during the studies were excluded (being listed for lung transplant was acceptable for inclusion). Patients with greater than 1.5 times ULN of ALT, AST, or bilirubin, patients with a known risk or predisposition to bleeding, patients receiving a full dose of anticoagulation treatment, and patients with a recent history of myocardial infarction or stroke were excluded from the studies. Patients were also excluded if they received other investigational therapy, azathioprine, cyclophosphamide, or cyclosporine A within 8 weeks of entry into this trial, or n-acetyl cysteine and prednisone (greater than 15 mg/day or equivalent) within 2 weeks. The majority of patients were Caucasian (60%) or Asian (30%) and male (79%). Patients had a mean age of 67 years and a mean FVC percent predicted of 80%.

Annual Rate of Decline in FVC

A statistically significant reduction in the annual rate of decline of FVC (in mL) was demonstrated in patients receiving OFEV compared to patients receiving placebo based on the random coefficient regression model, adjusted for gender, height, and age. The treatment effect on FVC was consistent in all 3 studies. See Table 3 for individual study results.

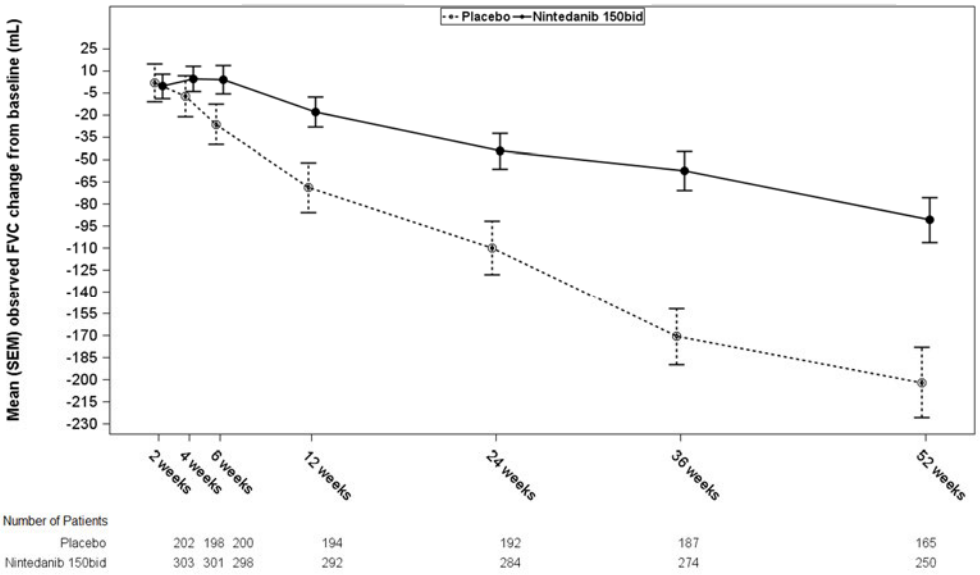
Table 3 Annual Rate of Decline in FVC (mL) in Studies 1, 2, and 3[a]

	Study 1		**Study 2**		**Study 3**	
	OFEV 150 mg twice daily	**Placebo**	**OFEV 150 mg twice daily**	**Placebo**	**OFEV 150 mg twice daily**	**Placebo**
Number of analyzed patients	84	83	309	204	329	219
Rate[a] of decline over 52 weeks	-60	-191	-115	-240	-114	-207
Comparison vs placebo Difference[b]	131		125		94	
95% CI	(27, 235)		(78, 173)		(45, 143)	

[a]Randomized set in Study 1; treated set in Studies 2 and 3
[b]Estimated based on a random coefficient regression model

Figure 1 displays the change from baseline over time in both treatment groups for Study 2. When the mean observed FVC change from baseline was plotted over time, the curves diverged at all timepoints through Week 52. Similar plots were seen for Studies 1 and 3.

Figure 1 Mean (SEM) Observed FVC Change from Baseline (mL) Over Time in Study 2

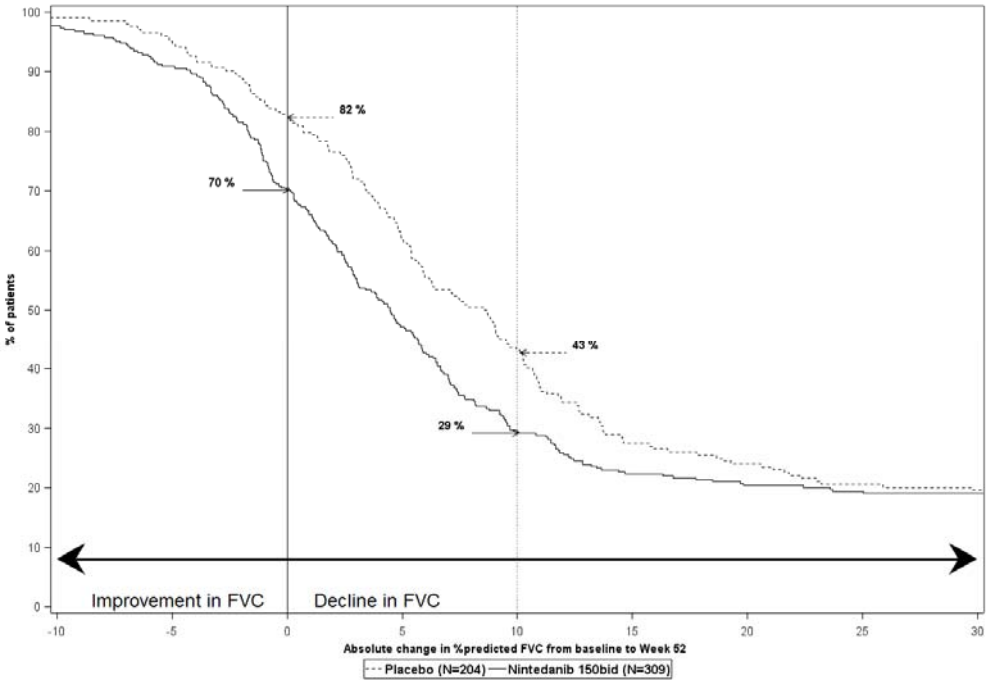


bid = twice daily

Change from Baseline in Percent Predicted Forced Vital Capacity

Figure 2 presents the cumulative distribution for all cut-offs for the change from baseline in FVC percent predicted at Week 52 for Study 2. For all categorical declines in lung function, the proportion of patients declining was lower on OFEV than on placebo. Study 3 showed similar results.

Figure 2 Cumulative Distribution of Patients by Change in Percent Predicted FVC from Baseline to Week 52 (Study 2).* The vertical lines indicate ≥0% decline or ≥10% decline.



*Missing data for change from baseline at Week 52 in percent predicted FVC (due to death, lost to follow-up or censoring before 52 weeks) was imputed using the worst decline from baseline at Week 52 observed among all patients with available data, regardless of treatment.
bid = twice daily

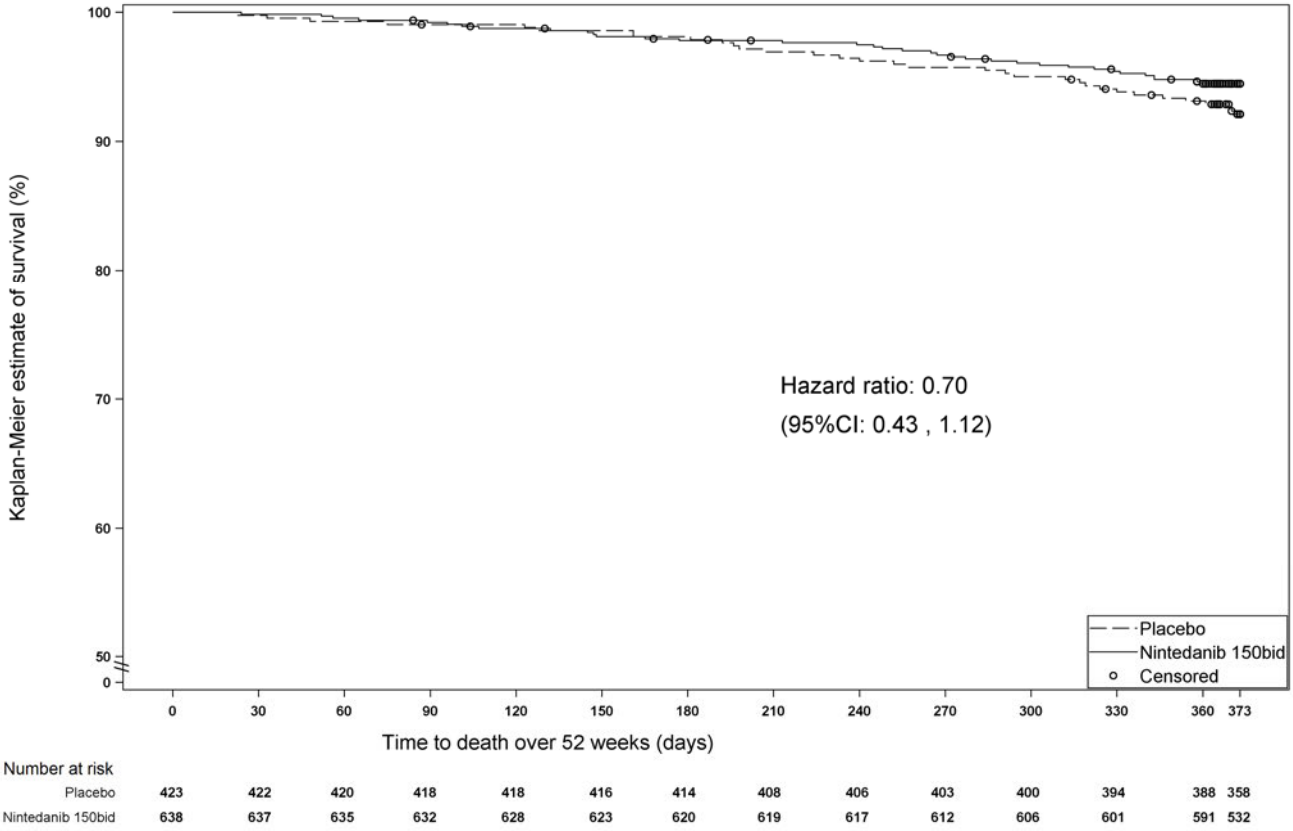
Time to First Acute IPF Exacerbation

Acute IPF exacerbation was defined as unexplained worsening or development of dyspnea within 30 days, new diffuse pulmonary infiltrates on chest x-ray, and/or new high-resolution CT parenchymal abnormalities with no pneumothorax or pleural effusion, and exclusion of alternative causes. Acute IPF exacerbation was adjudicated in Studies 2 and 3. In Studies 1 (investigator-reported) and 3 (adjudicated), the risk of first acute IPF exacerbation over 52 weeks was significantly reduced in patients receiving OFEV compared to placebo (hazard ratio [HR]: 0.16, 95% CI: 0.04, 0.71) and (HR: 0.20, 95% CI: 0.07, 0.56), respectively. In Study 2 (adjudicated), there was no difference between the treatment groups (HR: 0.55, 95% CI: 0.20, 1.54).

Survival

Survival was evaluated for OFEV compared to placebo in Studies 2 and 3 as an exploratory analysis to support the primary endpoint (FVC). All-cause mortality was assessed over the study duration and available follow-up period, irrespective of cause of death and whether patients continued treatment. All-cause mortality did not show a statistically significant difference (See Figure 3).

Figure 3 Kaplan-Meier Estimates of All-Cause Mortality at Vital Status – End of Study: Studies 2 and 3



bid = twice daily

14.2 Systemic Sclerosis-Associated Interstitial Lung Disease

The clinical efficacy of nintedanib has been studied in patients with SSc-ILD in a randomized, double-blind, placebo-controlled phase 3 trial (Study 4). A total of 580 patients were randomized in a 1:1 ratio to receive either OFEV 150 mg twice daily or matching placebo for at least 52 weeks, of which 576 patients were treated. Randomization was stratified by anti-topoisomerase antibody (ATA) status. Individual patients remained on blinded trial treatment for up to 100 weeks. The primary endpoint was the annual rate of decline in FVC over 52 weeks. The absolute change from baseline in the modified Rodnan skin score (mRSS) at Week 52 was a key secondary endpoint. Mortality over the whole trial was an additional secondary endpoint.

Patients were diagnosed with SSc-ILD based upon the 2013 American College of Rheumatology / European League Against Rheumatism classification criteria for SSc with onset of disease (first non-Raynaud symptom) of less than 7 years and greater than or equal to 10% fibrosis on a chest high resolution computed tomography (HRCT) scan conducted within the previous 12 months. Patients were required to have an FVC greater than or equal to 40% of predicted and a DLCO 30-89% of predicted. Patients with relevant airways obstruction (i.e., pre-bronchodilator FEV_1/FVC less than 0.7) or previous or planned hematopoietic stem cell transplant were excluded from the trial. Patients with greater than 1.5 times ULN of ALT, AST, or bilirubin, patients with a known risk or predisposition to bleeding, patients receiving a full dose of anticoagulation treatment, and patients with a recent history of myocardial infarction or stroke were excluded from the study. Patients were excluded if they had significant pulmonary hypertension, more than three digital fingertip ulcers, a history of severe digital necrosis requiring hospitalization, or a history of scleroderma renal crisis. Patients were also excluded if they received other investigational therapy, previous treatment with nintedanib or pirfenidone, azathioprine within 8 weeks prior to randomization, or cyclophosphamide or cyclosporine A within 6 months prior to randomization.

The majority of patients were female (75%). Patients were mostly Caucasian (67%), Asian (25%), or Black (6%). The mean age was 54 years. Overall, 52% of patients had diffuse cutaneous systemic sclerosis (SSc) and 48% had limited cutaneous SSc. The mean time since first onset of a non-Raynaud symptom was 3.49 years. At baseline, 49% of patients were on stable therapy with mycophenolate.

Annual Rate of Decline in FVC

The annual rate of decline of FVC (in mL) over 52 weeks was significantly reduced by 41 mL in patients receiving OFEV compared to patients receiving placebo, corresponding to a relative treatment effect of 44%. See Table 4.

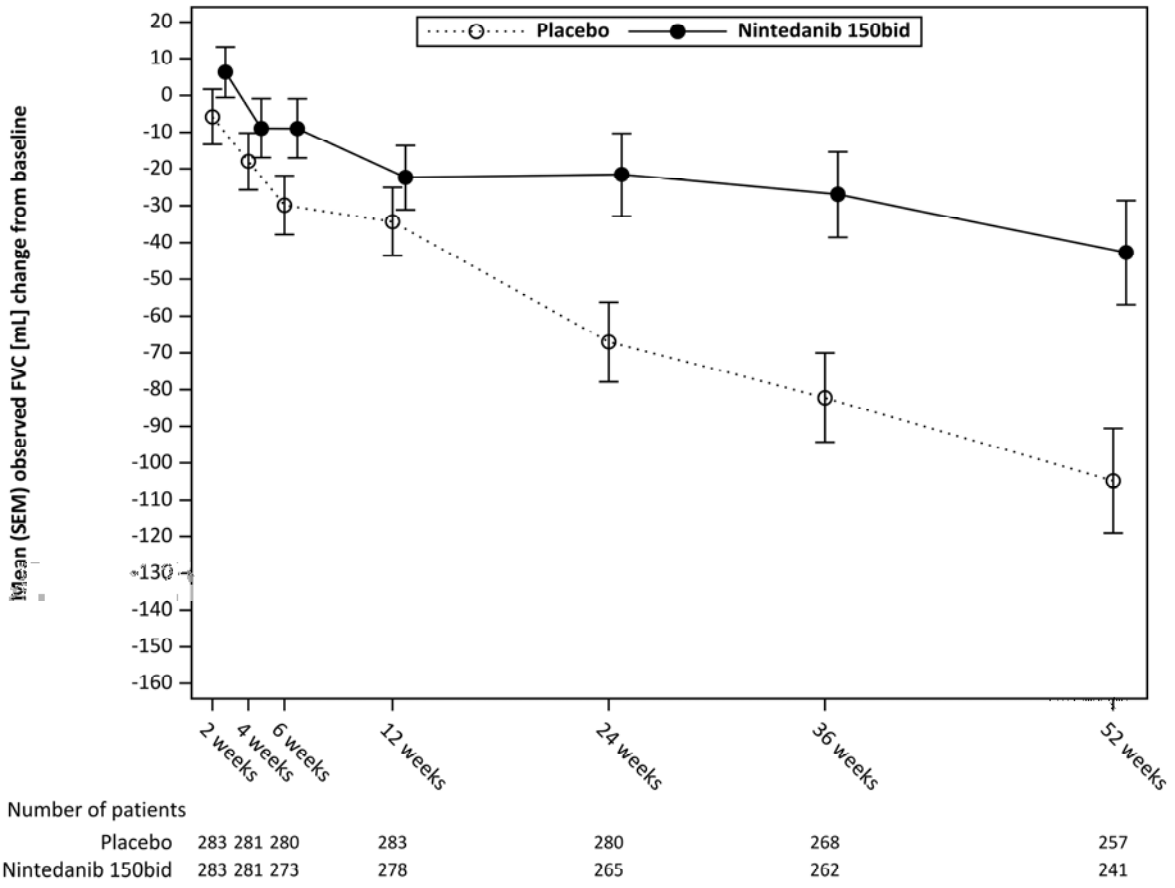
Table 4 Annual Rate of Decline in FVC (mL) in Study 4

	OFEV 150 mg twice daily	**Placebo**
Number of analyzed patients	287	288
Rate of decline over 52 weeks	-52	-93
Comparison vs placebo Difference[a]	41	
95% CI	(3, 79)	

[a]Based on a random coefficient regression model, adjusted for gender, height, age, ATA status, FVC at baseline, FVC at baseline-by-time

Figure 4 displays the change from baseline over time in both treatment groups. When the mean observed FVC change from baseline was plotted over time, the curves diverged at all timepoints through Week 52. Separation of the mean values is seen after 12 weeks of treatment.

Figure 4 Mean (SEM) Observed FVC Change from Baseline (mL) Over Time in Study 4

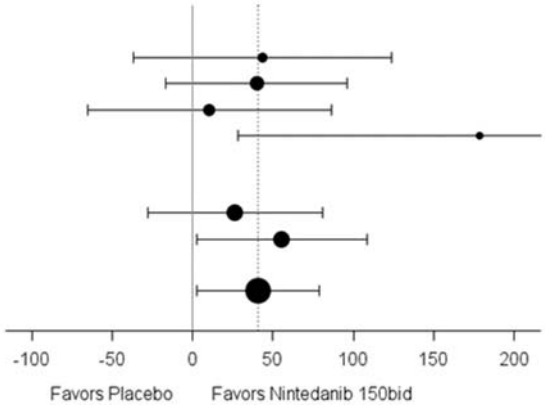


bid = twice daily

In two pre-specified subgroup efficacy analyses, the mean treatment difference in FVC decline at 52 weeks in patients were examined by region and mycophenolate use (Figure 5).

Figure 5 Subgroup Analyses of the Mean Treatment Difference in FVC (mL) Decline at Week 52 by Region and Mycophenolate Use (Study 4)

	Placebo		Nintedanib 150bid		Difference [95% CI]
	N	Rate of Decline	N	Rate of Decline	
Region					
Asia	71	-92	59	-48	43 [-37; 124]
Europe	126	-107	139	-67	40 [-17; 96]
Canada and United States	73	-52	69	-42	10 [-66; 86]
Rest of World	18	-176	20	2	178 [28; 329]
Mycophenolate use at baseline					
Yes	140	-67	138	-40	26 [-28; 81]
No	148	-119	149	-64	55 [2; 109]
ALL	288	-93	287	-52	41 [3; 79]

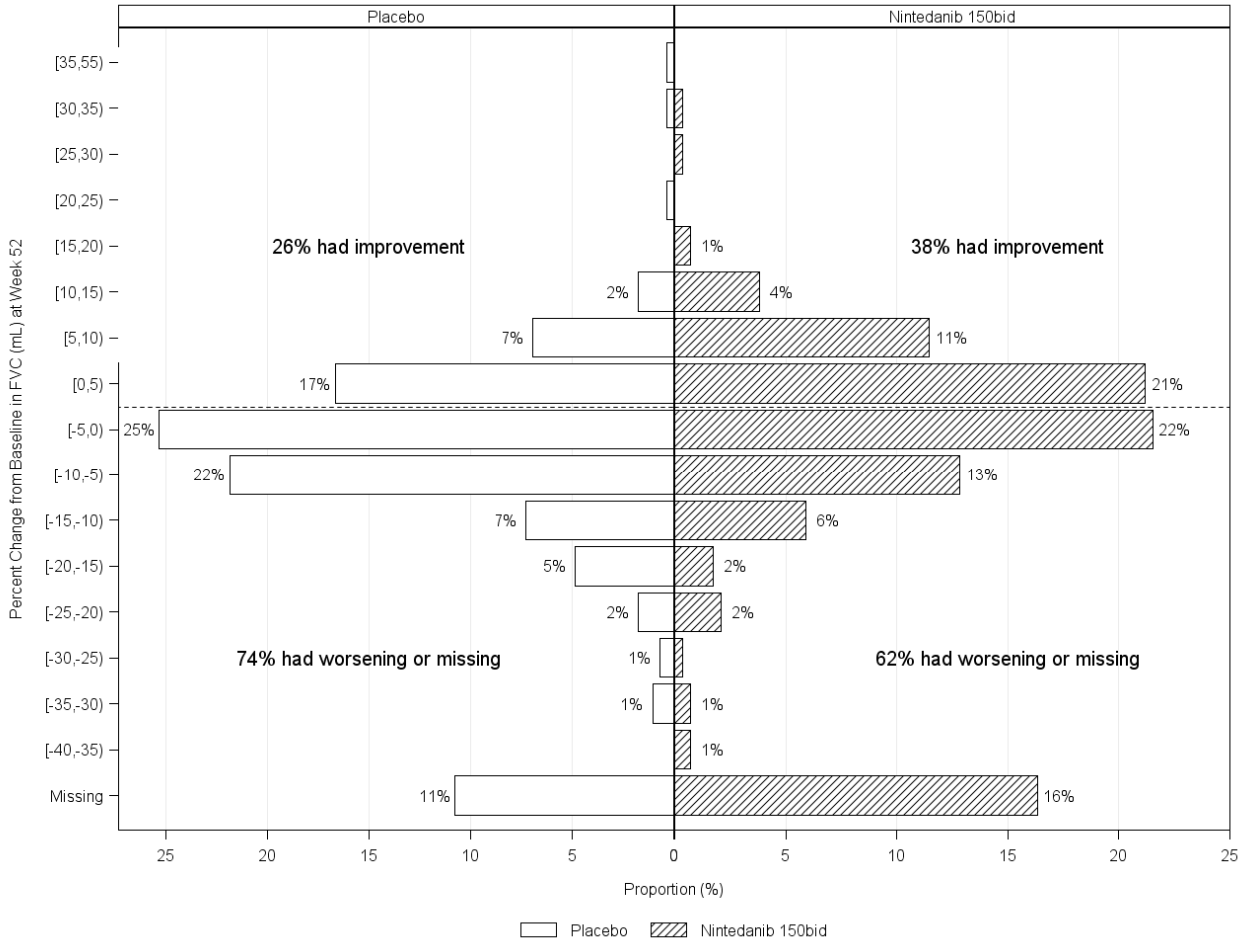


Nintedanib 150bid – Placebo difference in adjusted rate of decline in FVC [mL/yr] and 95% confidence interval

Percent Change from Baseline in Forced Vital Capacity

Figure 6 presents the percent change from baseline in FVC in mL at Week 52 for Study 4. For the majority of patients, the decline in lung function was less on OFEV than on placebo.

Figure 6 Histogram of the Percent Change in FVC (mL) from Baseline to Week 52 According to Treatment and Percent Increments or Decrements of 5 (Study 4)[a]



[a] Patients classified as having missing FVC data at Week 52 are those with no FVC assessment between Day 310 and Day 373.
bid = twice daily

Modified Rodnan Skin Score

No benefit in mRSS was observed in patients receiving OFEV. The adjusted mean absolute change from baseline in mRSS at Week 52 was comparable between the OFEV group (-2.17 (95% CI: -2.69, -1.65)) and the placebo group (-1.96 (95% CI: -2.48, -1.45)). The adjusted mean difference between the treatment groups was -0.21 (95% CI: -0.94, 0.53).

Survival

No difference in survival was observed in an exploratory analysis of mortality over the whole trial (OFEV: n=10 (3.5%) vs. placebo: n=9 (3.1%)). The analysis of time to death over the whole trial resulted in a HR of 1.16 (95% CI: 0.47, 2.84).

16 HOW SUPPLIED/STORAGE AND HANDLING

150 mg: brown, opaque, oblong, soft capsules imprinted in black with the Boehringer Ingelheim company symbol and "150". They are packaged in HDPE bottles with a child-resistant closure, available as follows:
Bottles of 60 NDC: 0597-0145-60

100 mg: peach, opaque, oblong, soft capsules imprinted in black with the Boehringer Ingelheim company symbol and "100". They are packaged in HDPE bottles with a child-resistant closure, available as follows:
Bottles of 60 NDC: 0597-0143-60

Storage

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from exposure to high humidity and avoid excessive heat. If repackaged, use USP tight container. Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Elevated Liver Enzymes and Drug-Induced Liver Injury

Advise patients that they will need to undergo liver function testing periodically. Advise patients to immediately report any symptoms of a liver problem (e.g., skin or the whites of eyes turn yellow, urine turns dark or brown (tea colored), pain on the right side of stomach, bleed or bruise more easily than normal, lethargy, loss of appetite) *[see Warnings and Precautions (5.2)]*.

Gastrointestinal Disorders

Inform patients that gastrointestinal disorders such as diarrhea, nausea, and vomiting were the most commonly reported gastrointestinal events occurring in patients who received OFEV. Advise patients that their healthcare provider may recommend hydration, antidiarrheal medications (e.g., loperamide), or anti-emetic medications to treat these side effects. Temporary dosage reductions or discontinuations may be required. Instruct patients to contact their healthcare provider at the first signs of diarrhea or for any severe or persistent diarrhea, nausea, or vomiting *[see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]*.

Embryo-Fetal Toxicity

Counsel patients on pregnancy prevention and planning. Advise females of reproductive potential of the potential risk to a fetus and to avoid becoming pregnant while receiving treatment with OFEV. Advise females of reproductive potential to use highly effective contraception during treatment, and for at least 3 months after taking the last dose of OFEV. Advise women using hormonal contraceptives to add a barrier method. Advise female patients to notify their doctor if they become pregnant or suspect they are pregnant during therapy with OFEV *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.1, 8.3)]*.

Arterial Thromboembolic Events

Advise patients about the signs and symptoms of acute myocardial ischemia and other arterial thromboembolic events and the urgency to seek immediate medical care for these conditions *[see Warnings and Precautions (5.5)]*.

Risk of Bleeding

Bleeding events have been reported. Advise patients to report unusual bleeding *[see Warnings and Precautions (5.6)]*.

Gastrointestinal Perforation

Serious gastrointestinal perforation events have been reported. Advise patients to report signs and symptoms of gastrointestinal perforation *[see Warnings and Precautions (5.7)]*.

Lactation
Advise patients that breastfeeding is not recommended while taking OFEV *[see Use in Specific Populations (8.2)]*.

Smokers
Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using OFEV *[see Clinical Pharmacology (12.3)]*.

Administration
Instruct patients to swallow OFEV capsules whole with liquid and not to chew or crush the capsules due to the bitter taste. Advise patients to not make up for a missed dose *[see Dosage and Administration (2)]*.

Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

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Boehringer Ingelheim International GmbH

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IT6996JI052019

Patient Information
OFEV® (OH-fev)
(nintedanib)
capsules

What is the most important information I should know about OFEV?

OFEV can cause birth defects or death to an unborn baby. Women should not become pregnant while taking OFEV. Women who are able to become pregnant should have a pregnancy test before starting treatment with OFEV.

Women who are able to become pregnant should use highly effective birth control during treatment and for at least 3 months after treatment. Talk with your doctor about what birth control method is right for you during this time.

Women using hormonal birth control should add a barrier method of birth control (such as male condoms or spermicide).

If you become pregnant or think you are pregnant while taking OFEV, tell your doctor right away.

What is OFEV?

- OFEV is a prescription medicine used:
  - to treat people with a lung disease called idiopathic pulmonary fibrosis (IPF).

  or
  - to slow the rate of decline in lung function in people with systemic sclerosis-associated interstitial lung disease (SSc-ILD) (also known as scleroderma-associated ILD).
- It is not known if OFEV is safe and effective in children.

What should I tell my doctor before taking OFEV?

Before you take OFEV, tell your doctor about all of your medical conditions, including if you:

- have liver problems.
- have heart problems.
- have a history of blood clots.
- have a bleeding problem or a family history of a bleeding problem.
- have had recent surgery in your stomach (abdominal) area.
- are a smoker.
- are pregnant or plan to become pregnant. OFEV can harm your unborn baby. OFEV can cause birth defects or death to an unborn baby. See **"What is the most important information I should know about OFEV?"**
- are breastfeeding or plan to breastfeed. It is not known if OFEV passes into your breast milk. You **should not** breastfeed while taking OFEV.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements such as St. John's wort. Keep a list of the medicines you take and show it to your doctor and pharmacist when you get a new medicine.

How should I take OFEV?

- Take OFEV exactly as your doctor tells you to take it.
- Your doctor will tell you how much OFEV to take and when to take it.
- Take OFEV with food. Swallow the OFEV capsules whole with a liquid.
- **Do not** chew or crush OFEV capsules.
- If you miss a dose of OFEV, take your next dose at your regular time. **Do not** take the missed dose.
- **Do not** take more than 300 mg of OFEV in 1 day.
- If you take too much OFEV, call your doctor or go to the nearest hospital emergency room right away.
- Your doctor should do certain blood tests before you start taking OFEV.

What are the possible side effects of OFEV?

OFEV may cause serious side effects, including:

- **See "What is the most important information I should know about OFEV?"**
- **liver problems.** Call your doctor right away if you have unexplained symptoms such as yellowing of your skin or the white part of your eyes (jaundice), dark or brown (tea colored) urine, pain on the upper right side of your stomach area (abdomen), bleeding or bruising more easily than normal, feeling tired, or loss of appetite. Your doctor will do blood tests to check how well your liver is working before starting and during your treatment with OFEV.
- **diarrhea, nausea, and vomiting.** While you are taking OFEV, your doctor may recommend that you drink fluids or take medicine to treat these side effects. Tell your doctor if you have diarrhea, nausea, or vomiting or if these

symptoms do not go away or become worse. Tell your doctor if you are taking over-the-counter laxatives, stool softeners, and other medicines or dietary supplements that can cause diarrhea.

- **heart attack.** Tell your doctor right away if you have symptoms of a heart problem. These symptoms may include chest pain or pressure, pain in your arms, back, neck or jaw, or shortness of breath.
- **stroke.** Tell your doctor right away if you have symptoms of a stroke. These symptoms may include numbness or weakness on 1 side of your body, trouble talking, headache, or dizziness.
- **bleeding problems.** OFEV may increase your chances of having bleeding problems. Tell your doctor if you have unusual bleeding, bruising, or wounds that do not heal. Tell your doctor if you are taking a blood thinner, including prescription blood thinners and over-the-counter aspirin.
- **tear in your stomach or intestinal wall (perforation).** OFEV may increase your chances of having a tear in your stomach or intestinal wall. Tell your doctor if you have pain or swelling in your stomach area.

The most common side effects of OFEV are diarrhea, nausea, stomach pain, vomiting, liver problems, decreased appetite, headache, weight loss, and high blood pressure.

These are not all the possible side effects of OFEV. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store OFEV?

- Store OFEV at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep OFEV dry and protect from high heat.

Keep OFEV and all medicines out of the reach of children.

General information about the safe and effective use of OFEV.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use OFEV for a condition for which it was not prescribed. Do not give OFEV to other people, even if they have the same symptoms you have. It may harm them. This Patient Information leaflet summarizes the most important information about OFEV. If you would like more information, talk to your doctor. You can ask your pharmacist or doctor for information about OFEV that is written for health professionals.
For more information, go to www.ofev.com or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257, or (TTY) 1-800-459-9906, or scan the code below to go to www.ofev.com.

What are the ingredients in OFEV?

Active ingredient: nintedanib.

Inactive ingredients: Fill Material: triglycerides, hard fat, lecithin. Capsule Shell: gelatin, glycerol, titanium dioxide, red ferric oxide, yellow ferric oxide, black ink.

Distributed by: Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877 USA

IT6996JI052019

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: September 2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205832Orig1s012

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	NDA 205832/ Supplement 12
Priority or Standard	Priority
Submit Date(s)	March 7, 2019
Received Date(s)	March 7, 2019
PDUFA Goal Date	September 6, 2019
Division/Office	DPARP/ OND
Review Completion Date	September 6, 2019
Established/Proper Name	Nintedanib
Trade Name	Ofev
Pharmacologic Class	Tyrosine Kinase Inhibitor
Applicant	Boehringer Ingelheim
Dosage form	Oral capsule
Applicant proposed Dosing Regimen	150 mg by mouth twice daily with recommended dosage in patients with mild hepatic impairment (Child Pugh A): 100 mg twice daily approximately 12 hours apart taken with food
Applicant Proposed Indication(s)/Population(s)	Treatment of systemic sclerosis-associated interstitial lung disease
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	To slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease
Recommended Dosing Regimen	150 mg by mouth twice daily with recommended dosage in patients with mild hepatic impairment (Child Pugh A): 100 mg twice daily approximately 12 hours apart taken with food

Table of Contents

Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Jessica Lee, PharmD
Nonclinical Reviewer	Luqi Pei, PhD
Nonclinical Team Leader	Carol Galvis, PhD
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Clinical Reviewer	Nadia Habal, MD
Clinical Team Leader	Rachel Glaser, MD
Statistical Reviewer	Yu Wang, PhD
Statistical Team Leader	Yongman Kim, PhD
Cross-Disciplinary Team Leader	Rachel Glaser, MD
Division Director (or designated signatory authority)	Nikolay Nikolov, MD

Additional Reviewers of Application

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Microbiology	N/A
OPDP	Kyle Synder, PharmD
OSI	N/A
OSE/DEPI	N/A
OSE/DMEPA	N/A
OSE/DRISK	N/A

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Luqi Pei, PhD	DPARP	Sections: 5	Select one: __√_Authored ___ Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Clinical Pharmacology Team Leader	Jianmeng Chen, MD, PhD	OCP/DCP2	Section: 6	Select one: ___ Authored _√__ Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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	Signature: Nadia Habal -S Digitally signed by Nadia Habal -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nadia Habal -S, 0.9.2342.19200300.100.1.1=0014318202 Date: 2019.09.06 13:10:19 -04'00'			
Clinical Team Leader	Rachel Glaser, MD	OND/DPARP	Sections: All	Select one: ___ Authored _√__ Approved
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Statistical Reviewer	Yu Wang, PhD	OTS/OB/DBII	Sections: 8, 19	Select one: __√_ Authored __√_ Approved
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OB DBII Director	Mark Rothmann, PhD	OTS/OB/DBII	Sections: 8	Select one: ___ Authored __√_Approved
	Signature: Mark D. Rothmann -S Digitally signed by Mark D. Rothmann -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300144907, cn=Mark D. Rothmann -S Date: 2019.09.06 12:00:56 -04'00'			
Division Director (Signatory)	Nikolay Nikolov, MD	OND/DPARP	Sections: All	Select one: __14_Authored __√_Approved
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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Nintedanib is a small molecule inhibitor of tyrosine kinases of vascular endothelial growth factor receptor (VEGFR) 1-3, platelet-derived growth factor receptor (PDGFR) α and ß, fibroblast growth factor receptor (FGFR) 1-3, and SRC family kinases. Nintedanib competitively binds the adenosine triphosphate (ATP) binding pocket of the receptors, blocking intracellular signaling. These growth factor pathways and down-stream signal cascades are involved in the pathogenesis of fibrotic tissue remodeling. Nintedanib was approved for the treatment of idiopathic pulmonary fibrosis (IPF) on October 15, 2014 under NDA 205832. The Applicant submitted supplement 12 for the treatment of SSc-ILD on March 7, 2019.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This application was based on a single study, 1199.214. The primary endpoint, the adjusted annual rate of decline in FVC over 52 weeks was lower in the nintedanib group (-52.4 mL/year) than in the placebo group (-93.3 mL/year), with a statistically significant treatment difference of 40.9 mL/year (95% CI: 2.9 to 79.0; p=0.035). The adjusted annual rate of decline in percent predicted FVC over 52 weeks was -1.4% predicted/year in the nintedanib group and -2.6% predicted/year in the placebo group; the adjusted difference between groups was 1.2% predicted/year (95% CI: 0.1 to 2.2; p=0.033). While the results for the primary endpoint were statistically significant based on the pre-specified analysis, the sensitivity analyses on missing data assumptions and responder analyses with various thresholds showed mixed results, mainly because the magnitude of the effect size was small. Differences of this magnitude did not result in improvement in measures of direct clinical benefit related to pulmonary involvement, such as SGRQ or FACIT-dyspnea score at Week 52. Also, there were no differences in other disease-related secondary endpoints, number of digital ulcers, or HAQ-DI. There was no difference in mortality. Additionally, a less robust treatment effect was observed in adjusted annual rate of decline in FVC in the subgroups of patients on mycophenolate mofetil at baseline (treatment difference 26.6 mL/year) and patients from the U.S. and Canada (treatment difference 10.2 mL/year. It is the view of the acting director of Biometrics 2 that, while the data from this clinical trial does not, on its own, provide substantial evidence of a treatment effect, when considered with the results from studies in related indication of IPF for which nintedanib is approved, a treatment effect in SSc-ILD appears real and can support approval for the sought indication.

In evaluating the evidence of effectiveness of nintedanib in SSc-ILD, the clinical review team also considered the totality of the data in the context of nintedanib experience in a distinct but related chronic progressive fibrosing lung disease, IPF, for which nintedanib is approved.

The primary endpoint, FVC, was selected by the Applicant based on their experience with the IPF program which used the same primary endpoint. Further analysis of data from IPF clinical

development programs has demonstrated that patients with less FVC decline also demonstrated an associated decrease in mortality.[1,2] In addition, FVC has been proposed as a validated outcome measure in patients with SSc according to the principles of Outcome Measures in Rheumatologic Clinical Trials (OMERACT).[3] While FVC is a surrogate endpoint that does not directly measure how a patient feels, functions, or survives, it has been demonstrated to reliably predict clinical benefit in IPF, another fibrotic disease in which FVC is known to decline, and in which FVC is monitored clinically. The clinical benefit from altering the rate of decline in lung function in patients with IPF, as measured by FVC over 52 weeks, has been shown to be consistent in two larger clinical programs, using two different products with different mechanisms of action, nintedanib and pirfenidone.[4,5] This additional contextual information supports the use of FVC as a clinically relevant primary endpoint in SSc-ILD to support traditional approval of nintedanib in SSc-ILD.[6]

While the absolute treatment effect was larger in the nintedanib IPF program (94 to 131 mL in IPF vs. 41 mL in SSc-ILD) due to faster rate of decline in IPF (-191 to -240 mL/year in IPF placebo group vs. -93 mL/year in SSc-ILD placebo group), the relative reduction in the annual rate of decline over placebo was similar between IPF and SSc-ILD programs (49% and 44%, respectively). Thus, it is reasonable to expect that the observed relative reduction in the annual rate of decline in FVC in SSc-ILD will also result in treatment effect on long-term clinical outcomes. However, given the slower rate of progression in SSc-ILD, as compared with IPF, demonstrating a clinical benefit on endpoints, such as mortality, will require a longer and larger clinical program in SSc-ILD which the Division considered to be challenging to design and execute due to the rarity of the condition. In assessing the need and feasibility of additional data, the Division considered several factors in this specific case. The adverse event profile of nintedanib will likely result in a significant proportion of patients needing to interrupt or discontinue therapy due to adverse events, which has the potential to result in a significant amount of missing data in a long-term clinical trial and respectively compromise the interpretability of such a study. Additional considerations included the practicality of enrolling patients in a long-term study given that nintedanib is available on the market, along with other standard of care therapies. Lastly, conducting a large and long study in SSc-ILD could divert resources and patients from other development programs in this therapeutic area which is in high need for treatment options. Based on the above considerations, the Division considered that requiring additional studies is not warranted or justified in this case.

---

[1] Karimi-Shah BA, Chowdhury BA, Forced vital capacity in idiopathic pulmonary fibrosis--FDA review of pirfenidone and nintedanib, N Engl J Med. 2015 Mar 26;372(13):1189-91

[2] Paterniti MO, et al, Acute Exacerbation and Decline in Forced Vital Capacity Are Associated with Increased Mortality in Idiopathic Pulmonary Fibrosis, Ann Am Thorac Soc. 2017 Sep;14(9):1395-1402

[3] Merkel P, Clements PJ, Reveille P, et al. Current status of outcome measure development for clinical trials in systemic sclerosis. J Rheumatol 2003;30:1630−47

[4] FDA-approved nintedanib labeling

[5] FDA-approved pirfenidone labeling

[6] Section 507(e)(9) of the FD&C Act

The data supporting this submission are derived from a single study. However, the effect of nintedanib on the lung function and clinical outcomes has been demonstrated in IPF using study design comparable to the one supporting the SSc-ILD application. With this prior experience, the Division and the acting director of Biometrics 2 conclude that the data from the single study in SSc-ILD is supported by the available data from nintedanib IPF program to provide substantial evidence of efficacy to support approval. Overall, in the context of SSc-ILD being a rare disease, we (the clinical review team and the Division Signatory) have determined that the benefit-risk for nintedanib is favorable in SSc-ILD to support an approval action with appropriate labeling. This determination also considers the discussion and input from the Arthritis Advisory Committee and the FDA Medical Policy and Program Review Council.

Benefit-Risk Summary and Assessment

The single clinical study 1199.214 in SSc-ILD showed a statistically significant lower rate of decline of FVC with nintedanib compared with placebo over 52 weeks, 41 mL/year (or approximately 1.2% predicted). Differences in key secondary endpoints were not seen for nintedanib over placebo during the 52-week duration of comparison in this study. FVC is a validated surrogate endpoint known to predict clinical benefit that can be used to support traditional approval of a drug in IPF.[7] FVC has been proposed as a validated outcome measure in patients with SSc according to the principles of Outcome Measures in Rheumatologic Clinical Trials (OMERACT).[8] Importantly, FVC is used in clinical practice to monitor and guide treatment decisions regarding the management of restrictive lung disease, including IPF and SSc-ILD. This additional contextual information supports the use of FVC as a primary endpoint in SSc-ILD to support traditional approval of nintedanib in SSc-ILD.

In evaluating the clinical significance of the treatment effect seen in the study, the Division considered the totality of the data in the context of nintedanib experience. The effect of nintedanib on the lung function and clinical outcomes has also been demonstrated in IPF using study designs similar to the one supporting the SSc-ILD application. Importantly, while the absolute treatment effect was larger in the IPF program (94 to 131 mL in IPF vs. 41 mL in SSc-ILD) due to faster rate of decline in IPF (-191 to -240 mL/year in IPF placebo group vs. -93 mL/year in SSc-ILD placebo group), the relative reduction in the annual rate of decline in FVC in mL over placebo was similar between IPF and SSc-ILD programs (49% and 44%, respectively). Thus, it is reasonable to expect that the observed relative reduction in the annual rate of decline in FVC in SSc-ILD will also result in a treatment effect on long-term clinical outcomes. However, given the slower rate of progression in SSc-ILD as compared with IPF, demonstrating a clinical benefit on endpoints, such as mortality, will require a longer and larger clinical program which the Division considered to be challenging to design and execute due to the rarity of the condition. In assessing the need and feasibility of additional data, the Division considered several factors in this specific case. The adverse event profile of nintedanib will likely result in a significant proportion of patients needing to interrupt or discontinue therapy due to adverse events, which has the potential to result in a significant amount of missing data in a long-term clinical trial and respectively compromise the interpretability of such a study. Additional considerations included the practicality of enrolling patients in a long-term study given that nintedanib is available on the market, along with other standard of care therapies. Lastly, conducting a large and long study in SSc-ILD could divert resources and patients from other development programs in this therapeutic area which is in high need for treatment options.

The safety of nintedanib in SSc-ILD is generally consistent with the established safety profile of nintedanib in IPF which includes risks of gastrointestinal disorders and liver toxicity. Gastrointestinal side effects need to be considered in patients with SSc-ILD who may also have

[7] Section 507(e)(9) of the FD&C Act

[8] Merkel P, Clements PJ, Reveille P, et al. Current status of outcome measure development for clinical trials in systemic sclerosis. J Rheumatol 2003;30:1630–47

gastrointestinal involvement from the disease. In addition to the established safety risks, in the SSc-ILD population, there were increased number of serious infections, driven by an increase in pneumonia in the nintedanib treatment group.

In summary, SSc-ILD is a rare and serious disease associated with high morbidity and mortality. It is also a disease with high unmet need for new therapies. In this context, the Division considered that the benefit-risk of nintedanib is justified for a modified indication, namely, to slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease. This indication more accurately reflects the demonstrated efficacy over 52 weeks of the clinical trial in SSc-ILD on the pulmonary function without a demonstration of direct patient benefit based on the secondary endpoints. This approval will provide a treatment option, in addition to the currently used off-label standard of care therapies.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• SSc-ILD is a serious condition with high morbidity and mortality and a large unmet need for clinical therapy • ILD is present in over half of patients with SSc • Median survival is 5-8 years in SSc-ILD	• SSc-ILD imposes a significant physical burden on the individual patient • Treatment to slow the progression of this disease is vital
Current Treatment Options	• Off label use of cyclophosphamide and mycophenolate	• There are no currently approved treatments for SSc or SSc-ILD • No treatment to date halts or reverses disease progression • Slowing the rate of decline in pulmonary function in patients with SSc-ILD will provide a treatment option
Benefit	• Decrease in adjusted annual FVC decline compared to placebo	• While FVC is a surrogate endpoint that does not directly measure how a patient feels, functions, or survives, it has been demonstrated to reliably predict clinical benefit in IPF, another fibrotic lung disease, in which FVC is similarly followed clinically. There was a statistically significant treatment effect on the pre-specified primary endpoint. Responder analyses and sensitivity analyses with respect to missing data provided some evidence to support the primary endpoint. While

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		the treatment effect was numerically small, it was supported by additional analyses which considered the totality of the data. • While the benefit is not supported by secondary endpoints, the small magnitude of the treatment effect may be difficult to translate to these other secondary endpoints, and therefore may be difficult to achieve in a one year study given the slower decline in lung function in SSc-ILD.
Risk and Risk Management	• Hepatic impairment • Elevated liver enzymes/drug-induced liver injury • Gastrointestinal disorders • Arterial thromboembolic events • Bleeding events • Gastrointestinal perforation • Pneumonia	• The safety of nintedanib in SSc-ILD is generally consistent with the established safety profile of nintedanib as communicated in the product labeling for the IPF indication.

1.3. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	SGRQ, FACIT-dyspnea score, HAQ-DI 8.1.2 Study Results
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		

2 Therapeutic Context

2.1. Analysis of Condition

Systemic sclerosis (SSc) is a rare, multisystem, connective tissue disease involving the skin, underlying tissues, blood vessels, and major organs. It is characterized by microvascular damage and fibrosis of the skin and of various internal organs, including the lung, heart, kidneys and the gastrointestinal tract. SSc is a serious disease associated with increased morbidity and mortality with a 10-year survival rate less than 70% from the time of diagnosis.[9] The primary causes of SSc-related deaths are pulmonary fibrosis, pulmonary arterial hypertension, heart failure, or cardiac arrhythmia. Interstitial lung disease (ILD), as detected by high resolution computed tomography (HRCT), is present in 55-65% of patients with SSc.[10] Severe ILD usually presents relatively early in the disease course within the first 3 years from time of diagnosis.[11] Median survival is 5-8 years in SSc-ILD.[12]

2.2. Analysis of Current Treatment Options

There are no FDA-approved therapies for treatment of systemic sclerosis or SSc-ILD. In clinical practice, patients with systemic sclerosis are treated based on expert-derived recommendations for the management of organ-specific manifestations and empirically with off-label products used for other rheumatic diseases. The Update of EULAR recommendations for the treatment of systemic sclerosis (April 2017), recommends consideration of cyclophosphamide for treatment of SSc-ILD, particularly in patients with progressive ILD.[13] The BSR and BHPR guidelines for the treatment of systemic sclerosis (June 2016) recommends treatment of extensive or progressive ILD with immunosuppression, including intravenous cyclophosphamide. Mycophenolate mofetil (MMF) may also be used as an alternative or after cyclophosphamide.[14]

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[9] Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972−2002. Ann Rheum Dis 2007;66:940−4

[10] Launay D, Remy-Jardin M, Michon-Pasturel U, et al. High resolution computed tomography in fibrosing alveolitis associated with systemic sclerosis. J Rheumatol 2006;33(9):1789-801

[11] Steen VD, Medsger TA Jr. Severe Organ Involvement in Systemic Sclerosis with Diffuse Scleroderma. Arthritis Rheum 2000:43:2437−44

[12] Herzog EL, Mathur A, Tager AM, Feghali-Bostwick C, Schneider F, Varga J. Interstitial lung disease associated with systemic sclerosis and idiopathic pulmonary fibrosis: how similar and distinct? Arthritis and Rheumatology, Accepted Article, Accepted: May 08, 2014, doi:10.1002/art.38702; 2014. p. 1967-1978

[13] Update of EULAR recommendations for the treatment of systemic sclerosis, April 2017 https://ard.bmj.com/content/annrheumdis/early/2017/04/25/annrheumdis-2016-209909.full.pdf

[14] BSR and BHPR guideline for the treatment of systemic sclerosis, June 2016 https://academic.oup.com/rheumatology/article/55/10/1906/2196591

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

On October 15, 2014, nintedanib was approved for the treatment of idiopathic pulmonary fibrosis.

3.2. Summary of Presubmission/Submission Regulatory Activity

On February 12, 2015 in written responses to pre-IND 124707, the Agency acknowledged that SSc-ILD is a slowly progressive disease manifestation and it may take years to show benefit on disease progression. In the absence of preliminary information on the effects of nintedanib on SSc-ILD, it was unclear if treatment could alter natural decline in forced vital capacity (FVC) in a one-year study in this patient population. However, the Agency also acknowledged that a longer study may be challenging in this rare disease. The Agency noted that it may be difficult to determine if a small improvement in FVC is meaningful without supportive efficacy endpoints that more directly measure how patients function and feel. Therefore, the Applicant was advised to continue to follow the patients to the conclusion of the study. In addition, the Applicant was advised to include all-cause mortality as an endpoint, and to include secondary endpoints that measure how patients feel and function. The Agency also advised the use of observed FVC rather than FVC % predicted. Whether a single well controlled study would be sufficient to provide substantial evidence of safety and efficacy of nintedanib in SSc-ILD to meet the regulatory standard would depend on the persuasiveness of the treatment effect.

On September 30, 2015, IND 124707 was considered safe to proceed.

On July 6, 2016, nintedanib was granted orphan designation for the treatment of systemic sclerosis (including the associated interstitial lung disease). On March 7, 2018, nintedanib was granted fast track designation for SSc-ILD.

On June 21, 2018 in pre-supplemental NDA (sNDA) written responses, the Agency acknowledged difficulties with enrollment in the terminated drug drug interaction study (DDI) in patients with non-small cell lung cancer and agreed that the proposed sNDA could be submitted in the absence of a nintedanib/hormonal contraceptive DDI study. The Agency recommended the Sponsor evaluate the DDI in a dedicated study in the SSc-ILD population as part of an ongoing or future study.

The Applicant submitted supplement 12 for the treatment of SSc-ILD on March 7, 2019.

On March 27, 2019, the Applicant's request for breakthrough designation was denied because the clinical meaningfulness of the modest observed treatment difference in the primary endpoint, the adjusted annual rate of decline in FVC over 52 weeks, between nintedanib and placebo, without observed benefit in the key secondary and other secondary endpoints, was not clear. In addition, the clinical evidence did not indicate a substantial improvement with nintedanib over available therapies/standard of care.

On July 25, 2019, an Arthritis Advisory Committee meeting was held to discuss the benefit/risk of nintedanib for systemic sclerosis associated interstitial lung disease (SSc-ILD). Please see discussion in Section 8.4.2.

On August 14, 2019, the Division discussed the considerations and proposed regulatory action for nintedanib NDA 205832/s012 with the Medical Policy and Program Review Council (MPPRC). The discussion focused on the following questions:

1. Does the Committee agree with the Division's plan to:
    a. Approved nintedanib for the treatment of SSc-ILD based on the available data?
    b. Not to require additional studies, i.e. confirmatory post-marketing clinical studies?
2. Does the Committee have other recommendations?

The Council acknowledged that there were some limitations to this study. The treatment effect was small, clinical benefit endpoints were not positive, and long-term data (FVC data up to 100 weeks) were available and exploratory analyses showed mixed results. It was not clear whether the benefits would accrue over the long-term. Additionally, data from secondary endpoints, and from specific subgroups (those on mycophenolate and US/Canada population), was not robust. However, the Council considered that the primary endpoint was convincing – and considered that given the rarity of the disease – and the low likelihood of acquiring further data, that an approval decision was reasonable. The Council did request further information from the second year data – to see if there was at least stable improvement or further benefit. The Council suggested a consideration of an indication to more accurately reflect the data, rather than the originally-proposed indication of "treatment of SSc-ILD". Additionally, it was pointed out that if extrapolated from the IPF program, reliability of FVC as an endpoint in fibrotic lung disease can be used as confirmatory evidence. There was a brief discussion on using FVC as a reasonably likely surrogate for accelerated approval. However, given the challenges of obtaining further data – and the robustness of FVC as an endpoint for traditional approval, the Council generally supported the Division's proposed action. Since the effect was less robust in the subgroup on mycophenolate, it was also recommended to clearly label the effect on people on immunosuppressive therapy vs those not on immunosuppressive therapy.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Division of Clinical Compliance Investigations from the Office of Scientific Investigations (OSI) was consulted to conduct clinical site inspections of two facilities:

- Petros Sfikakis, M.D. (Site #30001, Athens, Greece)
- Kristin Highland, M.D. (Site #10011, Cleveland, OH)

The two clinical sites were selected using risk ranking from the clinical site selection tool for the phase 3 studies based on high enrollment, better efficacy results for study drug, high discontinuation rate, and the number of adverse events and deaths reported at those sites.

Upon completion of study site inspections, OSI Investigations concluded the following: the two inspected sites are considered reliable and the studies in support of this application appear to have been conducted adequately.

The reader is directed to the review by OSI's Medical Officer, Min Lu, MD, MPH for detailed information regarding the clinical site inspections.

4.2. Product Quality

No new product quality information was submitted or required for this submission.

4.3. Clinical Microbiology

No new clinical microbiology information was submitted or required for this submission.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

This supplement contained no pivotal nonclinical data. All pivotal nonclinical data in support of the approval of OFEV capsules had been previously submitted and reviewed in the original NDA application.

This supplement did contain several reports of pharmacology studies and published scientific papers in support of the proposed changes in Section 12.1 Mechanism of Action of the OFEV label. A detailed review of the available data was completed. The review concluded that only portions of the proposed changes are warranted. Edits to the proposed changes in Section 12.1 of the OFEV label were recommended. See the end of this section for a brief summary of the nonclinical labeling issue.

The following summary of nonclinical data of nintedanib is based on the approved OFEV label and the current review. Nintedanib is a small molecule tyrosine kinase inhibitor (TKI). Tyrosine kinases include many families of receptor kinases (RTK) and non-receptor kinases (nRTKs). Nintedanib inhibits both RTK and nRTKs. Kinases of fibroblast growth factor receptors (FGFR) and Lck are examples of RTK and nRTK targets of nintedanib, respectively. The inhibition of RTK have been implicated in pathogenesis of interstitial lung disease (ILD) while the contribution of nRTKs inhibition to nintedanib efficacy is unknown. The proposed changes in nintedanib targets is of interest of this review as discussed at the end of this section.

The general toxicity of nintedanib was studied in multiple nonclinical species with treatment durations up to 3, 6, and 12 months in mice, rats, and monkeys, respectively. These studies revealed that the target organs of nintedanib toxicity include the bones (mice, rats, and monkeys), liver (mice and rats), kidney (rats), ovaries (mice and rats), and the immune system (mice, rats, and monkeys). The affected organs in the immune system included adrenal glands, bone marrow, spleen, and thymus. Nintedanib is non-genotoxic and non-carcinogenic. Nintedanib is a potent teratogen and reproductive toxicant.

The key discussions about the proposed changes to Section 12.1 of the OFEV label in the current submission is to (b) (4) (b) (4) (b) (4). This action should be supported by data and sound scientific justifications.

As alluded to earlier in this section, nintedanib inhibits a number of RTK and nRTKs. Nintedanib inhibits the following RTKs: platelet-derived growth factor receptor (PDGFR) α and β, FGFR 1-3, vascular endothelial growth factor receptor (VEGFR) 1-3, colony stimulating factor 1 receptor (CSF1R), and Fms-like tyrosine kinase-3 (FLT3). Nintedanib inhibits the following nRTKs: Lck, Lyn,

and Src kinases. The inhibition of RTKs have generally been implicated in pathogenesis of ILD while the contribution of nRTKs inhibition to nintedanib efficacy is unknown. The nRTK inhibition is considered off-target effect of nintedanib. Off-target effects are generally related to the side effects of drugs. A lack of off-target effects of a drug usually suggests a better safety profile.

The submission did not contain any relevant and sufficient nonclinical data or provide sufficient scientific rationale to support the proposed [redacted] (b) (4). The nonclinical review team recommends [redacted] (b) (4) [redacted] (b) (4). The Applicant has accepted the nonclinical review team's recommendation.

6 Clinical Pharmacology

6.1. Executive Summary

Boehringer Ingelheim (Applicant) has submitted the Supplement 12 to NDA 205832 (Ofev; nintedanib capsule) seeking approval for the addition of a new indication to treat systemic sclerosis associated interstitial lung disease (SSc-ILD). Nintedanib is approved for the treatment of idiopathic pulmonary fibrosis (IPF) via the original NDA 205832.

Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology data for NDA 205832 Supplement 12 and finds the data acceptable.

Postmarketing Requirement (PMR)

The Applicant needs to conduct a study titled "A drug-drug interaction trial to assess the pharmacokinetics, safety, and tolerability for the co-administration of a combined oral contraceptive (containing ethinyl estradiol and levonorgestrel) with Ofev 150 mg twice daily."

Based on findings from animal studies and its mechanism of action, Ofev may cause fetal harm when administered to a pregnant woman. There are no data on the use of Ofev during pregnancy. In animal studies of pregnant rats and rabbits treated during organogenesis, nintedanib caused embryo-fetal deaths and structural abnormalities at less than (rats) and about 5 times (rabbits) the maximum recommended human dose (300 mg nintedanib daily). This PMR trial will assess the pharmacokinetic effect of nintedanib on oral contraceptives such as ethinyl estradiol and levonorgestrel. This PMR trial's results will provide data to support the efficacy and safety of oral contraceptives when coadministered with nintedanib for female patients with SSc-ILD of child-bearing potential.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Nintedanib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs). Nintedanib inhibits the following RTKs: platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, vascular endothelial growth factor receptor (VEGFR) 1-3, and Fms-like tyrosine kinase-3 (FLT3). Among them, FGFR, PDGFR, and VEGFR have been implicated in IPF pathogenesis.

Nintedanib shows similar pharmacokinetic properties in healthy volunteers, patients with SSc-ILD, patients with IPF, and patients with cancer. Maximum plasma nintedanib concentrations are reached about 2 – 4 hours upon oral administration and thereafter decline at least bi-exponentially. Nintedanib exposure increases dose-proportionally over the dose range of 50 – 450 mg once daily and 150 – 300 mg twice daily. Nintedanib is metabolized via hydrolytic ester cleavage, resulting in the formation of the free acid moiety (BIBF 1202) that is subsequently glucuronidated (BIBF 1202 glucuronide) and excreted in the faeces. Less than 1% of drug-related radioactivity is eliminated in urine. The effective half-life of nintedanib in patients with IPF is 9.5 hours. Accumulation upon multiple administrations in patients with IPF is 1.76-fold for AUC. Steady-state plasma nintedanib concentrations are achieved within a week of dosing. Sex and renal function have no influence on nintedanib pharmacokinetics, whereas age and body weight are correlated with nintedanib exposure but no dose adjustments are necessary. Administration of nintedanib in patients with moderate or severe hepatic impairment is not recommended, and patients with mild hepatic impairment should be monitored closely and the dose adjusted accordingly. Nintedanib has a low potential for drug–drug interactions with drugs metabolized via the cytochrome P450 enzymes (CYP). Concomitant treatment with potent inhibitors or inducers of the P-glycoprotein transporter can affect nintedanib pharmacokinetics.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dosage of nintedanib is 150 mg twice daily administered with food approximately 12 hours apart for the treatment of IPF.

Therapeutic Individualization

In patients with mild hepatic impairment (Child Pugh A), the recommended dosage is 100 mg nintedanib twice daily about 12 hours apart taken with food.

In addition to symptomatic treatment, if applicable, the management of adverse reactions of nintedanib may require dose reduction or temporary interruption until the specific adverse reaction resolves to situations that allow continuation of therapy. Nintedanib treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice

daily), which subsequently may be increased to the full dosage. If a patient does not tolerate the 100 mg twice daily, discontinue treatment with nintedanib.

Outstanding Issues

Post marketing requirement as above.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

6.3.1.1 What is the Clinical pharmacology program that supports NDA 205832 Supplement 12?

The pharmacokinetics of nintedanib was assessed in patients with SSc-ILD (Trial 1199.214). In addition, the Applicant conducted the following 2 clinical drug interaction trials:

- Trial 1199.239: Influence of bosentan on the pharmacokinetics of nintedanib in healthy male subjects
- Trial 1199.238: Influence of nintedanib on the pharmacokinetics of the oral contraceptive Microgynon in patients with NSCLC

Drug-drug Interaction (DDI) with oral contraceptives

The Applicant stopped Trial 1199.238 prematurely because of poor recruitment with only 2 patients treated. Due to the very low number of valid observations, the Applicant cannot draw pharmacokinetic conclusions from Trial 1199.238. On Jun 3, 2019, the Applicant submitted a protocol 1199-0340 proposing a DDI study with ethinylestradiol and levonorgestrel in female patients with SSc-ILD.

Due to the strong teratogenic potential of nintedanib, and a significant portion of women of child-bearing potential in patients with SSc-ILD, a PMR for DDI study with oral contraceptives is issued.

DDI with bosentan

Briefly, Trial 1199.239 is an open-label trial in healthy men received a fixed sequence, 2-treatment, 2-period crossover design. Each man participated in 2 trial periods (Visit 2, Days -1 to 4, and Visit 3, Days 1 to 10). Period 1 (Reference treatment) consisted of receiving a single dose of 150 mg nintedanib on Day 1. Period 2 (Test treatment) consisted of receiving 125 mg bosentan twice daily on Days 1 to 8 and a single dose of 150 mg nintedanib on Day 7. No extra washout period between the trial periods existed because the 4 days of treatment Period 1 should be sufficient (terminal elimination half-life of nintedanib is 10 – 15 hours; Wind et al. *Clin Pharmacokinet* PMID: 31016670).

The Applicant collected serial blood samples up to 72 hours after the nintedanib dose and used validated bioanalytical assays to measure plasma nintedanib, its 2 metabolites (BIBF 1202 and BIBF 1202 glucuronide) concentrations. The Applicant also collected trough blood samples to measure plasma bosentan concentrations on Days 5, 6, and 7 via validated bioanalytical assays.

Table 1 shows the effect of bosentan on nintedanib pharmacokinetics. The trough plasma bosentan concentrations show that bosentan reached steady state by Day 5.

Table 1. Effect of multiple doses of bosentan on the pharmacokinetics of nintedanib

	Reference treatment Nintedanib 150 mg administered alone		**Test treatment Nintedanib 150 mg coadministered with multiple doses of bosentan 125 mg twice daily**		**Adjusted gMean ratio T/R** [%]	**90% confidence interval** [%]		**Intra-individ. gCV** [%]
	N	Adjusted gMean	N	Adjusted gMean		Lower limit	Upper limit	
AUC_{0-tz} [ng·h/mL]	13	194.858	13	192.624	98.85	91.320	107.010	11.4
C_{max} [ng/mL]	13	21.946	13	22.683	103.36	86.134	124.025	26.5
$AUC_{0-\infty}$ [ng·h/mL]	13	204.306	13	208.344	101.98	94.909	109.570	10.3

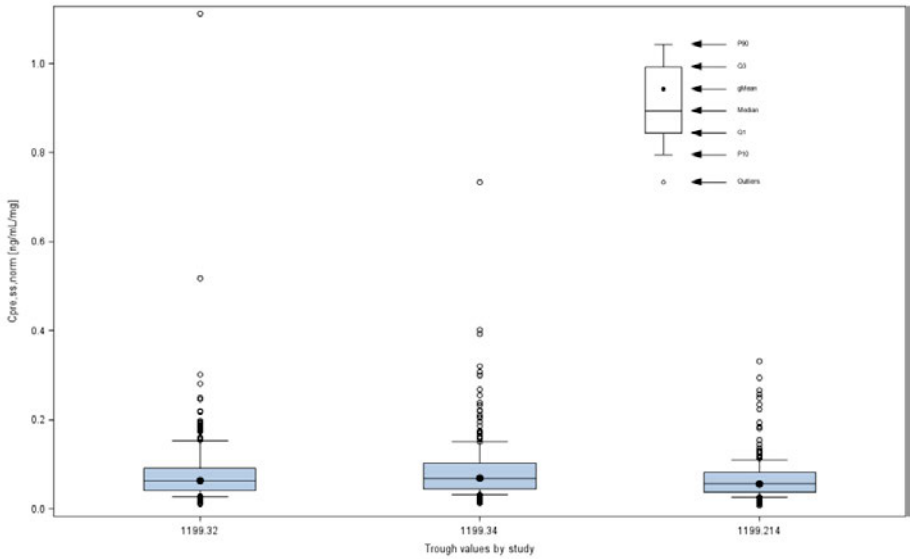
Source: Table 11.2.2.3:1 of Trial 1199.239's report

The pharmacokinetic results of BIBF 1202 and BIBF 1202 glucuronide are consistent with those of nintedanib on the coadministration with bosentan. The multiple-dose administration of bosentan does not affect the pharmacokinetics of a single dose of nintedanib.

Pharmacokinetics of nintedanib in patients with SSc-ILD

The Applicant conducted an efficacy and safety trial (1199.214) for nintedanib to treat patients with SSc-ILD. The Applicant measured trough plasma nintedanib concentrations for Trial 1199.214 and compared with those values of patients with IPF (Trials 1199.32 and 1199.34). Figure 1 shows that the dose-normalized steady state trough plasma nintedanib concentrations after multiple twice daily oral administration to patients with SSc-ILD were in a similar range to those observed in patients with IPF suggesting similar pharmacokinetics of nintedanib in both patient populations. Consistently, covariate effects for race, age, weight, and gender were similar in patients with SSc-ILD to those previous population pharmacokinetic analyses of patients with IPF.

Figure 1. Box-plot comparing dose-normalized steady state trough plasma nintedanib concentrations (Cpre,ss,norm) between patients with SSc-ILD and patients with IPF



Source: Figure 3.2:1 of Section 2.7.2 of the Applicant's submission

6.3.1.2 What are the validation of bioanalytical methods used to measure nintedanib, BIBF 1202, and BIBF 1202 glucuronide in plasma samples as well as that for bosentan?

The Applicant used a liquid chromatography with tandem mass spectrometry (LC/MS/MS) assay to simultaneously determine the nintedanib, BIBF 1202 and BIBF 1202 glucuronide concentrations in plasma samples. Table 2 and Table 3 detail the validation of the bioanalytical assays for nintedanib, BIBF 1202 and BIBF 1202 glucuronide for Studies 1199.239 and 1199.214. The Applicant used another LC/MS/MS assay to determine the bosentan concentrations in plasma samples. Table 2 also details the validation of the bioanalytical assay of bosentan Study 1199.239.

Bioanalytical validations for Study 1199.239

Table 2. Validation of the bioanalytical assay to measure nintedanib, BIBF 1202, BIBF 1202 glucuronide, and bosentan for Study 1199.239

	Nintedanib		BIBF 1202 ZW	BIBF1202 GLUC		Bosentan
Range, ng/mL	0.05 – 50	Range, ng/mL	0.1 – 100	0.1 – 100	Range, ng/mL	0.4 – 1600
LLOQ, ng/mL	0.05	LLOQ, ng/mL	0.1	0.1	LLOQ, ng/mL	0.4
Mean r^2 of linear standard curve	0.99960	Mean r^2 of linear standard curve	0.99957	0.99957	Mean r^2 of linear standard curve	0.99872

Accuracy (bias %) QC 0.05 ng/mL	-1.2	Accuracy (bias %) QC 0.1 ng/mL	-2.5	-4.5	Accuracy (bias %) QC 1.2 ng/mL	0.8
Precision (CV%) QC 0.05 ng/mL	3.8	Precision (CV%) QC 0.1 ng/mL	2.0	3.8	Precision (CV%) QC 1.2 ng/mL	6.7
Accuracy (bias %) QC 0.15 ng/mL	-4.0	Accuracy (bias %) QC 0.3 ng/mL	-3.5	-2.9	Accuracy (bias %) QC 40 ng/mL	-4.6
Precision (CV%) QC 0.15 ng/mL	5.3	Precision (CV%) QC 0.3 ng/mL	3.8	5.9	Precision (CV%) QC 40 ng/mL	3.7
Accuracy (bias %) QC 5 ng/mL	-4.5	Accuracy (bias %) QC 10 ng/mL	-3.9	-3.1	Accuracy (bias %) QC 1200 ng/mL	-3.2
Precision (CV%) QC 5 ng/mL	2.7	Precision (CV%) QC 10 ng/mL	3.1	3.7	Precision (CV%) QC 1200 ng/mL	2.7
Accuracy (bias %) QC 40 ng/mL	-4.7	Accuracy (bias %) QC 80 ng/mL	-6.1	-5.0		
Precision (CV%) QC 40 ng/mL	1.9	Precision (CV%) QC 80 ng/mL	2.1	2.5		

Volume of each plasma sample is 50 µL. The anticoagulant is KEDTA.
Source: Reviewer's compilation of BI Trial No.: 1199.239 16.1.9.4 Analytical reports c09412738-01 Pages 118 and 265 of 293

Validations for the bioanalytical assays of nintedanib, BIBF 1202, BIBF 1202 glucuronide, and bosentan appear acceptable with reasonable precision and accuracy for Study 1199.239.

Bioanalytical validations for Study 1199.214

Table 3. Validation of the bioanalytical assay to measure nintedanib, BIBF 1202, and BIBF 1202 glucuronide for Study 1199.214

	Nintedanib		BIBF 1202 ZW	BIBF1202 GLUC
Range, ng/mL	0.5 - 500	Range, ng/mL	1 - 1000	1 - 1000
LLOQ, ng/mL	0.5	LLOQ, ng/mL	1	1
Mean r^2 of linear standard curve	0.99873	Mean r^2 of linear standard curve	0.99862	0.99817
Accuracy (bias %) QC 1.25 ng/mL	-0.8	Accuracy (bias %) QC 2.5 ng/mL	-3.3	2.0
Precision (CV%) QC 1.25 ng/mL	83	Precision (CV%) QC 2.5 ng/mL	7.4	9.6
Accuracy (bias %) QC 25 ng/mL	0.6	Accuracy (bias %) QC 50 ng/mL	2.4	1.0

Precision (CV%) QC 25 ng/mL	4.7	Precision (CV%) QC 50 ng/mL	4.8	6.3
Accuracy (bias %) QC 400 ng/mL	-0.3	Accuracy (bias %) QC 800 ng/mL	-2.7	-0.8
Precision (CV%) QC 400 ng/mL	-5.4	Precision (CV%) QC 800 ng/mL	5.4	6.0

Volume of each plasma sample is 50 µL. The anticoagulant is KEDTA.

Source: Reviewer's compilation of BI Trial No.: 1199.214 16.1.13.4 Analytical reports c22686034-01 Page 167860 of 168520

Validations for the bioanalytical assay of nintedanib, BIBF 1202, and BIBF 1202 glucuronide appear acceptable with reasonable precision and accuracy for Study 1199.214.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The clinical development program of nintedanib for the treatment of SSc-ILD includes a single pivotal Phase 3 clinical study (1199.214). The proposed nintedanib dosing regimen for the treatment of SSc-ILD is the same as that for the treatment of IPF. No dose-ranging study was conducted for nintedanib to treat SSc-ILD.

For the review of the efficacy and safety of nintedanib to treat SSc-ILD (Study 1199.214), see Section 8 of this review.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, see Section 8 of this review.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The following dose adjustment is recommended by the current nintedanib label. There are no new dedicated studies for specific populations in this submission.

In patients with mild hepatic impairment (Child Pugh A), the recommended dosage of Ofev is 100 mg twice daily about 12 hours apart taken with food.

The management of adverse reactions of Ofev may require dose reduction or temporary interruption until the specific adverse reaction resolves to conditions that allow continuation of therapy. Ofev treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If a patient does not tolerate 100 mg twice daily, discontinue treatment with Ofev.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

As per the current label of nintedanib, nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4. Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, ketoconazole, increased the nintedanib exposure by 60%. Concomitant use of P-gp and CYP3A4 inhibitors (erythromycin) with Ofev may increase the nintedanib exposure. In such cases, patients should be monitored closely for tolerability of Ofev. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with Ofev.

Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased nintedanib exposure by 50%. Concomitant use of P-gp and CYP3A4 inducers (carbamazepine, phenytoin, and St. John's wort) with Ofev should be avoided because these drugs may decrease the nintedanib exposure.

This submission includes a dedicated DDI study (1199.239) for the concomitant administration of nintedanib with bosentan in healthy volunteers. Coadministration of nintedanib with bosentan did not alter the pharmacokinetics of nintedanib (see section 6.3.1), and no dose adjustment is recommended.

Question on clinically relevant specifications?

Not applicable.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 4. Key Design Elements of Study 1199.214

Study No.	Description	Subjects	Design	Treatment	Duration	Endpoints
1199.214	Phase 3 efficacy and safety	576 patients with SSc-ILD	R, DB, PC, PG	Nintedanib 150 mg BID, dose reduction to 100 mg BID PBO	52 weeks	- change in FVC (mL) - change in mRSS - change in SGRQ

Abbreviations: R: randomized; DB: double blind; PC: placebo controlled; PG: parallel group; BID: twice daily; PBO: placebo; FVC: forced vital capacity; SGRQ: St. George's Respiratory Questionnaire; mRSS: modified Rodnan skin score.

7.2. Review Strategy

The clinical data reviewed in this document are derived from a single study conducted in SSc-ILD, Study 1199.214. Efficacy and safety data were derived from the first 52 weeks of treatment. Individual patients remained on blinded study treatment up to 100 weeks, until the last patient completed 52 weeks of treatment, providing additional supportive data. The analysis sets and analysis periods are discussed under Statistical Analysis Plan below.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

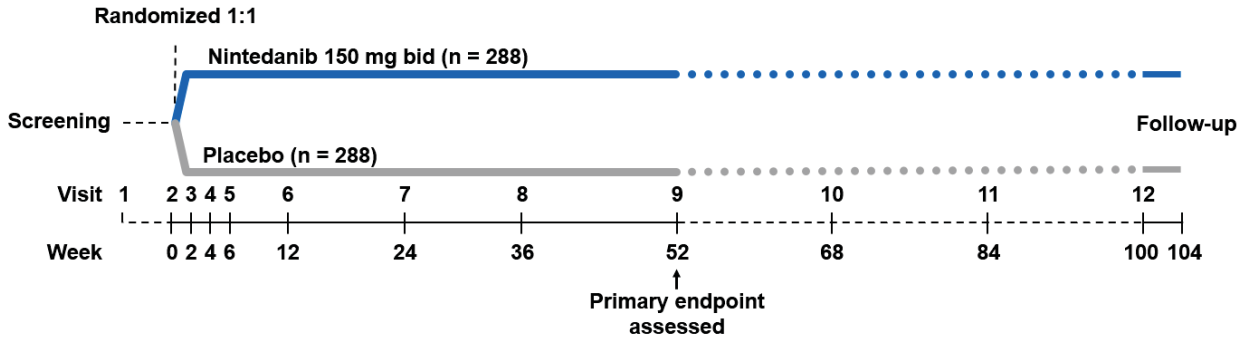
8.1.1. Study 1199.214

Study Design

Study Dates: November 30, 2015 to November 28, 2018
Study Sites: 194 sites (with screened patients) in 32 countries in Asia, Australia, Europe, North America, and South America

The nintedanib clinical development program for SSc-ILD consisted of a single, phase 3 study, 1199.214, which was a double blind, randomized, placebo-controlled, parallel group design to evaluate the efficacy and safety of oral nintedanib in patients with SSc-ILD. In Study 1199.214, 576 patients were randomized 1:1 to nintedanib 150 mg by mouth twice daily or matching placebo; randomization was stratified by antitopoisomerase (ATA) antibody status (positive or negative). The study design is presented in Figure 2. The primary endpoint was the annual rate of decline in FVC in mL over 52 weeks.

Figure 2. Study 1199.214 Design

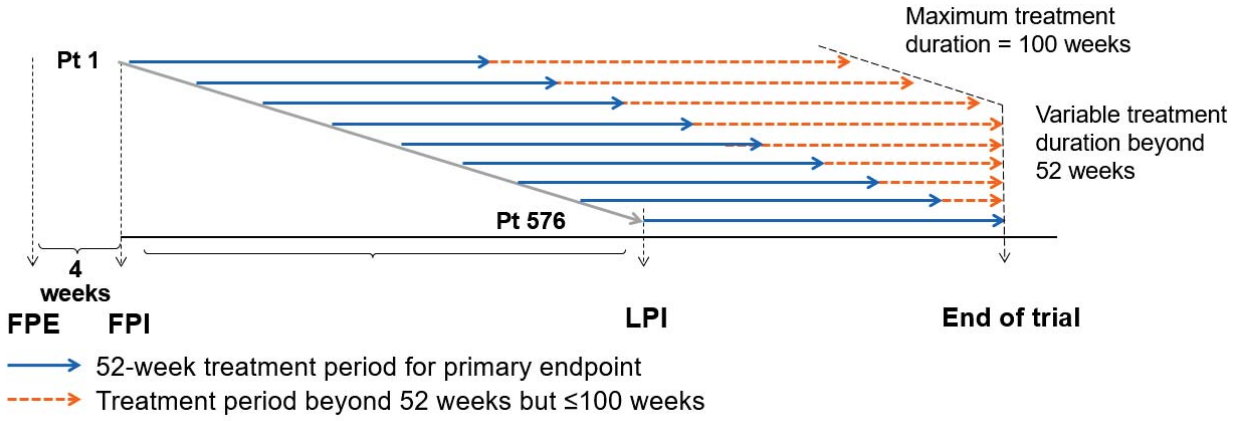


n = number of treated patients
The planned treatment duration was at least 52 weeks, up to 100 weeks.
Source: The Applicant, Advisory Committee Briefing Materials

The main efficacy analysis was assessed at Week 52, but patients could remain on treatment up to a maximum of 100 weeks to collect follow-up safety and efficacy information (Figure 3). Patients were evaluated for safety assessments at Weeks 2, 4, 6, 12, 24, 36, 52, 68, 84, and 100. A follow-up visit was scheduled 28 days after the End of Treatment Visit. Patients who experienced clinically significant deterioration of SSc could receive rescue therapy. Patients who permanently discontinued study medication were asked to return for future visits as planned; patients who declined further follow-up visits were asked for vital status assessment at 52 weeks and 100 weeks after their randomization, or at the time the last full visit would

have been scheduled, whichever occurred earlier. The schedule of assessments is summarized in Section 15.5.

Figure 3. Variable Treatment Duration in Study 1199.214



FPE = first patient enrolled; FPI = first patient in; LPI = last patient in; Pt = patient
Source: The Applicant, Advisory Committee Briefing Materials

In the event of adverse events (AEs) or liver enzyme elevations, dose reduction from 150 mg BID to 100 mg BID was to be considered (Section 15.5.1). For AEs considered drug-related, treatment could be interrupted for up to 4 weeks; resumption of study drug at 100 mg BID was recommended with re-escalation within 4 weeks to 150 mg BID. If AEs were not considered drug-related, treatment could be interrupted for up to 8 weeks; resumption of the same dose of study drug was recommended. If AEs persisted at the lower dose, or if they were severe while on 150 mg BID, treatment discontinuation was to be considered. For elevated liver enzymes without signs of hepatic injury, dose reduction or interruption (AST or ALT increase to ≥3x to <5x ULN) and dose interruption (AST or ALT increase to ≥5x to <8x ULN) was recommended. If repeat liver enzymes were ≥3x ULN, permanent discontinuation was recommended.

Study Population

The study was conducted in adult patients 18 years of age or older with SSc of less than 7 years duration from first non-Raynaud symptom, with confirmed SSc-ILD based on HRCT.

Key Inclusion Criteria

1. Patient ≥18 years at time of informed consent
2. Patients had to have fulfilled the 2013 ACR/EULAR classification criteria for SSc
3. SSc disease onset (defined by first non-Raynaud symptom) within 7 years of Visit 1
4. SSc-related ILD pattern confirmed by HRCT performed within 12 months of Visit 1. The extent of fibrotic disease in the lung had to be ≥10% on HRCT, assessed by central review
5. FVC ≥40% of predicted normal at Visit 2
6. DLco (corrected for hemoglobin [Visit 1]): 30% to 89% of predicted at Visit 2

Key Exclusion Criteria

1. AST, ALT, Bilirubin >1.5 times upper limit of normal (ULN)
2. Creatinine clearance <30 mL/min
3. Airway obstruction (pre-bronchodilator FEV1/FVC <0.7) at Visit 2
4. In the opinion of the investigator, other clinically significant pulmonary abnormalities
5. Significant pulmonary hypertension (PH) defined by any of the following:
    - Previous clinical or echocardiographic evidence of significant right heart failure
    - History of right heart catheterization showing a cardiac index ≤2 L/min/m2
    - PH requiring parenteral therapy with epoprostenol/treprostinil
6. Cardiovascular diseases, including:
    - Severe hypertension, uncontrolled under treatment (≥160/100 mmHg) within 6 months of Visit 1
    - Myocardial infarction within 6 months of Visit 1
    - Unstable cardiac angina within 6 months of Visit 1
7. More than 3 digital fingertip ulcers at Visit 2 or a history of severe digital necrosis requiring hospitalization or severe other ulcers at discretion of investigator
8. Bleeding risks, including:
    - Known genetic predisposition to bleeding
    - Patients who require
        - Fibrinolysis, full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, direct thrombin inhibitors, heparin, hirudin)
        - High dose antiplatelet therapy. Prophylactic low dose heparin or prophylactic use of antiplatelet therapy (e.g. acetyl salicylic acid up to 325 mg/day, or clopidogrel at 75 mg/day, or equivalent doses of other antiplatelet therapy) are not prohibited.
    - History of hemorrhagic central nervous system (CNS) event within 12 months of Visit 1
    - Any of the following within 3 months of Visit 1:
        - Hemoptysis or hematuria
        - Active gastro-intestinal (GI) bleeding or GI ulcers
        - Major injury or surgery (investigators judgment)
    - Coagulation parameters: International normalized ratio (INR) >2x ULN, prolongation of prothrombin time (PT) and partial thromboplastin time (PTT) by >1.5 x ULN at Visit 1
9. History of thrombotic event (including stroke and transient ischemic attack) within 12 months of Visit 1
10. Known hypersensitivity to study medication or its components
11. Other disease or condition that may interfere with testing procedures or in the judgment of the investigator could have interfered with study participation or put patient at risk from participation
12. Life expectancy of <2.5 years for disease other than SSc in investigator assessment
13. Patients with clinical signs of malabsorption or needing parenteral nutrition
14. Previous treatment with nintedanib or pirfenidone
15. Other investigational therapy received within 1 month or 6 half-lives (whichever was greater) before Screening Visit (Visit 1)

16. Treatment with:
    - Prednisone >10 mg/d or equivalent received within 2 weeks before Visit 2
    - Azathioprine, hydroxychloroquine, colchicine, D-penicillamine, sulfasalazine, received within 8 weeks before Visit 2
    - Cyclophosphamide, rituximab, tocilizumab, abatacept, leflunomide, tacrolimus, newer anti-arthritic treatments like tofacitinib and cyclosporine A, potassium para-aminobenzoate, received within 6 months before Visit 2
17. Unstable background therapy with either mycophenolate mofetil/sodium or methotrexate (combined therapy was not allowed). Patients had to be either:
    - Not on mycophenolate mofetil/sodium or methotrexate within at least 8 weeks before Visit 2, or
    - On stable therapy with either mycophenolate mofetil/sodium or methotrexate for 6 months before Visit 2 and were to remain stable on this background therapy for at least 6 months after randomization
18. Previous hematopoietic stem cell transplantation (HSCT), or HSCT planned within the next year
19. Major surgical procedures planned to occur during study period
20. Women who were pregnant, nursing, or who planned to become pregnant while in the study
21. Women of childbearing potential not willing or able to use highly effective birth control methods for 28 days before and 3 months after nintedanib administration
22. Active alcohol or drug abuse, in the opinion of the investigator
23. Patients with underlying chronic liver disease (Child Pugh A, B, C hepatic impairment)
24. Patients with a history of scleroderma renal crisis

Study Treatments

During the 52-week treatment period the treatment arms were as follows:

- Nintedanib 150 mg soft gelatin capsule by mouth twice per day (BID)
- Control product: matching placebo

Concomitant Medications

Continuation of stable doses of mycophenolate mofetil or methotrexate was permitted in the study. Corticosteroid doses ≤ 10 mg/day prednisone or equivalent were allowed if the dose was stable for at least 8 weeks prior to Visit 2. Other permitted immunosuppression was allowed in the event of clinical deterioration (see Rescue Therapy). Use of pirfenidone or nintedanib (outside of the study) was not permitted throughout the study. Treatment with full dose therapeutic anticoagulation and high-dose antiplatelet therapy during the treatment period was not permitted. Close monitoring was advised with concomitant use of P-gp and CYP3A4 inhibitors that may increase exposure to nintedanib.

Rescue Therapy

Patients who experienced clinically significant deterioration of SSc could receive additional treatment. A clinically significant deterioration was defined as:

- Absolute decline in FVC percent predicted > 10% compared to baseline
- A relative change from baseline in mRSS of >25% and absolute change from baseline >5 points, or
- Clinically significant deterioration in other organ systems or clinical parameters at the discretion of the investigator

Other causes for FVC decline were to be excluded. Permitted medications for management of deterioration include prednisone > 10 mg/day, azathioprine, cyclophosphamide, cyclosporine A, hydroxychloroquine, colchicine, D-penicillamine, sulfasalazine, rituximab, tocilizumab, abatacept, leflunomide, tacrolimus, tofacitinib, and potassium para-aminobenzoate.

Study Endpoints

Primary Endpoint:

• Annual rate of decline in FVC in mL over 52 weeks

Key Secondary Endpoints:

• Absolute change from baseline in the mRSS at Week 52
• Absolute change from baseline in SGRQ total score at Week 52

Other Secondary endpoints:

• Annual rate of decline in FVC in percent predicted over 52 weeks
• Absolute change from baseline in FVC in mL at Week 52
• Relative change from baseline (%) of mRSS at Week 52
• Time to all-cause mortality
• Absolute change from baseline at Week 52 in CRISS index score
• Absolute change from baseline in DL_{CO} in percent predicted at Week 52
• Absolute change from baseline in digital ulcer net burden at Week 52
• Absolute change from baseline in HAQ-DI score at Week 52.
• Absolute change from baseline in FACIT dyspnea score at Week 52

Further endpoints:

• Proportion of patients with a relative decline from baseline in FVC in mL at Week 52 of >5%
• Proportion of patients with a relative decline from baseline in FVC in mL at Week 52 of >10%
• Proportion of patients with an absolute decline from baseline in FVC in percent predicted at Week 52 of >5%
• Proportion of patients with an absolute decline from baseline in FVC in percent predicted at Week 52 of >10%
• Absolute change from baseline in SHAQ domain scores at Week 52

Statistical Analysis Plan

Analysis Sets

The following analysis sets were defined in the Statistical Analysis Plan (SAP):

- Randomized set (RS): This set included all randomized patients, whether treated or not.

- Treated set (TS): This set included all randomized patients who received at least one dose of study medication. This set was used for all analyses of efficacy and safety endpoints.

Analysis Definitions for Periods

The SAP defined the following periods while not necessarily all of them existed for every patient. The last day of each of the following periods was excluded from the respective period. It defined the first day of the subsequent period.

- Screening: from informed consent to randomization
- Post-randomization: from randomization to first study drug intake in treatment period
- Treatment period: from first study drug intake (or re-start of treatment if interruption) to last study drug intake (or the day before start date of interruption if interruption) plus one day
- Off-treatment: from start date of interruption to re-start of treatment
- Residual effect period: from the last study drug intake plus one day to last study drug intake plus 28 days plus one day or to date of first study drug intake in extension study, whichever occurred earlier
- Follow-up: from last study drug intake plus 29 days up to the beginning of post-study period. This period was only created if last study drug intake took place more than 28 days before study completion, or for patients having prematurely discontinued the treatment and still continuing the study
- Post-study: from the latest between last study drug intake plus 29 days, 'date of study completion' (from the study completion part of the eCRF) plus one day, and 'date of Informed Consent in extension study' (if applicable). This period was not created if date of first study drug intake in extension study was before last study drug intake plus 28 days

For Safety Data:

- For safety analyses, data from the treatment period, possible off-treatment periods and residual effect period were considered as on-treatment.

For Efficacy Data:

- For efficacy analyses, data from randomization date up to week 52 were considered.
- For efficacy descriptive analyses over the whole study period, all data collected after randomization date were considered.

Estimands

While no estimand was referenced or defined throughout the protocol or SAP, the overall approach of the primary analysis of the primary efficacy endpoint and the supporting sensitivity analyses implicitly targeted the de facto or treatment policy estimand as mentioned later in the study report.

Primary Efficacy Endpoint

Primary Analysis: The annual rate of decline in FVC in mL over the 52-week treatment period (with measurements at Week 2, 6, 12, 24, 36 and 52) was compared between the two treatment groups with a restricted maximum likelihood-based approach using a random coefficient regression model. This model included the fixed categorical effects of treatment group, ATA status, and gender, fixed continuous effects of time, baseline FVC (mL), age and height as well as the interaction terms treatment group-by-time and baseline-by-time.

An unstructured variance-covariance structure was used to model the random slope and intercept. The Kenward-Roger approximation was used to estimate denominator degrees of freedom and adjust standard errors. Least squares (LS) means of slope for each treatment group and mean treatment group difference, standard error (SE), 95% confidence intervals (CIs) and the p-value for the treatment group effect were to be presented. The primary treatment comparison of slopes was assessed through the treatment-by-time interaction coefficient. The primary analysis was performed on the TS (according to randomized treatment), using all available data from baseline (excluded) up to Week 52 (after time-windowing), including visits done after premature treatment withdrawal, EOT visits and follow-up visits done before Week 52.

Multiple sensitivity analyses were performed for the primary endpoint, including:

- Sensitivity analyses to investigate the potential effect of missing data assumption on the results of the primary analysis:
    1. On-treatment Analysis
    2. Pattern Mixture Model (PMM) Approaches
    3. Tipping Point Analyses (Added during FDA Review of the sNDA)
- Sensitivity analyses to investigate the patient level linear decline in FVC model assumption on the results of the primary analysis.

Sensitivity Analysis for Missing Data Handling 1 (On-treatment Analysis):

This analysis was the same as the primary analysis for the primary efficacy endpoint, except that only on-treatment measurement of FVC (mL) were used. This approach implicitly assumes data were missing at random (MAR) and that patients who discontinued treatment would have behaved similarly to those who remained on treatment. Because this assumption for the missingness mechanism is rather strong, results for Sensitivity Analysis 1 are not presented in this review.

Sensitivity Analysis for Missing Data Handling 2 (PMM Approaches):

To investigate the potential impact of missing data on the treatment effect, patients were classified into four different patterns depending on the availability of FVC data at Week 52:

- Patients with a 52-week FVC value:
    1. those who received study drug until 52 weeks (defined as patients who did not prematurely discontinue the study medication before 52 weeks (pattern 1)

2. those who prematurely discontinued study drug before 52 weeks but who were followed up until week 52 (pattern 2)

- Patients without a 52- week FVC value:
  3. those who were alive at 52 weeks (pattern 3)
  4. those who died before 52 weeks (pattern 4)

These four patterns were used in sensitivity analyses to estimate the treatment effect under differing assumptions regarding the persistence of efficacy post withdrawal of randomized treatment. As described in Table 5, missing data were imputed (resulting in 1000 multiply imputed datasets) and three resulting alternative analyses were defined. For each imputed dataset, the same statistical model as defined for the primary analysis was used for the analysis. The results were pooled following the standard multiple imputation procedure.[15]

Table 5. Primary and Sensitivity Analyses for Missing Data Handling (Pattern Mixture Model Approaches)

	Pattern 3: Missing week 52 data in patients still alive at 52 weeks		**Pattern 4: Missing week 52 data in patients who died before 52 weeks**	
Analysis	**Handling of missing week 52 data**	**Underlying assumption regarding persistence of efficacy post-withdrawal**	**Handling of missing week 52 data**	**Underlying assumption regarding persistence of efficacy after death**
Primary	No imputation	Assumes MAR	No imputation	Assumes MAR
Pattern Mixture Model 1	Based upon the slope (SE) estimates in Drug and Placebo in patients of pattern 2, multiple imputation of missing week 52 data in the respective treatment group	Rate of decline in patients with missing week 52 data is similar to rate of decline in patients of pattern 2 in the respective treatment group (e.g. treatment effect persists in same manner as for pattern 2 patients after study drug discontinuation)	Multiple imputation of missing 52 week data due to death based on the same slope (SE) estimates in Placebo patients of pattern 2, but truncated to force the slope in patients who died to be more severe than in those who survived	Assuming that deaths observed in the study will likely be related to worsening of SSc, it seems reasonable to assume that the unobserved FVC values should on average be lower than those in patients who did not die prior to week 52. Rate of decline in patients who died before week 52 is similar to rate of decline in the Placebo patients of pattern 2 with most severe slopes.
Pattern Mixture Model 2	Based upon the slope (SE) estimates in Placebo patients of pattern 2: multiple imputation of missing week 52 data in all patients regardless of treatment group	Rate of decline in all patients with missing week 52 data is similar to rate of decline in Placebo patients of pattern 2 (e.g. treatment effect does not persist after study drug discontinuation)		
Pattern Mixture Model 3	Based upon the slope (SE) estimates in Placebo patients	Rate of decline in all patients with missing week 52 data is similar to rate of decline in all	Multiple imputation of missing 52 week data due to death based on the same	Assuming that deaths observed in the study will likely be related to worsening of SSc, it

[15] Rubin D. Multiple Imputation for Nonresponse in Surveys, John Wiley & Sons, 1987.

	from the primary analysis model, i.e. in patients from pattern 1 or 2: multiple imputation of missing week 52 data in all patients regardless of treatment group	Placebo patients (e.g. treatment effect does not persist after study drug discontinuation)	slope (SE) estimates in all Placebo patients (i.e. in patients from pattern 1 or 2), but truncated to force the slope in patients who died to be more severe than in those who survived	seems reasonable to assume that the unobserved FVC values should on average be lower than those in patients who did not die prior to week 52. Rate of decline in patients who died before week 52 is similar to rate of decline in the Placebo patients with most severe slopes.

Abbreviations: SSc: systemic sclerosis; FVC: forced vital capacity; SE: standard error; MAR: missing at random
Source: SAP Table 7.4.2.1.2:1

Sensitivity Analysis for Missing Data Handling 3 (Tipping Point Analysis)

While the above Pattern Mixture Model (PMM) sensitivity analyses represent reasonable assumptions alternative to the assumption of the primary analysis, they do not comprehensively explore the plausible space of missing data assumptions. Therefore, the FDA review team requested additional analyses that systematically and comprehensively explore the space of plausible missing data assumptions. In particular, we recommended the inclusion of tipping point (TP) analyses that vary assumptions about the missing outcomes on the two treatment arms. The analyses should be two-dimensional, i.e., should allow assumptions about the missing outcomes on the two arms to vary independently, and should include scenarios where dropouts on nintedanib have worse slopes than dropouts on placebo. The goal is to explore the plausibility of missing data assumptions under which the conclusions change, i.e., under which there is no longer evidence of treatment effect. These analyses should include all observed data, regardless of whether measurements were made on- or off-treatment.

Sensitivity to the Analysis Model

Sensitivity to linearity assumption and sensitivity to covariates analyses results were consistent with the primary analysis model and will not be presented in this review.

Multiplicity Control Procedure

A hierarchical testing procedure was used, in that if results from the primary analysis for an endpoint were found to be statistically significant at the two-sided significance level of 0.05, the following endpoint in the hierarchy was to be tested at the same significance level in its primary analysis. If results for any of these endpoints were found to be not statistically significant, formal hypothesis testing was not performed for any remaining endpoints in the hierarchy. The procedure began with the primary efficacy endpoint, and the hierarchy was as shown below:

- Absolute change from baseline in the mRSS at Week 52
- Absolute change from baseline in SGRQ total score at Week 52

Primary Analyses for the Key/Hierarchical Secondary Efficacy Endpoints

Absolute change from baseline in the mRSS at Week 52: A restricted maximum likelihood (REML) based mixed effect model for repeated measures (MMRM) model was used for the analysis of continuous longitudinal secondary endpoints. The model included the fixed, categorical effects of treatment, ATA status, visit, and treatment-by-visit interaction, and continuous, fixed covariates of baseline and baseline-by-visit interaction. An unstructured variance-covariance structure was used to model the within patient measurements. Missing data were not imputed and assumed as missing-at-random.

Absolute change from baseline in the total SGRQ score at Week 52: This endpoint was analyzed in the same manner as in the primary analysis of the absolute change from baseline in mRSS at Week 52, using the same missing data handling methods.

Primary Analysis for Selected Other Secondary Efficacy Endpoints

Annual rate of decline in FVC in percent predicted over 52 weeks: This endpoint was analyzed in the same manner as in the primary analysis of the primary efficacy endpoint, using the same missing data handling methods.

Primary Analysis for Selected Further Efficacy Endpoints

In the analysis of binary endpoints, the categorical endpoints representing proportion of patients were summarized descriptively. In the SAP, it was pre-planned that Wilson 95% confidence interval and a nominal p-value were to be calculated for each proportion of patients. Patients with missing data were considered as non-responders. In the Applicant's CSR, analyses of these endpoints were performed using a Cohchran-Mantel-Haenszel (CMH) model adjusting for ATA status. Adjusted Mantel-Haenszel odds ratios (OR) with 95% confidence intervals (CI) were used to quantify the treatment effect of nintedanib relative to placebo.

Safety Analyses

In general, safety analyses were descriptive in nature. No inferential statistical testing was planned on the safety data.

Protocol Amendments

There were 3 global amendments of study 1199.214.
Global amendment 1 (March 02, 2016) included the following key protocol changes:

- Women of childbearing potential had to perform a pregnancy test every 4-6 weeks. Urine dipstick tests were done at every visit and then were provided for at home pregnancy testing as soon as visit intervals were > 6 weeks
- The inclusion criterion was revised to change the reference time point for historical HRCT within 12 months to Visit 1 instead of Visit 2
- Exclusion criteria were updated to clarify exclusion for:
    - Severe ulcers other than digital ulcers, at discretion of the investigator
    - Severe GI symptoms due to SSc

- Underlying chronic liver disease (Child Pugh A, B, C hepatic impairment)

Global amendment 2 (January 26, 2017) included the following key protocol changes:

- The inclusion criteria revised for SSc disease onset from within 5 years to within 7 years of Visit 1
- Exclusion criteria revised as follows:
  - To exclude patients not on mycophenolate mofetil / sodium or methotrexate within at least 8 weeks prior to Visit 2
  - Reference time point for airway obstruction assessment was changed from Visit 1 to Visit 2
  - History of Scleroderma Renal Crisis added as exclusion
- Clarification that all fatal cases would be reviewed by independent adjudication committee
- Absolute change from baseline at Week 52 in CRISS index score was added as a secondary endpoint
- Added analysis of rate of decline in FVC in percent predicted in the same way as the primary endpoint, including ATA status and baseline FVC% predicted as covariates
- The study sites were increased from 170 to 230 and in 33 instead of 20 countries worldwide

Global amendment 3 (February 15, 2018) included the following changes:

- Clarification of end of study management for patients who prematurely discontinued study medication
- Definition of clinically significant deterioration extended to other clinical parameters than mRSS and FVC
- Based on the half-life of the study drug, adverse events that occur between the start of treatment and up to 7 days after the date of the last dose of study medication will also be analyzed

The changes contained in the protocol amendments are not expected to have impacted study outcomes in a biased manner.

8.1.2. Study Results

Compliance with Good Clinical Practices

The IECs and/or IRBs met the requirements of the International Council for Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and local legislation. The constitution of the IRBs/IECs met the requirements and definitions of ICH GCP (ICH E6), 21 CFR 312.3, and of the participating countries.

Financial Disclosure

There were six investigators with disclosable financial interests/arrangements.

1) [redacted] disclosed that an [redacted] $200,000 was received. Steps taken to minimize bias included: This was a double-blind study meaning investigators did not know treatment assignment. In addition, the site [redacted].
2) [redacted] disclosed that his spouse is a [redacted] employee. Steps taken to minimize bias included: [redacted] was the [redacted] at this center, he was the main contact for this study. [redacted] provided backup support when required (e.g. medical oversight of patients if [redacted] was away). The site was adequately monitored throughout the trial to ensure that no indication of bias was perceived and to ensure adherence to protocol requirements was maintained. In addition, this study was double-blinded, so both site and [redacted] staff were unaware of trial medication assignment. [redacted] wife was not assigned to work on this trial.
3) [redacted] disclosed that he was on [redacted] and received less than 10,000€ in total compensation. He had preclinical scientific research projects with his companies [redacted]. There was no involvement of [redacted]" or "[redacted] during the trial. In addition, this was a double-blind study.
4) [redacted] disclosed being [redacted] and receiving $30,272 USD. Steps taken to minimize the potential for bias included: ILD was measured by HRCT and also reviewed by pulmonologists if necessary. The eligibility of patients for this trial was checked by multiple investigators, including rheumatologist and pulmonologists. The trial was double-blinded and the primary endpoint, FVC was an objective index, which was measured by spirometry. The numerical number should not have been biased by the sub-investigator.
5) [redacted] disclosed involvement in [redacted] and receiving a total estimated [redacted] of $47,550. Steps taken to minimize the potential for bias included that [redacted] was the [redacted] under the PI [redacted] who was expected to provide the required oversight of his staff and ensure appropriate delegation of tasks that would also ensure control and reduce bias. The CRA also monitored the work that the [redacted] did and assessed his role as a [redacted] and his contribution to the study through data monitoring and on site monitoring. The study also had a global Data Monitoring Committee.
6) [redacted] disclosed receiving $4000 as a [redacted] and $24,000 as a "[redacted]." Steps taken to minimize the potential for bias included that [redacted] was serving in the capacity of [redacted]. It was the expectation that the PI [redacted] provided the required oversight of his staff and ensured appropriate delegation of tasks that would also ensure control and reduction of bias. The CRA also monitored the work that the [redacted] did and assessed his role as a [redacted] and his contribution to the study through data monitoring and on site monitoring. The study also had a global Data Monitoring Committee.

The disclosable interests are unlikely to have influenced the outcomes of the studies given that the trial was double-blinded, there was a global Data Monitoring Committee, and the primary endpoint, FVC was an objective index, which was measured by spirometry.

Patient Disposition

At 52 weeks, of the 576 patients, 86.5% had FVC data, the study primary endpoint; the nintedanib group had a numerically higher missing data rate (16%) compared with the placebo group (11%). Treatment discontinuations occurred in 15% of patients: the nintedanib group had a numerically higher treatment discontinuation rate (19%) compared with the placebo group (11%). The most common reason for study withdrawal was adverse event (Table 6).

Table 6. Patient Disposition

	Placebo N=288	Nintedanib N=288	Total N=576
	n (%)	n (%)	n (%)
Prematurely Discontinued from Study Medication before 52 Weeks and Reason			
No	257 (89.2%)	232 (80.6%)	489 (84.9%)
Yes	31 (10.8%)	56 (19.4%)	87 (15.1%)
Reasons for Discontinuing Study Medication			
Adverse Event	21 (7.3%)	40 (13.9%)	61 (10.6%)
Patient refusal to continue taking study medication	7 (2.4%)	9 (3.1%)	16 (2.8%)
Non-compliant with protocol	1 (<1%)	1 (<1%)	2 (<1%)
Other	2 (<1%)	6 (2.1%)	8 (1.4%)
Primary Efficacy Follow-up Status at Week 52			
FVC Data Available at 52 Weeks			
FVC at 52 weeks, trial drug until 52 weeks	245 (85.1%)	217 (75.3%)	462 (80.2%)
FVC at 52 weeks, trial drug prematurely discontinued	12 (4.2%)	24 (8.3%)	36 (6.3%)
No FVC Data at 52 Weeks			
No FVC at 52 weeks, alive at 52 weeks	25 (8.7%)	36 (12.5%)	61 (10.6%)
No FVC at 52 weeks, died before 52 weeks	6 (2.1%)	11 (3.8%)	17 (3.0%)

Source: FDA Statistical Reviewer

Protocol Violations/Deviations

In study 1199.214, important protocol deviations (iPDs) were defined as those protocol deviations that could potentially impact the efficacy assessments or the patients' rights or safety. Important protocol deviations were pre-defined in the SAP and assessed before the locking and unblinding of data; note that the term "deviation" is a synonym for "violation", which is used in the SAP. As no per protocol set was defined in this study, none of the iPDs led to exclusion of patients from any analyses. Over 52 weeks, 18.9% of patients were reported with iPDs (20% in the nintedanib group and 18% in the placebo group). Overall compliance was

the largest protocol deviation in the nintedanib group (6%) compared to the placebo group (3%). Overall compliance was defined as between 80% and 120% and the calculation was based on capsule count. In cases where capsules were not returned or returned incomplete to the study site, actual compliance could not be calculated. The decision, whether or not this constitutes an iPD, was based on investigator's assessment. The other protocol deviations were proportionally similar in both treatment groups.

Table of Demographic Characteristics

The study was conducted as planned. A total of 576 patients were randomized and treated, 288 in each treatment arm (Table 7). The demographic characteristics of the two treatment arms were generally balanced. As expected for the target population of SSc-ILD, this was a predominantly female (75.2%) population. The patients were predominantly White (67.2%) and Asian (24.8%), of non-Hispanic ethnicity (93.1%), with a median age of 54 years, and similar by treatment group. The proportion of patients by age group were also similar by treatment group. Approximately 46% of the patients were enrolled at sites in Europe, while 25% were enrolled in Canada and the United States, and 23% in Asia. Overall, the patient demographic characteristics were balanced and representative of the intended patient population.

Table 7. Demographics

		Placebo N=288	Nint 150bid N=288	Total N=576
		n (%)	n (%)	n (%)
Sex	Female	212 (73.6)	221 (76.7)	433 (75.2)
	Male	76 (26.4)	67 (23.3)	143 (24.8)
Race	American Indian or Alaska Native	3 (1.0)	2 (<1)	5 (<1)
	Asian	81 (28.1)	62 (21.5)	143 (24.8)
	Black or African American	16 (5.6)	20 (6.9)	36 (6.3)
	Multiple	2 (<1)	2 (<1)	4 (<1)
	Native Hawaiian or other Pacific Islander	0	1 (<1)	1 (<1)
	White	186 (64.6)	201 (69.8)	387 (67.2)
Ethnicity	Hispanic/Latino	18 (6.3)	22 (7.6)	40 (6.9)
	Not Hispanic/Latino	270 (93.8)	266 (92.4)	536 (93.1)
Region	Asia	71 (24.7)	59 (20.5)	130 (22.6)
	Canada and United States	73 (25.3)	69 (24.0)	142 (24.7)
	Europe	126 (43.8)	140 (48.6)	266 (46.2)

		Placebo N=288	Nint 150bid N=288	Total N=576
		n (%)	n (%)	n (%)
	Rest of World	18 (6.3)	20 (6.9)	38 (6.6)
Age (Years)	Mean (Standard Deviation)	53.4 (12.6)	54.6 (11.8)	54.0 (12.2)
	Median (Minimum, Maximum)	54.0 (21, 78)	57.0 (20, 79)	55.0 (20, 79)
Age Group 1	<30	12 (4.2)	8 (2.8)	20 (3.5)
	>=30 to <45	54 (18.8)	48 (16.7)	102 (17.7)
	>=45 to <60	122 (42.4)	118 (41.0)	240 (41.7)
	>=60 to <75	91 (31.6)	112 (38.9)	203 (35.2)
	>=75	9 (3.1)	2 (<1)	11 (1.9)
Age Group 3	<65	229 (79.5)	224 (77.8)	453 (78.6)
	>=65	59 (20.5)	64 (22.2)	123 (21.4)
Weight (Unit: kg)	Mean (Standard Deviation)	70.0 (16.4)	69.4 (15.4)	69.7 (15.9)
	Median (Minimum, Maximum)	68.0 (36, 124)	68.0 (37, 127)	68.0 (36, 127)
Height (Unit: cm)	Mean (Standard Deviation)	164.5 (10.3)	163.2 (9.3)	163.8 (9.8)
	Median (Minimum, Maximum)	163.0 (144, 192)	162.0 (145, 193)	162.0 (144, 193)

Source: FDA Statistical Reviewer

Other Baseline Characteristics

The baseline disease characteristics are summarized in Table 8. Baseline disease characteristics were similar between treatment groups. Sixty-one percent of the patients had anti-topoisomerase antibodies. The mean time since first onset of non-Raynaud symptoms was 3.5 years. Approximately half of the patients had diffuse cutaneous systemic sclerosis and approximately half of the patients had limited cutaneous disease. In addition to SSc-ILD, patients had a history of other SSc manifestations including pulmonary hypertension (9%), digital ulcers (39%), diarrhea/malabsorption/bacterial overgrowth (18%), esophageal dysphagia/reflux (74%), synovitis (24%), friction rubs (9%), and Raynaud phenomenon (97%), which were similar by treatment group. Measures of lung function, including mean percent predicted FVC, and percent predicted DLCO were generally balanced by treatment group. Interstitial lung disease was assessed by HRCT within 12 months of screening. The mean extent of fibrosis on HRCT, as determined by centralized reading, was 36%; the majority of patients had evidence of ground glass opacities (84.5%), and the minority had honeycombing (15.5%).

Anti-RNA polymerase III antibodies and anti-centromere antibodies were present in a minority of patients (8.5% and 7.1%, respectively).

In addition to the characteristics in Table 8, the percentage of patients with pulmonary hypertension at screening and the mean baseline mRSS were also balanced by treatment group.

At baseline, 48% of the patients received treatment with mycophenolate and 7% received methotrexate. Use of mycophenolate and methotrexate was similar by treatment group.

Table 8. Baseline Disease Characteristics

		Placebo N=288	Nintedanib N=288	Total N=576
		n (%)	n (%)	n (%)
Lung Function				
FVC (L)	Mean (SD)	2.54 (0.82)	2.46 (0.74)	2.50 (0.78)
FVC (% predicted)	Mean (SD)	72.7 (16.6)	72.4 (16.8)	72.5 (16.7)
DL_{CO} (% predicted)	Mean (SD)	53.2 (15.1)	52.8 (15.1)	53.0 (15.1)
SSc-ILD History				
Time since first onset of non-Raynaud symptom (Years)	Mean (SD)	3.50 (1.78)	3.48 (1.62)	3.49 (1.70)
	Median (Min, Max)	3.47 (0.36, 7.16)	3.40 (0.26, 7.07)	3.41 (0.26, 7.16)
SSc subtype	Diffuse cutaneous SSc	146 (50.7)	153 (53.1)	299 (51.9)
	Limited cutaneous SSc	142 (49.3)	135 (46.9)	277 (48.1)
Autoantibody Status				
Anti-topoisomerase antibodies	Negative	111 (38.5)	115 (39.9)	226 (39.2)
	Positive	177 (61.5)	173 (60.1)	350 (60.8)
Immunosuppressive Agent Use at Baseline				
Mycophenolate mofetil	No	148 (51.4)	149 (51.7)	297 (51.6)
	Yes	140 (48.6)	139 (48.3)	279 (48.4)
Methotrexate	No	273 (94.8)	265 (92.0)	538 (93.4)
	Yes	15 (5.2)	23 (8.0)	38 (6.6)
Mycophenolate Mofetil Use at Baseline by Region* (US and Canada vs. Rest)				
Mycophenolate mofetil Use at baseline*	US and Canada	73 (25.3)	69 (24.0)	142 (24.7)
	No MMF Use	16 (5.6)	12 (4.2)	28 (4.9)
	MMF Use	57 (19.8)	57 (19.8)	114 (19.8)

		Placebo N=288	Nintedanib N=288	Total N=576
		n (%)	n (%)	n (%)
	Other than US and Canada	215 (74.7)	219 (76.0)	434 (75.3)
	No MMF Use	132 (45.8)	137 (47.6)	269 (46.7)
	MMF Use	83 (28.8)	82 (28.5)	165 (28.6)
HRCT Assessment Results				
Extent of fibrotic disease in the lung (%)	Median (Min, Max)	30 (5, 90)	30 (10, 95)	30 (5, 95)
Ground Glass Opacities	Missing	6 (2.1)	5 (1.7)	11 (1.9)
	No	36 (12.5)	42 (14.6)	78 (13.5)
	Yes	246 (85.4)	241 (83.7)	487 (84.5)

Source: FDA Statistical Reviewer

Concomitant Medications, and Rescue Medication Use

Overall, 98% of patients received at least 1 concomitant baseline therapy and it was generally balanced across treatment groups. Aside from mycophenolate (49%), the most commonly used therapies at baseline were omeprazole (24%), nifedipine (19%), prednisone (18%), acetylsalicylic acid (18%), paracetamol (9%), sildenafil (8%), Bactrim (7%), methotrexate (7%), and bosentan (6%).

Over 52 weeks, nearly all patients (99.7%) received at least 1 concomitant medication. Generally, the proportion of patients taking concomitant therapies was comparable between the 2 treatment groups. In the nintedanib group, 69% of patients used steroids vs 64% in the placebo group. As compared to use at baseline, in total, an increase was seen in the use of corticosteroids (baseline: 50%, all therapies: 66%), disease-modifying antirheumatic drugs (baseline: 57%, all therapies: 64%), drugs used in pain therapies (baseline: 53%; all therapies: 76%), and antidiarrheal therapies (baseline: 4%, all therapies: 31%). More patients in the nintedanib group (50% vs 12%) reported antidiarrheal therapies. This difference was not observed at baseline and reflects the higher incidence of diarrhea on the drug. In addition, azithromycin was used by 12% of patients (11% nintedanib and 13% placebo) vs 1% at baseline. Use of proton pump inhibitors and nifedipine/amlodipine was similar by treatment group. Few patients received additional immunosuppression with cyclophosphamide (4.2% nintedanib, 1.4% placebo) or rituximab (1.4% nintedanib, 0.7% placebo) during or post-treatment.

Efficacy Results – Primary Endpoint

The primary endpoint was the annual rate of decline in forced vital capacity (FVC) in mL over 52 weeks. FVC has been used previously to support regulatory decision making for drugs approved for the treatment of IPF. While there is no regulatory precedent for its use in SSc-ILD, FVC has

been proposed as a validated outcome measure in patients with SSc according to the principles of Outcome Measures in Rheumatologic Clinical Trials (OMERACT).[16]

This section contains the four steps the review team took in assessing the treatment effect of nintedanib on FVC in Study 1129.214: evaluating the effect size through the primary analysis, assessing the robustness of the effect through sensitivity analyses on missing data assumptions, evaluating the effect size in terms of the FVC percent predicted, and interpreting the data using responder analyses of FVC change from baseline. All the four steps are based on pre-planned analyses in the study protocol or SAP with addition of tipping point analyses and graphical approaches to facilitate understanding.

The Primary Analysis

In Study 1199.214, there was a statistically significant difference in annual rate of decline in FVC in mL over 52 weeks, when comparing nintedanib to placebo (p=0.035). The adjusted mean difference between nintedanib and placebo was 40.9 mL/year (95% CI: 2.9 to 79.0) (Table 9).

Table 9. Annual Rate of Decline in FVC in mL over 52 Weeks Primary Analysis (Treated Set)

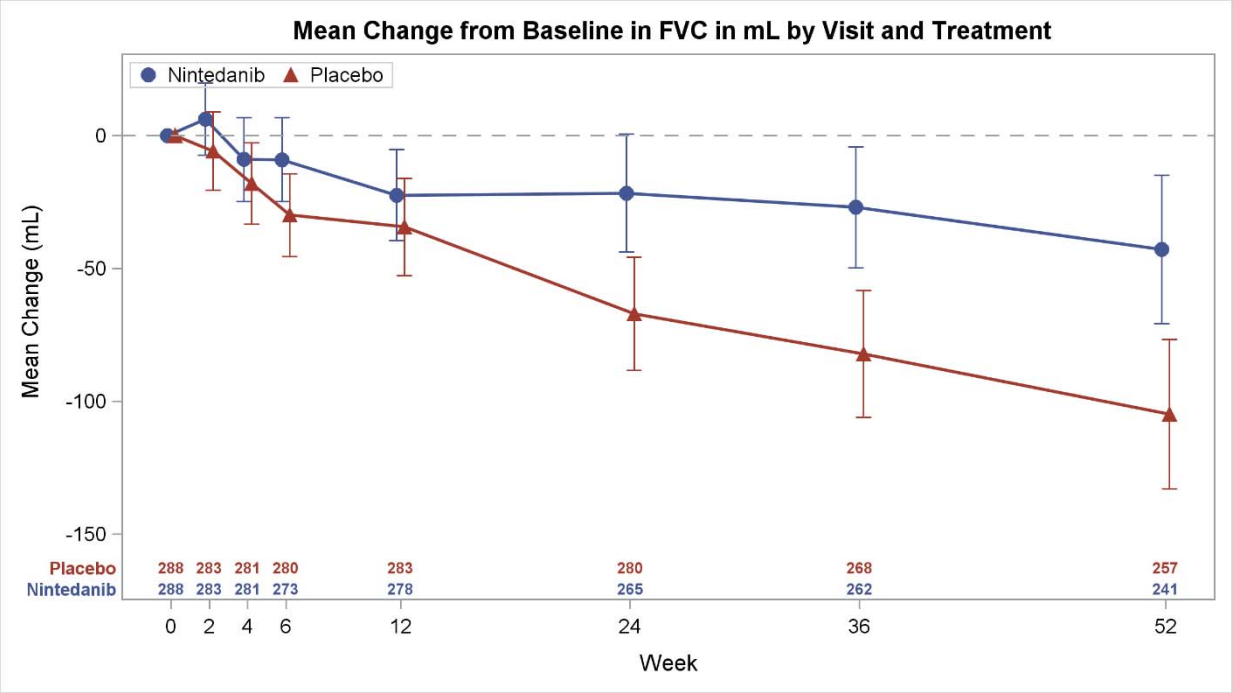
	Placebo (N=288)	Nintedanib (N=288)
Number Analyzed	288	287
Adjusted Annual Rate of Decline, mL/Year (SE)	-93.3 (13.5)	-52.4 (13.8)
Nintedanib vs. Placebo		
Difference (SE)		40.9 (19.4)
95% CI		2.9, 79.0
p-value		0.035

Abbreviations: N: sample size in Treated Set; SE: standard error; CI: confidence interval
Source: FDA Statistical Reviewer

The mean change from baseline in FVC in mL over 52 weeks by treatment group is shown in Figure 4. Data are observed values; vertical lines represent 95% confidence intervals. Numbers of patients with non-missing FVC data by week are displayed above the x-axis.

[16] Merkel P, Clements PJ, Reveille P, et al. Current status of outcome measure development for clinical trials in systemic sclerosis. J Rheumatol 2003;30:1630–47.

Figure 4. Mean (95% CI) Observed Change from Baseline in FVC in mL over 52 Weeks by Treatment (Treated Set)



Abbreviations: mL: milliliter.
Source: FDA Statistical Reviewer

Sensitivity Analyses on Missing Data Assumptions

Multiple sensitivity analyses to missing data assumptions were performed for the primary endpoint, including a series of analyses that utilized the Pattern Mixture Model (PMM) approach with multiple imputation and the tipping point analysis.

1. PMM Approaches with Multiple Imputation

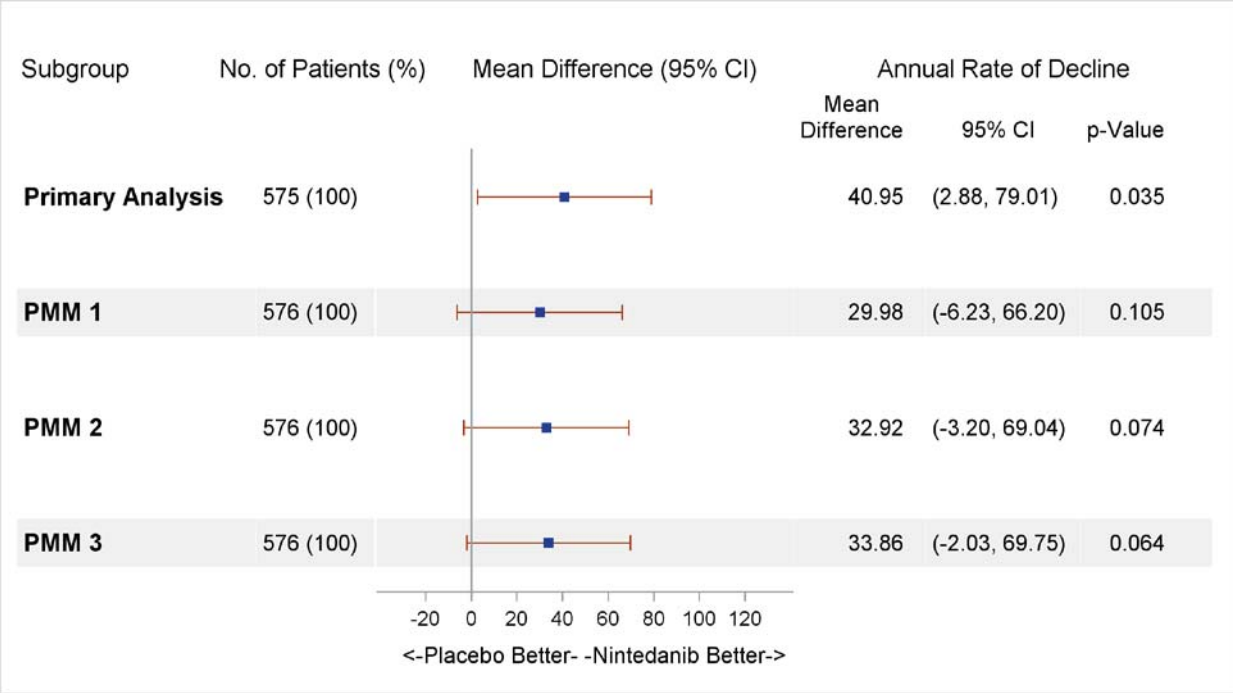
All the three PMM analyses assumed unfavorable scenarios for the nintedanib group, to different degrees. By dividing the observed FVC data up to Week 52 into 4 complete/missing patterns, as discussed in Statistical Analysis Plan section, these PMM approaches were:

- PMM1:
  - Patients who were alive at Week 52: the rate of decline in patients who discontinued treatment and study visits (Pattern 3) was assumed to be similar to the rate of decline in patients who discontinued treatment but continued study visits till Week 52 (Pattern 2) in the ***respective treatment*** group;
  - Patients who were dead at Week 52: the rate of decline in patients who discontinued treatment and study visits (Pattern 4) was assumed to be similar to the rate of decline in the worst half of the patients who discontinued treatment but continued study visits till Week 52 (Pattern 2) in the ***placebo*** group.

- PMM2:
    - Patients who were alive at Week 52: the rate of decline in patients who discontinued treatment and study visits (Pattern 3) was assumed to be similar to the rate of decline in patients who discontinued treatment but continued study visits till Week 52 (pattern 2) in the ***placebo*** group;
    - Patients who were dead at Week 52: the rate of decline in patients who discontinued treatment and study visits (Pattern 4) was assumed to be similar to the rate of decline in the worst half of the patients who discontinued treatment but continued study visits till Week 52 (Pattern 2) in the ***placebo*** group.
- PMM3:
    - Patients who were alive at Week 52: the rate of decline in patients who discontinued treatment and study visits (Pattern 3) was assumed to be similar to the rate of decline in patients who continued study visits till Week 52 (Patterns 1 and 2) in ***placebo*** group;
    - Patients who were dead at Week 52: the rate of decline in patients who discontinued treatment and study visits (Pattern 4) was assumed to be similar to the rate of decline in the worst half of the patients who continued study visits till Week 52 (Pattern 2) in the ***placebo*** group.

All the three analyses resulted in reduced treatment effects, confidence intervals that include 0, and p-values greater than 0.05. The results of the three PMM analyses are summarized in Figure 5.

Figure 5. Forest-plot for Rate of Decline in FVC [mL/Year] over 52 Weeks Sensitivity Analyses (Treated Set)



Abbreviations: No.: Number; PMM: pattern mixture model; CI: confidence interval
Source: FDA Statistical Reviewer following the Applicant's proposed analyses

In all three alternative PMM approach analyses, nintedanib was no longer statistically significantly separated from placebo.

2. Tipping Point Analysis

A tipping point analysis was then performed to evaluate how robust the primary analysis results were across varying missing data assumptions, a more comprehensive range over scenarios assumed in the PMM analyses. The objective of this analysis was to more precisely identify the point at which the conclusion changes. In this analysis, missing data with monotone missingness patterns were first multiply imputed assuming that missingness was at random among those in the same treatment group, with the same sex, age, height at baseline, ATA status, and with comparable FVC values from baseline through discontinuation. Then, departures from missing-at-random assumption were investigated using the delta adjustment method. That is, subjects who discontinued early would have, on average, efficacy outcomes after discontinuation shifted by some amount delta compared to otherwise similar subjects with observed data in their treatment arm. The results over a relatively comprehensive range of by-arm shift (S) values are summarized in Table 10. The header rows show the shifts applied to dropouts in the placebo group: with -60 an additional 60 mL/year decline was imposed on the assumed background missing-at-random rate of decline in placebo; similarly, the header columns show the same range of shifts applied to dropouts in the nintedanib arm. The body of the table provides p-values for the comparisons for the nintedanib group to the placebo group

for the corresponding shifts. The blue boxed cell in the table, corresponds to shifts of 0 in both arms, which is analogous to the primary analysis under the missing-at-random assumption. The pink shaded region shows shifts which are sufficient to "tip" the rate of decline conclusion; that is, the results are no longer statistically significant at 0.05 level. The blue shaded region shows cases where significance was maintained. The red boxes corresponds to a relative shift of 45 mL/year, so if the dropouts in nintedanib are assumed to progress at the rate seen in placebo, then nintedanib will not have a significant effect in the overall trial.

Table 10. Annual Rate of Decline in FVC in mL over 52 Weeks, Tipping Point Analysis (Treated Set)

		Shift in Placebo (Unit: mL/Year)						
		-60	**-45**	**-30**	**-15**	**0**	**15**	**30**
Shift in Nintedanib (Unit: mL/Year)	-60	**0.048**	0.052	0.056	0.060	0.065	0.070	0.075
	-45	0.042	**0.046**	0.049	0.053	0.057	0.061	0.066
	-30	0.037	0.040	**0.043**	0.046	0.0498	0.054	0.058
	-15	0.032	0.035	0.037	**0.040**	0.044	0.047	0.051
	0	0.028	0.030	0.032	0.035	**0.038**	0.041	0.044
	15	0.024	0.026	0.028	0.030	0.033	**0.036**	0.039
	30	0.020	0.022	0.024	0.026	0.029	0.031	**0.034**

Abbreviation: mL: milliliter.
Each cell contains p-value.
Source: Analysis results by FDA Statistical Reviewer per the Applicant's Response to FDA Information Request

While the results for the primary endpoint were statistically significant based on the pre-specified analysis, the sensitivity analyses showed mixed results, mainly because the magnitude of the treatment effect size was small. The pre-planned pattern mixture model analyses did not maintain the statistical significance seen in the primary analysis and the additional tipping point analyses did not provide a clear robustness of the primary analysis result and warranted further clinical interpretation.

Annual Rate of Decline in FVC in Percent Predicted – A Secondary Endpoint

Annual rate of decline in FVC in percent predicted was analyzed using a similar model as in the analysis of the primary endpoint. There was a statistically significant difference in annual rate of decline in FVC in percent predicted over 52 weeks, when comparing nintedanib to placebo (p=0.033). The adjusted mean difference between nintedanib and placebo was 1.2 %/year (95% CI: 0.1 to 2.2) (Table 11).

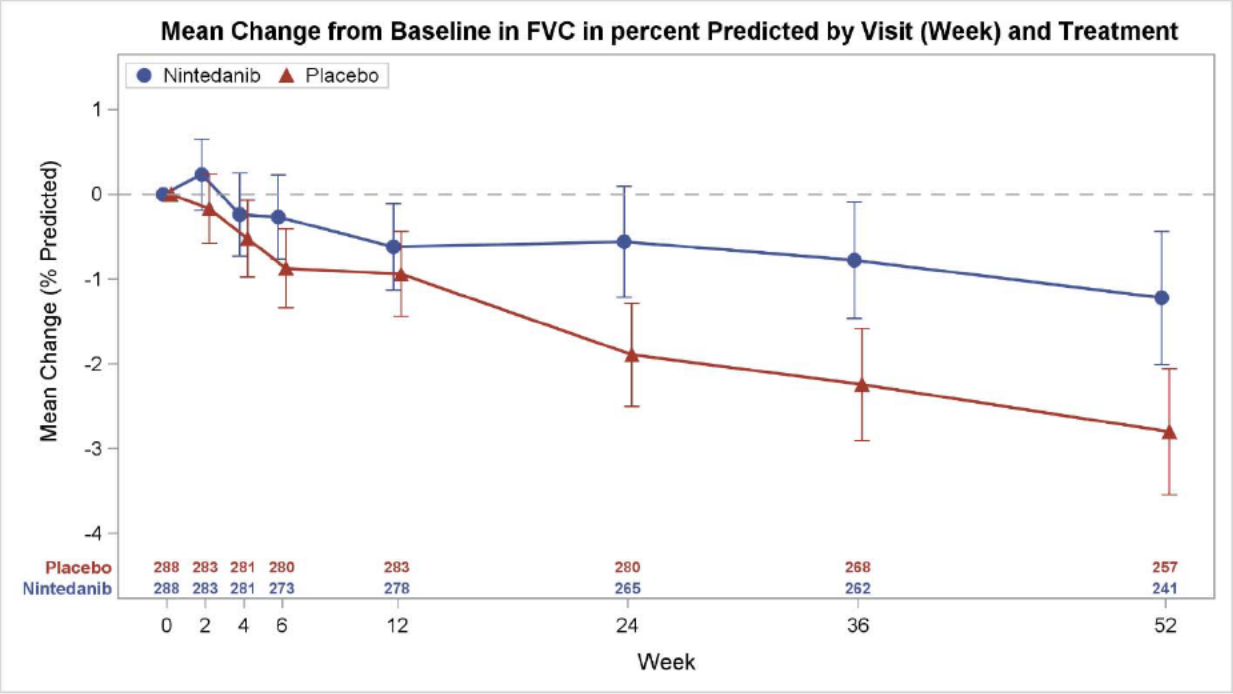
Table 11. Annual Rate of Decline in FVC in Percent Predicted over 52 Weeks Primary Analysis (Treated Set)

	Placebo (N=288)	Nintedanib (N=288)
Number Analyzed	288	287
Adjusted Annual Rate of Decline, %/year (SE)	-2.6 (0.38)	-1.4 (0.4)
Nintedanib vs. Placebo		
Difference (SE)		1.2 (0.5)
95% CI		(0.1, 2.2)
p-value		0.033

Abbreviations: N: sample size in Treated Set; SE: standard error; CI: confidence interval
Source: FDA Statistical Reviewer

The mean change from baseline in FVC in percent predicted over 52 weeks by treatment group is shown in Figure 6. Data are observed values; vertical lines represent 95% confidence intervals. Numbers of patients with non-missing FVC data by week are displayed above the x-axis.

Figure 6. Mean (95% CI) Observed Change from Baseline in FVC in Percent Predicted over 52 Weeks by Treatment (Treated Set)



Source: FDA Statistical Reviewer

Categorical Endpoints Representing Proportion of Patients with a Decline in FVC at *Week 52 – Further Endpoints*

In Further Endpoints, the protocol/SAP also defined categorical "non-responder" variables based on either relative change from baseline in FVC in mL or absolute change from baseline in FVC in percent predicted, as follows:

- patients with a relative decline from baseline in FVC in mL at Week 52 of >5%
- patients with a relative decline from baseline in FVC in mL at Week 52 of >10%
- patients with an absolute decline from baseline in FVC in percent predicted at Week 52 of >5%
- patients with an absolute decline from baseline in FVC in percent predicted at Week 52 of >10%

However, to facilitate the interpretation of benefit (response), as opposed to no benefit (non-response), the FDA review team converted the protocol-specified endpoints to "responder" variables corresponding to favorable outcomes:

- patients with a relative decline from baseline in FVC in mL at Week 52 of ≤5%
- patients with a relative decline from baseline in FVC in mL at Week 52 of ≤10%
- patients with an absolute decline from baseline in FVC in percent predicted at Week 52 of ≤5%
- patients with an absolute decline from baseline in FVC in percent predicted at Week 52 of ≤10%

These endpoints are summarized in Table 12. In these analyses, patients with missing data at Week 52 were categorized as non-responders. To explore the treatment effect of nintedanib group relative to placebo, a Cochran-Mantel-Haenszel (CMH) model adjusting for ATA status was performed for each responder variable. The adjusted Mantel-Haenszel odds ratios (OR) with associated 95% confidence intervals (CI), and nominal p-values are also reported in Table 12.

The proportion of responders with 5% threshold (relative decline ≤5%) was numerically higher in the nintedanib group (59.4%) than in the placebo group (51.7%), favoring nintedanib over placebo; the odds ratio was 1.37 (95% CI 0.98, 1.89; nominal p-value = 0.066). The proportion of responders with 10% threshold (relative decline ≤10%) was numerically lower in the nintedanib group (72.2%) than in the placebo group (73.6%), not favoring nintedanib over placebo; the odds ratio was 0.93 (95% CI 0.65, 1.35; nominal p-value = 0.704), indicating an inconsistent direction of the treatment effect, likely due to the small effect size and the disproportionately higher missing data in the nintedanib group and the assumption that missing data represent worse outcome. Responder analyses using absolute decline in FVC in percent predicted showed a similar pattern with the analyses using relative decline in FVC in mL (Table 12).

Table 12. Proportions of Responders with Certain Thresholds Over 52 Weeks (Treated Set)

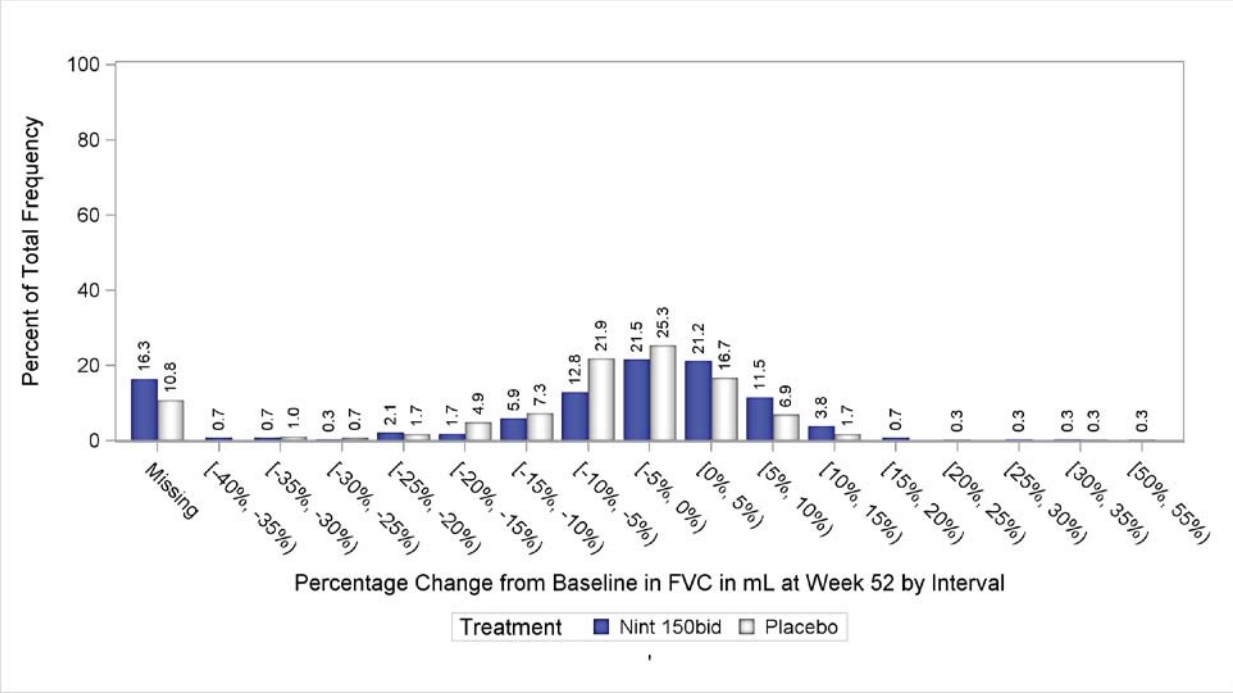
	Placebo (N=288)	Nintedanib (N=288)	Comparison vs. Placebo*			
	n (%)	n (%)	Odds ratio	95% CI		Nominal p-value
				Lower	Upper	
Responder definition using relative decline from baseline in FVC in mL at Week 52						
Relative decline ≤5%	149 (51.7%)	171 (59.4%)	1.36	0.98	1.89	0.066
Relative decline ≤10%	212 (73.6%)	208 (72.2%)	0.93	0.64	1.34	0.704
Responder definition using absolute decline from baseline in FVC in % predicted at Week 52						
Absolute decline ≤5%	186 (64.6%)	196 (68.1%)	1.16	0.82	1.64	0.386
Absolute decline ≤10%	236 (81.9%)	227 (78.8%)	0.82	0.54	1.24	0.348

Abbreviations: N: sample size in Treated Set; n: number of patients within category; SE: standard error; CI: confidence interval
Note: Patients with missing data at Week 52 were considered as non-responders.
* Based on Cochran-Mantel-Haenszel tests stratified on baseline ATA status.
Source: FDA Statistical Reviewer

The Applicant conducted similar analyses on the "non-responder" variables. We note that, the FDA and Applicant analyses convey identical information because non-response is just a complementary event of response. Of note, unlike FDA, the Applicant used the worst observation carried forward approach to imputing missing data at Week 52 and then applied the threshold to define non-response.

We also used graphical approaches to investigate the distribution of change from baseline in FVC by treatment group, through distributional bar chart and cumulative responder rate (through empirical distribution function). Figure 7 displays percent change from baseline in FVC in mL at Week 52 distribution as a bar chart with the x-axis comprising of different groups of percent change from baseline as bars and y-axis represents its proportion as the height of the bar. In this plot, missing data were represented in a group on the left, reflecting the assumption that missing data have worse outcome.

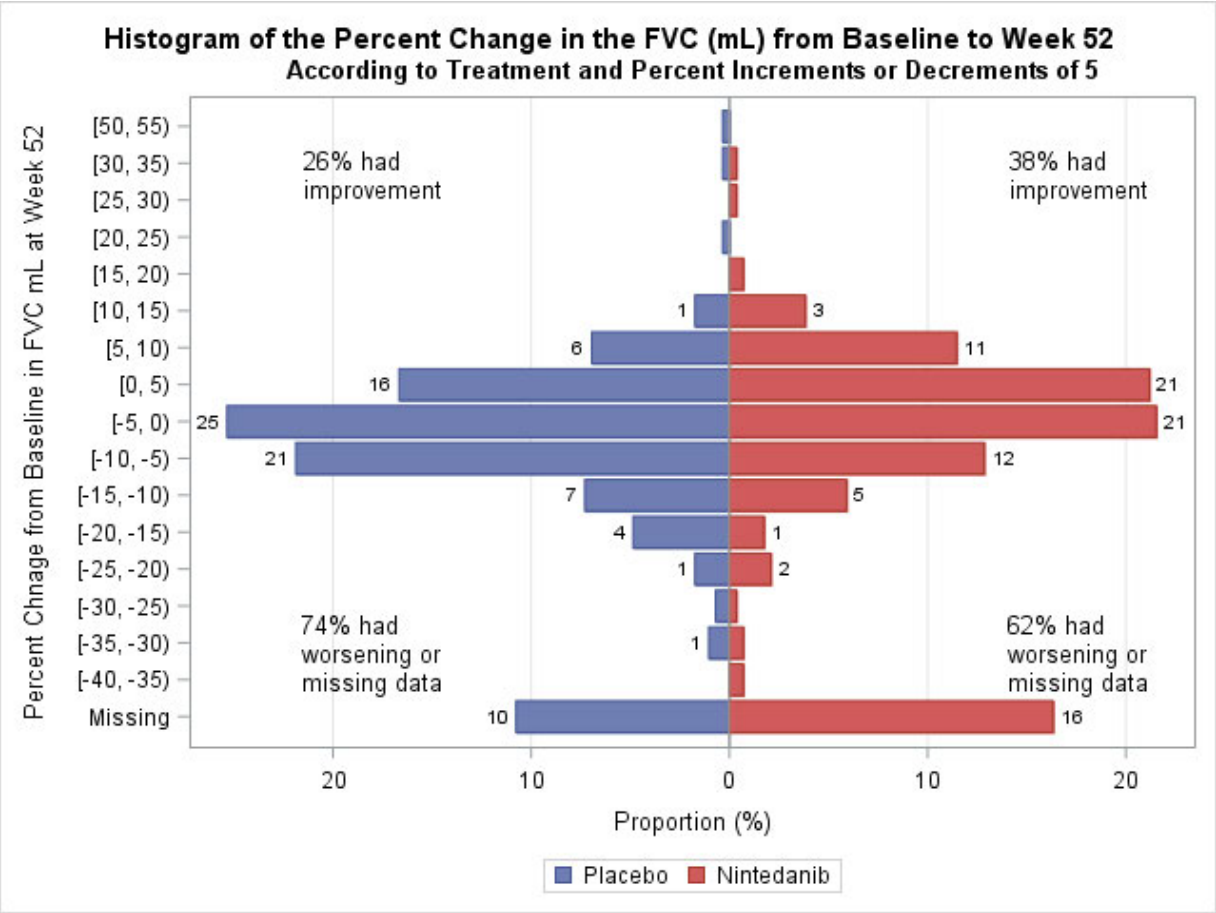
Figure 7. Bar Chart of Percent Change from Baseline in FVC in mL at Week 52 (Treated Set)



Abbreviations: mL: milliliter
Source: FDA Statistical Reviewer

As a supportive description of the data, a butterfly plot in Figure 8 is recommended. In the plot, four quadrants contains a summary statistics of relative frequency by treatment and decline status ('improvement' vs 'worsening or missing'). (b) (4)

Figure 8. Histogram of the Percent Change in the FVC (mL) from Baseline to Week 52 (Treated Set)



Source: FDA Statistical Reviewer

A sensitivity analysis based on the assumption that the expected value of the measure for those who drop out is not better than that for those who complete the study was conducted to evaluate the robustness of the primary analysis findings to missing data. The cumulative responder rate approach is an adjustment to the usual test for a difference between treatments that allows for the inclusion of the probable effect of the dropouts; it provides a bound on the test for efficacy of the treatment.

There are different ways to impute missing data under the cumulative responder rate approach by assigning different response values to the dropouts. Considering that across the arms, significant proportion of the early withdrawals was due to “adverse events” and “patient refusal to continue taking trial medication”, by imputing all missing percent change from baseline values with worst values across the two treatment arms, we treat subject with missing data and subjects with worst outcomes equally.

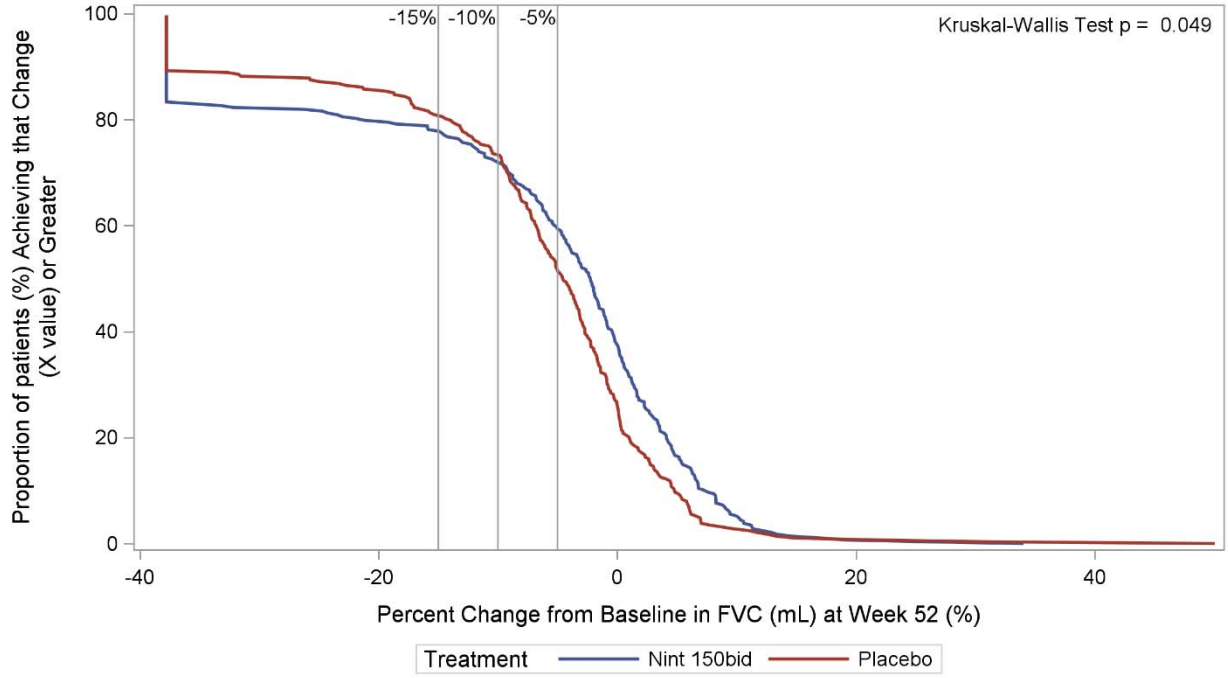
Figure 9 provides continuous responder curves (i.e., empirical distribution functions) for percent change from baseline in FVC in mL at Week 52. This presentation is developed as

follows. Each patient is classified as having been successfully or unsuccessfully treated according to whether or not the patient reached a certain threshold for the percent change from baseline in FVC at Week 52. This dichotomization of the percent change from baseline in FVC in mL is repeated across a range of possible thresholds, in this case from the minimum to the maximum percent change from baseline value across the two arms in the study. Patients with missing data at Week 52 are classified as unsuccessfully treated for all thresholds. In the continuous responder curve, the x-axis displays the thresholds required to classify a patient as a successfully treated patient. The y-axis represents the proportion of treated set patients who achieved the corresponding threshold. For example, at the vertical reference line of a percent change from baseline in FVC in mL of -10%, the continuous responder plot illustrates that 72.2% of nintedanib patients had FVC percent change from baseline greater or equal to -10% while 73.6% of placebo patients experienced such a change.

As shown in the figure, there is an initial dramatic drop from 100% to approximately 83% (nintedanib) or 89% (placebo) in the y-axis, corresponding to the proportion of patients who dropped out since patients with missing data were classified as unsuccessfully treated for all thresholds. Also evident from the figure is that a separation is observed between curves corresponding to nintedanib and placebo.

Then a corresponding rank sum statistic of Kruskal-Wallis test is calculated on the modified data. That is, output of the cumulative responder rate approach is in the form of an empirical distribution function plot and a corresponding p-value of the separation of the two distributions. Result from the Kruskal-Wallis test in Figure 9 is consistent with the primary and sensitivity analysis results.

Figure 9. Empirical Distribution Function for Percent Change from Baseline in FVC at Week 52 (Treated Set)



Abbreviations: mL: milliliter
Source: FDA Statistical Reviewer

To visually aid the understanding of the responder analysis, in which responders were defined as patients with no worse outcome than certain thresholds, we also produced bar charts displaying the proportions of responders at various response definitions and can be found in Appendix 15.5.1.

Efficacy Results – Key Secondary endpoints

The key secondary efficacy endpoints were as follows:

- Absolute change from baseline in the mRSS at Week 52
- Absolute change from baseline in SGRQ total score at Week 52

Key secondary endpoints were analyzed in a hierarchical manner such that if the previous endpoint failed to reach statistical significance, the subsequent endpoints were not considered statistically significant.

Absolute Change from Baseline in mRSS at Week 52

Modified Rodnan Skin Score (mRSS)[17] is a widely accepted measure of skin involvement in SSc. It consists of an evaluation of patient's skin thickness rated by clinical palpation using a 0–3 scale for each of 17 surface anatomic areas of the body. The minimum clinically important difference (MCID) of the mRSS has been estimated in the range of 3.2 - 5.3 mRSS units anchored on physician global assessment.[18] A negative change indicates improvement in skin thickening.

For the first key secondary endpoint of absolute change from baseline in mRSS at Week 52, there was a -0.21 (95% CI: -0.94 to 0.53) difference between the nintedanib group compared to placebo, based on the FDA statistician's analysis. This was not statistically significant (p=0.579) (Table 13). Given the hierarchical analysis structure, the subsequent secondary endpoint was not considered statistically significant.

Table 13. Absolute Change from Baseline in mRSS at Week 52 (Treated Set)

	Placebo (N=288)	Nintedanib (N=288)
Number Analyzed	286	288
Baseline Mean mRSS Score (SD)	10.91 (8.81)	11.33 (9.18)
Adjusted Mean Change from Baseline (SE)	-1.96 (0.26)	-2.17 (0.27)
Nintedanib vs. Placebo		
Difference (SE)		-0.21 (0.37)
95% CI		-0.94, 0.53
p-value		0.579

Abbreviations: N: sample size in Treated Set; SD: standard deviation; SE: standard error; CI: confidence interval; mRSS: Modified Rodnan Skin Score.
Source: FDA Statistical Reviewer

The absolute change from baseline in mRSS was similar in both the nintedanib and placebo treatment groups and did not exceed the MCID.

Absolute change from baseline in SGRQ total score at Week 52

For the second key secondary endpoint of absolute change from baseline in SGRQ total score at Week 52, there was a 1.69 (95% CI: -0.73 to 4.12) difference between the nintedanib group

[17] Steen VD, Medsger TA Jr. Improvement in skin thickening in systemic sclerosis associated with improved survival. Arthritis Rheum 2001:44:2828–35.
[18] Khanna D, Furst DE, Hays RD, et al. Minimally important difference in diffuse systemic sclerosis: results from the D-penicillamine study. Ann Rheum Dis 2006;65:1325–9.

compared to placebo, based on the FDA statistician's analysis (Table 14). This comparison shows a numerically worse outcome in the nintedanib group as compared with the placebo group.

Table 14. Absolute Change from Baseline in SGRQ Total Score at Week 52 (Treated Set)

	Placebo (N=288)	Nintedanib (N=288)
Number Analyzed	283	282
Baseline Mean SGRQ total Score (SD)	39.4 (20.9)	40.7 (20.2)
Adjusted Mean Change from Baseline (SE)	-0.88 (0.87)	0.81 (0.88)
Nintedanib vs. Placebo		
Difference (SE)		1.69 (1.24)
95% CI		-0.73, 4.12

Abbreviations: N: sample size in Treated Set; SD: standard deviation; SE: standard error; CI: confidence interval; SGRQ: St. George's Respiratory Questionnaire.
Source: FDA Statistical Reviewer

In summary, the key secondary endpoints were not supportive of a direct treatment benefit for nintedanib over placebo at Week 52 in this study.

Other Efficacy Results – Selected Endpoints

Time to Death over the Whole Trial

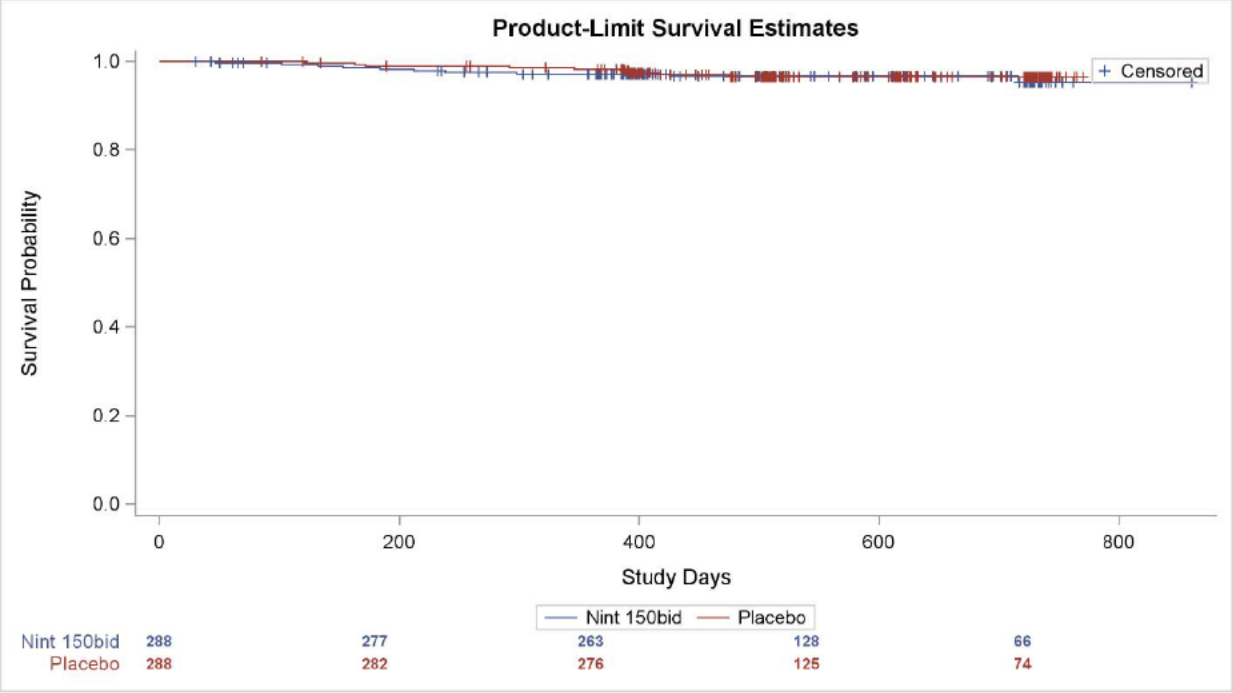
Of the total 576 TS patients, survival status at the end of study was followed-up for 570 patients, with 6 lost to follow-up (1 patient in placebo group, and 5 in nintedanib group). There were 19 deaths in total across the two treatment groups at the end of study, with the rest of patients censored. Table 15 summarizes the analysis results for the mortality endpoint through 2 approaches: Crude rate of death, and Cox proportional hazard regression model for time to death. The crude probability of death was 3.1% in the placebo group, and 3.5% in the nintedanib group. The hazard ratio of nintedanib group versus placebo group was 1.16 (95% CI: from 0.47 to 2.84), numerically favoring placebo. Figure 10 displays the probability of survival using Kaplan-Meier estimates.

Table 15. Cox Proportional Hazards Analysis of Time to Death Over the Entire Study Duration (Treated Set)

	Placebo (N=288)	Nintedanib (N=288)
Survival status at the end of study, n (%)		
Dead	9 (3.1%)	10 (3.5%)
Lost to follow-up (Vital status at the End of Study Unknown)	1 (0.3%)	5 (1.7%)
Alive (Censored at the End of Study)	278 (96.5%)	273 (94.8%)
Cox Proportional Hazard Model Analysis		
Nintedanib vs. Placebo		
Hazard Ratio		1.16
95% CI		0.47, 2.85
p-value		0.751

Abbreviations: N: sample size in Treated Set; CI: confidence interval.
Source: FDA Statistical Reviewer

Figure 10. Kaplan-Meier Estimate of Probabilities of Survival (Treated Set)



Abbreviations: Nint 150bid: nintedanib 150 milligram twice daily.
Source: FDA Statistical Reviewer

Of note, in the IPF clinical program, there were trends toward improvement in mortality.[19] This was not observed in Study 1199.214. This may be due to the relatively short duration of the study to assess long term changes in a chronic disease, differences in the progression of the underlying diseases between IPF and SSc-ILD, and/or the smaller study sample size.

There were no differences in other secondary endpoints, including FACIT-dyspnea score and DL_{CO} at Week 52. Additionally, there were no differences in other disease-related secondary endpoints, including ACR CRISS responder and number of digital ulcers, or in HAQ-DI.

Additional Analyses

The Applicant pre-planned subgroup analyses for the primary and both key secondary efficacy endpoints with subgroups based on antitopoisomerase (ATA) status, age, gender, race, geographical region, mycophenolate mofetil/sodium use at baseline, and SSc subtype. No significant interaction was found between treatment and these subgroups at the 5% level of statistical significance.

In this review, subgroup analyses were only performed for the primary efficacy endpoint. This section provides the reviewer's subgroup analyses by gender, race, age, and geographical region. Subgroup analyses were also performed for selected baseline SSc disease and treatment factors to inform the potential effect of these factors on efficacy.

Gender, Race, Age, and Geographic Region

For each subgroup factor, the model was adapted from the pre-specified primary efficacy analysis model. For the annual rate of decline in FVC endpoint, an interaction analysis was performed with the primary analysis random coefficient model by including the subgroup variable, the subgroup variable-by-time interaction, and the subgroup variable-by-time-by-treatment interaction as covariates. When a covariate in the model is the subgroup variable, it is replaced with the categorical version of itself when needed. By-subgroup mean annual rates of decline in FVC were estimated to illustrate the treatment effects under each subgroup. Under each subgroup, the mean difference estimate between the nintedanib group and the placebo group together with associated CIs was presented using a forest plot.

The rate of decline in FVC (mL/year) over 52 weeks by demographic subgroup is seen in Figure 11. Overall, the difference between the nintedanib and placebo groups was 40.95. The numbers are generally similar between females and males. There was less of a treatment difference in the over 65 years of age group category as compared to under 65. In addition, the treatment difference was not the same by race. White and Asian patients had a similar treatment difference that was consistent with the overall analysis, but the Black or African American subgroup of patients appeared to have less of a response to study drug. Definitive conclusions

[19] FDA-approved nintedanib labeling

regarding this observation are limited due to the small subgroup sample size. Finally, there was also difference in subgroup by region. Notably, the patient population in Canada and the United States only had a mean treatment difference of 10.22 mL/year vs the overall of 40.95 mL/year.

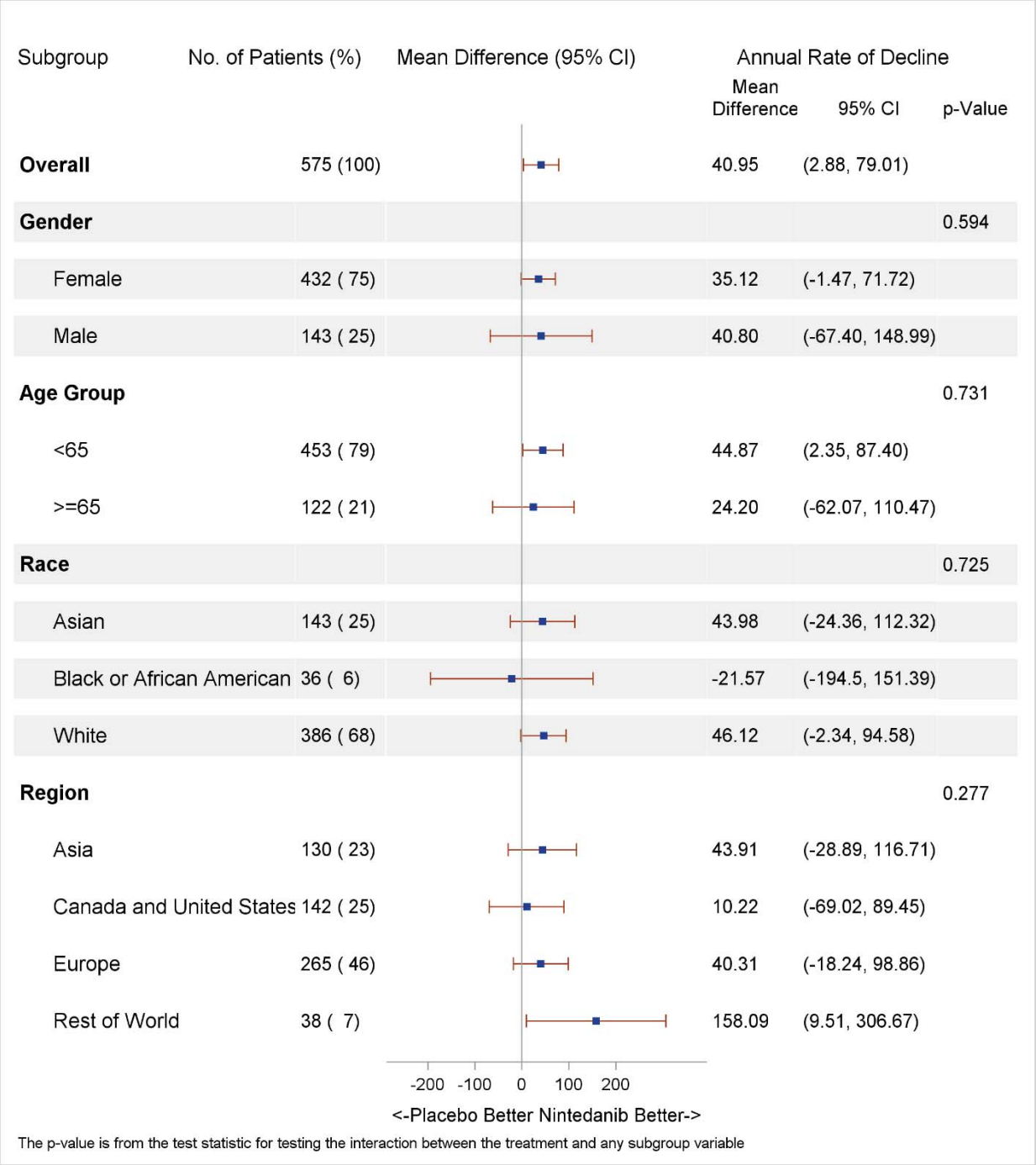
Other Special/Subgroup Populations

The protocol pre-planned subgroup analyses on SSc-ILD baseline disease characteristic subgroup factors included ATA status and SSc subtype (Figure 12).

To evaluate the influence of stable background immunosuppressive therapy to study treatment, the protocol pre-planned subgroup analyses also included mycophenolate mofetil/sodium use at baseline. A less robust treatment effect was observed in adjusted annual rate of decline in FVC in the subgroups of patients on MMF at baseline (treatment difference 26.6 mL/year). We also investigated the influence of baseline HRCT assessment patterns including ground glass opacities to nintedanib (Figure 12). The modeling approach was similar as that for the demographic subgroup analyses.

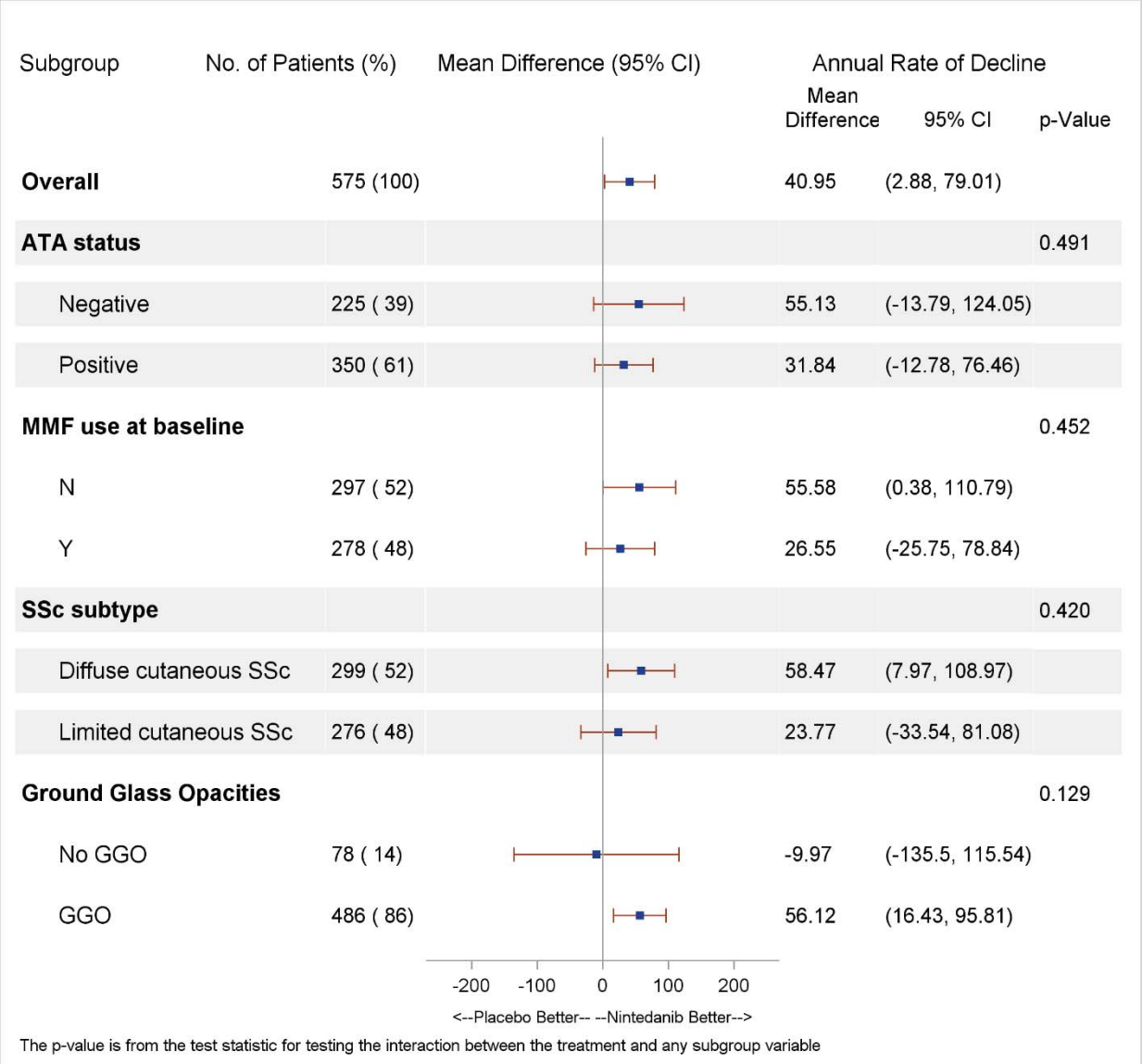
As clinical practice may differ across countries, the FDA review team also performed a subgroup analysis defined by both region (US and Canada, vs. Other than US and Canada) and baseline MMF use to evaluate the influence of stable background MMF use to study treatment by region (Figure 13). A less robust treatment effect was observed in adjusted annual rate of decline in FVC in the subgroups of patients from the US and Canada (treatment difference 10.2 mL/year). In the US and Canada subgroup, approximately 80% of the patients received MMF at baseline.

Figure 11. Forest Plot of the Rate of Decline in FVC (mL/year) Over 52 Weeks by Demographic Subgroup (Treated Set)



Abbreviations: No.: number; mL: milliliter; CI: confidence interval
Source: FDA Statistical Reviewer

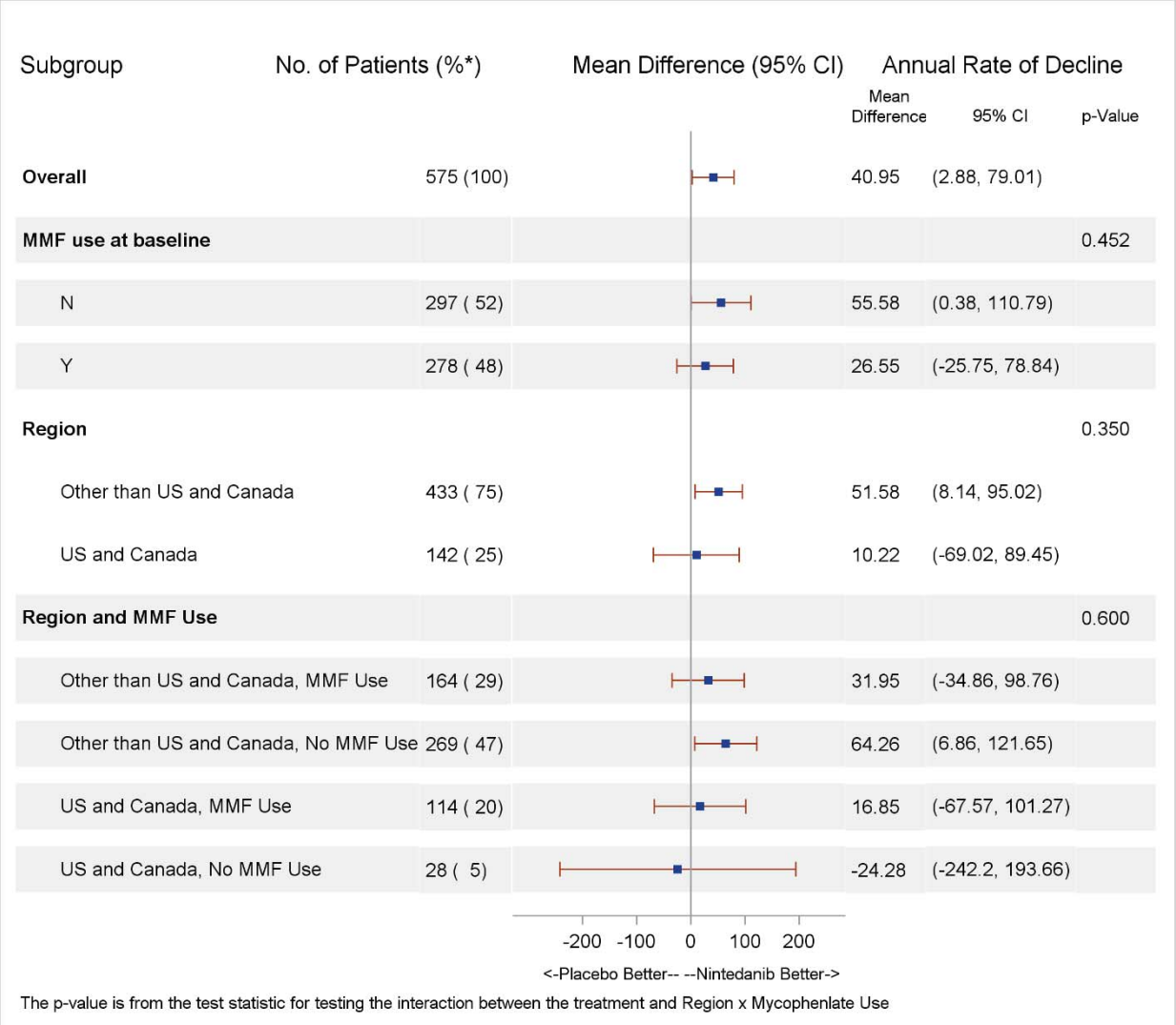
Figure 12. Forest Plot of the Rate of Decline in FVC (mL/year) Over 52 Weeks by Baseline Disease Characteristics Subgroup (Treated Set)



The p-value is from the test statistic for testing the interaction between the treatment and any subgroup variable

Abbreviations: No.: number; mL: milliliter; CI: confidence interval; MMF: Mycophenolate.
Source: FDA Statistical Reviewer

Figure 13. Forest Plot of the Rate of Decline in FVC (mL/year) over 52 weeks by Region by MMF Use Subgroup (Treated Set)



Abbreviations: No.: number; mL: milliliter; CI: confidence interval; MMF: Mycophenolate.
*: The common denominator N=576 was used in calculating the proportions of patients in each combination level defined by Region x MMF Use.
Abbreviation: MMF=Mycophenolate Mofetil.
Source: FDA Statistical Reviewer

Across the subgroup factors, there was no significant interaction between subgroups and treatment. However, lack of a significant treatment-by-subgroup interaction could be due to small subgroup sample size and should not be interpreted as evidence that no interaction exists.

Data up to 100 Weeks (maximum treatment duration in Study 1199.214)

As discussed in Section 8.1, efficacy and safety data were derived from the first 52 weeks of treatment. However, the protocol provided for individual patients to remain on blinded study

treatment up to 100 weeks, until the last patient completed 52 weeks of treatment (see also Figure 3). This resulted in a subgroup of patients enrolled earlier in the study to continue treatment beyond the primary timepoint and for some to complete 100 weeks of blinded treatment. The analyses of the 100-week data, summarized in Table 16, were exploratory. While there appears to be a separation between placebo and nintedanib treatment arms over the longer duration on treatment data only, there are methodological limitations, that preclude definitive conclusions regarding the long-term effect of nintedanib, (b) (4)

(b) (4)

Table 16. Rate of decline in FVC [mL/yr] Up to 100 Weeks of Treatment

FVC mL/yr	Nintedanib	Placebo	Treatment difference
TS (on and off treatment data)	-62	-86	24 (95% CI: -6, 53)
TS (on treatment data only)	-55	-94	39 (95% CI: 6, 72)

Source: NDA 205832/s12, Adapted from Summary of Clinical Efficacy

Efficacy Summary

The adjusted annual rate of decline in FVC over 52 weeks was lower in the nintedanib group (-52.4 mL/year) than in the placebo group (-93.3 mL/year), with a statistically significant treatment difference of 40.9 mL/year (95% CI: 2.9 to 79.0; p=0.035). The adjusted annual rate of decline in percent predicted FVC over 52 weeks was -1.4% predicted/year in the nintedanib group and -2.6% predicted/year in the placebo group; the adjusted difference between groups was 1.2% predicted/year (95% CI: 0.1 to 2.2; p=0.033). While the results for the primary endpoint were statistically significant based on the pre-specified analysis, the sensitivity analyses on missing data assumptions and responder analyses with various thresholds showed mixed results, mainly because the magnitude of the effect size was small. Differences of this magnitude did not result in improvement in measures of direct clinical benefit related to pulmonary involvement, such as SGRQ or FACIT-dyspnea score, at Week 52. Also, there were no differences in other disease-related secondary endpoints, number of digital ulcers, or HAQ-DI. There was also no improvement in mortality. Additionally, a less robust treatment effect was observed in adjusted annual rate of decline in FVC in the subgroups of patients on mycophenolate mofetil at baseline (treatment difference 26.6 mL/year) and patients from the U.S. and Canada (treatment difference 10.2 mL/year).

Data Quality and Integrity

In general, the quality of data submitted for review was adequate.

Integrated Review of Effectiveness

8.1.3. Assessment of Efficacy Across Trials

Not applicable. A single study was submitted in support of NDA 205832/s12.

8.1.4. Integrated Assessment of Effectiveness

Not applicable. A single study was submitted in support of NDA 205832/s12.

8.2. Review of Safety

8.2.1. Safety Review Approach

The assessment of safety is based on data from the single pivotal study, Study 1199.214, conducted in 576 patients with SSc-ILD, randomized 1:1 to treatment with nintedanib or placebo. Overall, the size of the safety database is adequate to assess the safety of nintedanib in SSc-ILD, in the context of the known safety profile in IPF.

All safety analyses were performed on the Treated Set (TS). The TS consisted of patients who were randomized and received at least one dose of study medication. The primary safety analysis was based on events occurring within the first 52 weeks of treatment (through Day 373). Additional supportive safety analyses were conducted for the whole study period, including the residual effect period, defined as 28 days after the last dose of study drug.

8.2.2. Review of the Safety Database

Overall Exposure

In Study 1199.214, 288 patients were exposed to nintedanib 150 mg BID and 288 patients received placebo. Over 52 weeks, the mean (SD) exposure was 10.52 (3.43) months in the nintedanib group and 11.35 (2.39) months in the placebo group. Similarly, over the whole study, the mean exposure was lower in the nintedanib group (14.51 months) as compared to the placebo group (15.70 months).

Exposure data during the 52-week treatment period are summarized in Table 17. A greater proportion of patients in the nintedanib group had duration of exposure ≤3 months and 3-6 months, while a greater proportion of placebo-treated patients had exposures > 12-14 months, reflecting the greater number of patients who discontinued from the nintedanib treatment group. See Table 6 for patient disposition. A greater proportion of patients in the nintedanib treatment group than in the placebo group had at least 1 dose reduction (40.6% and 4.5%, respectively) or at least 1 treatment interruption (37.8% and 11.5%, respectively). This likely reflects tolerability issues with nintedanib treatment. See discussion below of AEs leading to treatment interruption.

Table 17. Exposure to Study Drug Over 52 Weeks, Treated Set

	Placebo N=288	Nintedanib N=288
Duration of exposure [1] (months)		
Mean (SD)	11.35 (2.39)	10.52 (3.43)
Median (min, max)	12.21 (0.4, 12.2)	12.21 (0, 12.2)
Duration of exposure, [1] categories (months), (N, %)		
≤3	10 (3.5)	25 (8.7)
>3–6	9 (3.1)	16 (5.6)
>6–12	75 (26.0)	73 (25.3)
>12–14	194 (67.4)	174 (60.4)
Total exposure [patient years]	273.0	253.0
Patients with at least 1 dose reduction (N, %)	13 (4.5)	117 (40.6)
Patients with at least 1 treatment interruption, (N, %)	33 (11.5)	109 (37.8)

1 Duration of exposure over 52 weeks was defined from first study drug intake up to:
a. Last drug intake for patients who prematurely discontinued before 52 weeks (included) or
b. Week 52 (ie 372 days after first drug intake) for patients who did not prematurely discontinue the study drug before 52 weeks (included)
Adapted from Study 1199.214 CSR Table 10.5:1

Adequacy of the safety database

The sample size was appropriate for the population and objectives of the study. The types of safety assessments conducted were also consistent with reasonable monitoring for the known AEs of nintedanib and for this patient population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There were no specific concerns regarding data integrity and submission quality as they relate to the safety assessment.

Categorization of Adverse Events

The definitions used for adverse events (AEs) and serious AEs (SAEs) were per 21CFR 312.32. All AEs that occurred between the first dose of study drug until the last dose plus 28 days were considered 'treatment-emergent.' AEs that started before the first dose of study drug and worsened during the treatment period were also considered as 'treatment-emergent.' Adverse events occurring between the start of an interruption of study drug and the end of the interruption of study drug were considered 'off-treatment.'

Adverse events that occurred after the last dose of study drug plus 28 days were assigned to 'follow-up' or 'post-study.' The post treatment period was defined by the Applicant as follow-up period (occurring between last drug intake +29 days and beginning of post-study period) and

post-study period [occurring on or after last drug intake +29 days, date of completion +1 day, or date of informed consent in extension (whichever was latest)].

Adverse events of special interest were AEs relating to gastrointestinal perforation and hepatic injury. In addition to the specified adverse events of special interest, the study statistical analysis plan (TSAP) specified Gastrointestinal AEs (diarrhea, nausea, vomiting, dehydration, weight decrease, and decreased appetite) as AEs of particular note. The intensity of AEs was categorized as mild (awareness of signs or symptoms which are easily tolerated), moderate (enough discomfort to cause interference with usual activity), or severe (incapacitating or causing inability to work or to perform usual activities). In addition, AEs of diarrhea were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.

An independent adjudication committee reviewed all deaths to adjudicate cause to cardiovascular death, respiratory related death, non-cardiovascular/non-respiratory death, or undetermined cause of death. The adjudication committee also reviewed all adverse events categorized as major adverse cardiovascular events (MACE).

In Study 1199.214, a 4-point MACE definition was used, including any fatal event in system organ class (SOC) of cardiac disorders, any fatal event in SOC vascular disorders, any fatal or nonfatal event in SMQ 'myocardial infarction (broad)', and 'any fatal or nonfatal stroke'.

Routine Clinical Tests

Clinical laboratory evaluations included:
Hematology

- Red blood cell count, Hemoglobin, Hematocrit, Mean corpuscular volume, White blood cell count including differential, Platelet count

Biochemistry

- Aspartate aminotransferase, Alanine transaminase, Gamma-glutamyl transferase, Alkaline phosphatase, Creatine kinase, Lactate dehydrogenase, Total protein, Total bilirubin, Brain natriuretic peptide (BNP; only at Visits 2, 7, 9, and 12/EOT), Creatinine Glucose (non-fasting), Uric acid, Thyroid stimulating hormone (only at Visits 2, 7, 9, and 12/EOT), ß-Human chorionic gonadotropin (HCG; at Visit 2 only)

Electrolytes

- Sodium, Potassium, Calcium, Chloride, Inorganic phosphorus

Coagulation

- International normalized ratio, Partial thromboplastin time, Prothrombin time

Urinalysis

- Semi-quantitative measurements of: pH, Glucose, Erythrocytes, Leukocytes, Protein, Nitrite, Pregnancy testing (dipstick)

8.2.4. Safety Results

Deaths

In Study 1199.214, there were 19 deaths overall in the treated set, balanced by treatment group (Table 18). During the treatment period, there were 11 patients with treatment-emergent AEs (TEAEs) leading to death, including 6 patients (2.1%) in the nintedanib group and 5 patients (1.7%) in the placebo group. TEAEs that lead to death in the nintedanib group included 1 patient each with: arrhythmia, scleroderma renal crisis with thrombotic microangiopathy, acute lung injury, pneumonia, lung adenocarcinoma, and malignant mesothelioma. These were adjudicated as 2 CV deaths due to sudden cardiac death and ischemic stroke, 2 respiratory deaths due to pneumonia, and 2 non-CV/non-respiratory deaths. In the placebo group, the TEAEs that lead to death included 1 patient each with: cardiac arrest, dyspnea, acute myocardial infarction, pneumonia, and interstitial lung disease. The causes of death in the placebo group were adjudicated as 3 CV deaths due to sudden cardiac death and acute MI, and 2 respiratory deaths due to underlying ILD.

During the post treatment period, there were 4 AEs leading to death in each treatment arm. Deaths in patients randomized to the nintedanib group included 1 patient each with: chest pain, circulatory collapse, respiratory failure, and small cell lung cancer. These were determined by adjudication to be undetermined death, respiratory death due to other respiratory causes, respiratory death due to underlying ILD, and non-CV/non-respiratory death, respectively. The 4 post-treatment deaths in the placebo group were due to 1 patient each with: cardiac arrest, lung neoplasm malignant, septic shock and sudden death. These were determined by adjudication to be respiratory death/ underlying ILD, undetermined death, non-CV/non-respiratory death, and respiratory death.

Table 18. AEs Leading to Death over Entire Study by Preferred Term, Treated Set

	Treatment Period	*Post-Treatment Period*
Nintedanib	Acute lung injury	Chest pain
	Arrythmia	Circulatory collapse
	Lung adenocarcinoma	Respiratory failure
	Mesothelioma malignant	Small cell lung cancer
	Pneumonia	
	Scleroderma renal crisis/thrombotic microangiopathy	
Placebo	Cardiac arrest	Cardiac arrest
	Acute myocardial infarction	Lung neoplasm malignant
	Interstitial lung disease	Septic shock
	Pneumonia	Sudden death
	Dyspnea	

Treatment Period is between the first dose of study drug until the last dose plus 28 days.
Post-Treatment Period is 29 days and over, after last drug intake.
Adapted from Study 1199.214 CSR, Table 12.1.1:1 and Table 12.2.1:2

Overall, the types and frequencies of AEs leading to death were balanced by treatment group in the treatment-emergent and post-treatment periods. AEs leading to death by adjudicated cause were also similar between treatment groups.

Serious Adverse Events

Serious adverse events (SAEs) were reported by 69 patients (24%) in the nintedanib and 62 patients (21.5%) in the placebo group over the 52 week period. The most frequently reported SAEs were in the Respiratory, Thoracic, and Mediastinal Disorders system organ class (SOC), and were similar between treatment groups (nintedanib 9.4%, placebo 8.7%).

A greater proportion of nintedanib-treated patients had SAEs within the Infections and Infestations system organ class (SOC) compared to placebo-treated patients (6.6% and 3.5% respectively). This was largely driven by an increase in SAEs of pneumonia in the nintedanib group (2.8% vs. 0.3%).

SAEs within the Gastrointestinal Disorders system organ class (SOC) occurred in 11 nintedanib-treated patients (3.8%) on as compared to 5 placebo-treated patients (1.7%). Two patients (0.7%) in each treatment group had SAEs of diarrhea, while 2 patients (0.7%) in the nintedanib group had intestinal pseudo-obstruction, and 2 patients (0.7%) in the placebo group had vomiting. Other SAEs were singular by PT. There were 6 patients (2%) with SAEs within the hepatobiliary disorders SOC, including 1 patient (0.3%) in each group with drug-induced liver

injury, and 1 nintedanib patient (0.3%) each with hepatocellular injury and liver disorder. All patients recovered after treatment discontinuation or dose reduction. Other SAEs in the hepatobiliary disorders SOC included bile duct stone and cholecystitis, each in 1 nintedanib-treated patient (0.3%).

Serious cardiovascular events were similar between the treatment groups. In the nintedanib group there was 1 patient (0.3%) with MACE of arrhythmia, while in the placebo group there were 3 patients (1%) with MACE events of acute myocardial infarction, cardiac arrest, and cerebral infarction.

SAEs during the 52-week treatment period occurring in > 1% of patients in either treatment group are summarized by PT in Table 19. SAEs that were more frequent in the nintedanib group than in the placebo group were pneumonia (2.8% vs. 0.3%), interstitial lung disease (2.4% vs. 1.7%), pulmonary arterial hypertension (1.0% vs. 0), and acute kidney injury (1.0% vs. 0.3%).

Three patients (1%) developed acute kidney injury in the nintedanib group, as compared to 1 patient in the placebo group (0.3%). Review of the narratives identified one nintedanib-treated patient with scleroderma renal crisis, one nintedanib-treated patient who developed ANCA positive vasculitis following nintedanib discontinuation, one nintedanib-treated patient with acute kidney injury in setting of diarrhea, hypovolemia, hypotension, with fall complicated by subarachnoid hemorrhage, and one placebo-treated patients who experienced acute respiratory failure complicated by acute kidney injury. Of the 4 SAEs of acute kidney injury, only the SAE in the setting of fall complicated by subarachnoid hemorrhage was considered related to study drug by the investigator. SAEs of renal failure (PT) as well as SMQ analysis for chronic kidney disease [broad] were similar between treatment groups.

Overall, aside from pneumonia, the types and frequencies of SAEs were generally balanced by treatment group in the treatment-emergent period.

Table 19. Serious Adverse Events by Preferred Term for > 1% of Patients in Either Treatment Group Over 52 Weeks

	Placebo N=288 (n, %)	Nintedanib N=288 (n, %)
Patients with ≥1 SAE	62 (21.5)	69 (24)
Interstitial lung disease	5 (1.7)	7 (2.4)
Pneumonia	1 (0.3)	8 (2.8)
Pulmonary hypertension	4 (1.4)	4 (1.4)
Dyspnea	5 (1.7)	3 (1.0)
Pulmonary fibrosis	4 (1.4)	3 (1.0)
Systemic sclerosis pulmonary	3 (1.0)	2 (0.7)
Acute kidney injury	1 (0.3)	3 (1.0)
Pulmonary arterial hypertension	0	3 (1.0)

Adapted from Study 1199.214 CSR, Table 15.3.1.1.1: 17

Dropouts and/or Discontinuations Due to Adverse Effects

The proportions of patients with AEs leading to drug discontinuation over 52 weeks was 16% in the nintedanib group and 8.7% in the placebo group. The most frequently reported AEs leading to drug discontinuation in the nintedanib group were diarrhea (7%), nausea (2%), and vomiting (1.4%). In the placebo group, the most common reasons for drug discontinuation were interstitial lung disease in 3 patients (1%). Other AEs leading to drug discontinuation in the placebo group occurred in single patients.

Over 52 weeks, AEs leading to dose decrease occurred in 98 patients (34%) in the nintedanib group and 10 patients (3%) in the placebo group. In the nintedanib group, the most common reasons for decrease of dose was diarrhea (22%), nausea (2%), vomiting (2%), and elevation in alanine aminotransferase (1.4%). The most common reason for decrease of dose in the placebo group was diarrhea in 3 patients (1%).

AEs leading to treatment interruptions occurred more frequently in the nintedanib group (79%) than the placebo group (69%). The most frequent AEs leading to treatment interruptions were diarrhea (41% nintedanib, 19% placebo) and upper abdominal pain (10% nintedanib, 10% placebo).

The proportions of patients with AEs leading to drug discontinuation, dose decrease, and treatment interuptionwere higher in the nintedanib group than in the placebo group. The most frequently reported AE leading to drug discontinuation, dose decrease, and treatment

interruption in the nintedanib group was diarrhea, consistent with the known safety profile of nintedanib.

Treatment Emergent Adverse Events and Adverse Reactions

Treatment-emergent AEs (TEAEs) included all AEs with an onset after the first dose of study medication up to the end of the residual effect period (28 days) were considered on-treatment. There were 283 (98%) of patients in the nintedanib group and 276 (96%) of patients in the placebo group who had TEAEs.

Overall, the most common TEAEs by PT were diarrhea (nintedanib 76% vs. placebo 32%), nausea (nintedanib 32% vs. placebo 14%), vomiting (nintedanib 25% vs. placebo 10%). Other TEAEs that occurred more frequently in patients treated with nintedanib than placebo were skin ulcer (18% vs 17%, respectively), abdominal pain including abdominal pain, abdominal pain upper, abdominal pain lower, and esophageal pain (18% vs. 11%), liver enzyme elevation including alanine aminotransferase increased, gamma-glutamyltransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, blood alkaline phosphatase increased, transaminase increased, and hepatic function abnormal (13% vs. 3%), and weight decreased (12% vs. 4%).

Severe AEs occurred in a greater proportion of patients in the nintedanib group (18.1%) compared to placebo (12.5%). The most common severe AEs reporting more frequently in the nintedanib group were diarrhea (4.2% vs. 1.0% in the nintedanib and placebo groups, respectively), pneumonia (2.1% vs. 0.3%), upper abdominal pain (1.0% vs. 0.3%), vomiting (1.0% vs. 0.3%), while dyspnea (0.3% vs. 1.4%) and interstitial lung disease (0.3% vs. 1.0%) were more frequently reported in the placebo group.

The most frequently reported TEAEs in the nintedanib treatment group compared to placebo included TEAEs of gastrointestinal disorders and liver enzyme abnormalities. These are consistent with the known safety profile of nintedanib in IPF.

Laboratory Findings

There were no notable differences between the nintedanib and placebo groups in mean hematology, coagulation, electrolyte, biochemistry, and urinalysis parameters or in patients with possibly clinically significant abnormalities in these parameters over 52 weeks.

More patients in the nintedanib group had elevations in liver enzymes, with any ALT or AST elevation > 3 times ULN reported in 14 patients (4.9%) compared to 2 patients (0.7%) in the placebo group. Individually, ALT elevations ≥ 3x ULN were more frequently reported in nintedanib treated patients than placebo (3.5% vs. 0.7% respectively); similarly, AST elevations ≥ 3x ULN were also more frequently reported in the nintedanib group (2.8% vs. 0.3%). No patients had liver enzyme elevations ≥ 3x ULN concurrent with an elevation in bilirubin ≥ 2x ULN that met Hy's law criteria.

Seven patients (2.4%) in the nintedanib group and one patient (0.3%) in the placebo group met protocol-specified criteria for hepatic injury: ALT and/or AST ≥ 8x ULN (1 placebo-treated patients), ALT and/or AST ≥ 3xULN and unexplained eosinophilia (3 nintedanib-treated patients), ALT and/or AST ≥ 3x ULN and appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever and/or rash within 7 days of abnormal lab value, (4 nintedanib-treated patients). In the patients in the nintedanib group, signs of hepatic injury occurred within the first month of treatment; most patients could resume nintedanib at a reduced dose and continue treatment with stable liver function tests.

Vital Signs

There were no significant changes in mean blood pressure or pulse over 52 weeks. In Study 1199.214, a marked increase in systolic blood pressure was defined as >150 mmHg and increase ≥25 mmHg above baseline, in diastolic blood pressure >90 mmHg and increase >10 mmHg above baseline, and in pulse rate >100 bpm and increase >10 bpm above baseline. Over 52 weeks, in the nintedanib group, 6% of patients had an increase in systolic blood pressure vs 2% in placebo meeting this criteria, while15% of the nintedanib patients had an increase in diastolic blood pressure vs 6% of patients in placebo met the criteria for marked increase. In addition, 15% of nintedanib patients had a marked increase in pulse rate vs 12% of placebo patients. A greater proportion of patients on nintedanib had marked changes in blood pressure and pulse. Hypertension is a labeled adverse reaction in the nintedanib product labeling.

See section Analysis of Submission-Specific Safety Issues 8.2.5 for discussion of body weight changes over 52 weeks.

Immunogenicity

Not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

Adverse events of special interest were defined as hepatic injury and gastrointestinal perforations. Gastrointestinal AEs, i.e. diarrhea, nausea, vomiting, as well as dehydration, weight decrease, and decreased appetite were defined as AEs of particular note in the TSAP. In addition, arterial thromboembolic events and bleeding events, both labeled warnings and precautions of nintedanib treatment are reviewed below. These submission-specific safety issues over 52 weeks are shown in Table 20.

Table 20. Study 1199.214: Submission-Specific Safety Issues Over 52 Weeks

	Placebo N=288 (n, %)	Nintedanib N=288 (n, %)
Elevated liver enzymes	9 (3)	38 (13)
DILI	1 (0.3)	1 (0.3)
Diarrhea	91 (32)	218 (76)
Nausea	39 (14)	91 (32)
Vomiting	30 (10)	71 (25)
Arterial thromboembolic events	2 (0.7)	2 (0.7)
Bleeding	24 (8)	32 (11)
GI Perforation	1 (0.3)*	0

Adapted from Study 1199.214 CSR, Table: 15.3.1.1.1: 5 and Table: 15.3.1.1.5: 1
DILI: drug induced liver injury
GI: Gastrointestinal
*GI perforation based on SMQ analysis, PT anal abscess

Hepatic Injury

Elevated liver enzymes and patients meeting protocol-specified criteria for hepatic injury are discussed in Laboratory Findings. As noted above, 7 patients (2.4%) in the nintedanib group and 1 patient (0.3%) in the placebo group met protocol-specified criteria for hepatic injury. One patient (0.3%) in both the nintedanib and placebo groups had SAEs of drug induced liver injury (DILI):

- 59 year old Asian female with SSc-ILD who presented to hospital for a scheduled visit and based on her laboratory values, on the 16th day since the 1st intake of the study drug (nintedanib), she was reported to have drug-induced liver injury. She did not have symptoms of hepatic injury.
- 46 year old Asian female with SSc-ILD, on the 127th day since the 1st intake of the study drug (placebo), the patient had acute worsening of liver function without any recent symptoms of hepatic injury. Subsequently, a serious adverse event of drug-induced liver injury was reported.

Both patients recovered after treatment discontinuation.

GI perforation

There were no AEs of GI perforation reported during the first 52 weeks. SMQ 'gastrointestinal perforation' analysis idenitifed 1 patient in the placebo group (PT anal abscess). There were no GI perforations in the nintedanib group over the first 52 weeks, however, one patient in the nintedanib group had a large intestine perforation (sigmoid, rectosigmoid perforation) in the post-treatment period, 42 days following discontinuation of treatment. The AE was complicated by a diagnosis of anti-neutrophil cytoplasmic antibody positive vasculitis, hospitalization in the

intensive care unit, enterococcus faecium infection, and clostridium difficile infection. The AE of GI perforation was assessed by the investigator as not related to the study drug.

Gastrointestinal AEs
Gastrointestinal AEs, including diarrhea, nausea, and vomiting were more frequently reported by patients treated with nintedanib than placebo. This is consistent with the known safety profile of nintedanib. See additional discussion under the Serious Adverse Events and Treatment Emergent Adverse Events and Adverse Reactions sections above.

Weight decrease
Over 52 weeks, 20.5% of patients in nintedanib group lost > 10% of their body weight at some point during the first 52 weeks of treatment vs 4.5% of the placebo group. In the nintedanib group, 47% of patients had weight loss of at least 5% of their body weight vs 19% in the placebo group. Patients in the nintedanib group more frequently had AEs of weight decreased (nintedanib 12%, placebo 4%) and decreased appetite (nintedanib 9.4%, placebo 4.2%), while AEs of dehydration were balanced by treatement group (nintedanib 0.3%, placebo 0.3%).

Adjudicated MACE and arterial thromboembolic events
The proportion of patients with AEs adjudicated as MACE events over 52 weeks was balanced between the treatment groups (nintedanib 1.4%, placebo 1.7%). The types of MACE events are discussed under SAEs above. The proportions of patients with arterial thromboembolic events over the 52 week period were also balanced between the treatment groups (nintedanib 0.7%, placebo 0.7%).

Bleeding events
Bleeding events were more frequently reported in nintedanib-treated patients (nintedanib 11%, placebo 8%). The most common bleeding events in both groups were epistaxis (nintedanib 2.8% vs. placebo 3.8%) and skin contusion (nintedanib 2.4% vs. placebo 1.0%). In addition, the nintedanib group had 5 patients (2%) with rectal hemorrhage and two (0.7%) with hematochezia. In the placebo group, there was 1 patient (0.3%) with hematochezia. Central nervous system (CNS) bleeding occurred in 2 patients in the nintedanib group and no patients in the placebo group. Events of CNS bleeding included 1 patient in the nintedanib group who had cerebral amyloid angiopathy with cerebral microhemorrhage and 1 patient who had diarrhea due to nintedanib, developed hypovolemia and hypotension, followed by syncope and a fall that caused subarachnoid hemorrhage.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

Over 52 weeks, safety analysis by gender showed that the incidence of AEs was higher in females than in males in both the nintedanib and placebo groups. However, SAEs and fatal SAEs Occurred more frequently in male patients in both treatment groups. The incidence of other significant AEs (ICH E3) was higher in females than in males in both treatment groups. The incidence of diarrhea was similar between males and females in both treatment groups, however the incidence of nausea and vomiting was higher in the females. Adverse events of "hepatic disorders combined" were also reported more frequently for females than for males in the nintedanib group (19.0% vs. 11.9%).

Safety analysis by age (< 65 and ≥ 65 years) was generally similar over 52 weeks, including number of patients with AEs and SAEs. Patients ≥ 65 years had a greater incidence of AEs leading to discontinuation and Other significant AEs (ICH E3). While AEs within the SOC gastrointestinal disorders were balanced between the age groups, SAEs in this SOC were more frequently reported for older patients than younger patients. Adverse events of "hepatic disorders combined' was higher for older than for younger patients in the nintedanib group (23.4% vs. 15.6%).

Over 52 weeks, safety analysis by race (Asian, Black/African American, and White) showed that Black/African American patients had a higher incidence of SAEs (40% in the nintedanib group and 44% in the placebo group) vs Whites (22% in nintedanib and 23% in placebo) and Asians (26% in nintedanib and 15% in placebo). However, conclusions are limited based on the relatively small number of Black/African American patients. Adverse events of "hepatic disorders combined" in the nintedanib group were reported more frequently in Asians (35.5%) than in Blacks/African Americans (15.0%) and Whites (12.4%). In addition, the 2 DILI cases in the trial were reported for Asian patients (1 in each treatment group).

Safety analysis was analyzed by body weight (≤65 kg, > 65 kg) over 52 weeks. Overall AEs and SAEs were balanced by weight group. There were small numerical differences between groups in AEs leading to discontinuation and Other significant AEs (ICH E3), with a greater proportion of patients with events in the lower weight group. Adverse events within the 'hepatic disorders combined' safety topic were more frequently reported in patients ≤ 65 kg than > 65 kg in both treatment groups (nintedanib 20% vs. 15.5%, placebo 20.0% vs. 6.8%).

Safety analyses by region was generally similar for: Asia, Canada/United States, Europe, and the Rest of World including number of patients with AE. The incidence of diarrhea was higher in the nintedanib group in Canada/ United States (91% vs 81% in Asia and 67% in Europe). Patients in Europe had slightly higher incidence of SAEs on nintedanib (27% vs 20% in Asia and Canada/United States. Incidence of death was also slightly higher in Europe for patients on nintedanib (2.1% vs 1.7% in Asia and 1.4% in Canada/United States).

For the subgroup of patients on MMF at baseline, overall AEswere similar between the treatment groups across the subgroups. SAEs were numerically higher in the nintedanib treated

patients on MMF at baseline (25.9%) vs. the nintedanib treated patients not on MMF at baseline (22.1%), however a greater proportion of placebo-treated patients not on MMF at baseline had SAEs (27.0%) vs. placebo-treated patients on MMF at baseline (15.7%). AEs leading to discontinuation and Other significant AEs (ICH E3) were more frequent in the subgroup not on MMF at baseline. With regard to the submission specific safety concerns, there was overall less hepatic impairment and elevation in liver enzymes in the MMF subgroup. Gastrointestinal disorders were similar between the groups; however, there was less weight decrease in the MMF group. There were fewer serious adverse events of pneumonia in the MMF subgroup (3 vs. 6 patients); however, there were slightly more adverse events of pneumonia in the MMF subgroup (10 vs. 8 patients). Bleeding events were slightly higher in the MMF subgroup (25 vs. 31 patients). Adverse events of SMQ arterial thromboembolic events were reported in 3 patients in the MMF subgroup (1 mesenteric artery stenosis, 1 peripheral arterial occlusive disease, and 1 thrombotic microangiopathy) and 1 patient not on MMF with an acute myocardial infarction.

The currently approved nintedanib labeling notes that patients with low body weight, Asian and female patients may have a higher risk of elevations in liver enzymes. Nintedanib exposure increased with patient age, which may also result in a higher risk of increased liver enzymes. In Study 1199.214, increased "hepatic disorders combined" were observed in females, older patients, and Asian patients. This is consistent with the known safety profile of nintedinab.

8.2.8. Specific Safety Studies/Clinical Trials

Not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No information regarding human carcinogenicity is included nor required for this supplement.

Human Reproduction and Pregnancy

There is no new human reproduction and pregnancy data is included nor required for this supplement.

Pediatrics and Assessment of Effects on Growth

Not applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable.

Expectations on Safety in the Postmarket Setting

No specific REMS or postmarket study for the purposes of evaluating safety have been recommended.

8.2.11. Integrated Assessment of Safety

Not applicable, a single study was conducted in SSc-ILD.

8.3. Statistical Issues

The main review issue focused on the robustness of the primary analysis results to deviations from the strong and unverifiable missing-at-random assumption. As the pattern mixture sensitivity analyses assuming certain missing not at random assumptions showed a lack of robustness in the primary analysis result and the tipping point analysis exploring a broader space of assumptions did not provide a clear robustness of the primary analysis result and necessitated a further clinical interpretation, the Applicant proposed a post hoc, second tipping point analysis plan and submitted with the requested tipping point analysis results. The Applicant's rationale was:

At week 52, 31 (11%, 31/288) patients from placebo arm and 47 (16%, 47/288) patients from nintedanib arm had missing data during the 52 week time window (from day 310 to day 373) which was pre-specified in the trial statistical analysis plan. Among these patients, 12 of 31 and 16 of 47 patients in the placebo and nintedanib group, respectively, actually had an FVC assessment after the week 52 time window. As observed data >= 52 weeks after start of treatment was available for these patients (and not missing), this data can be used as their 52 week assessment and does not need to be imputed based on data observed in other patients. Therefore, the corresponding tipping point analysis was performed in the following way:

> *In order to use all observed data, a second tipping point analysis was performed which used the first available assessment after day 373 for the missing 52 week assessment (28 patients) and only imputed data for the remaining 50 patients with missing FVC assessments at 52 weeks and beyond (no available later FVC assessment).*

During the FDA Arthritis Advisory Committee (AC) Meeting discussion, the Applicant refined the proposal and showed on site preliminary analyses results. The proposed analysis plan is:

For 24 out of the 28 patients (14 in the nintedanib group and 10 in the placebo group), the first FVC measurement after week 52 occurred no later than 28 days after the end of the week 52 time window, i.e. these patients had an FVC assessment between day 374 and day 401. Tipping point analyses including observed FVC data beyond 52 weeks for these 24 patients will be presented as supportive post hoc analysis.

Based on the expanded Week 52 window, the FDA review team requested three analyses after the AC meeting: repeating the primary analysis, the pattern mixture analyses, and the tipping point analyses with the expanded dataset.

Table 21 summarizes the primary analysis and post hoc analysis results side by side, with the post hoc analysis repeating the primary analysis using the expanded dataset. The treatment difference is now 43 mL/Year, while the primary analysis result was 41 mL/Year. The associated p-value is 0.026, as compared to 0.035.

Table 21. Annual Rate of Decline in FVC in mL Primary Analysis (over 52 weeks, Treated Set) and Post hoc (52 Weeks + 28 Days for missing data, Expanded Set)

	Primary (52 Weeks)		Post hoc (52 Weeks + 28 Days)	
	Placebo (N=288)	Nintedanib (N=288)	Placebo (N=288)	Nintedanib (N=288)
Number Analyzed	288	287	288	287
Adjusted Rate of Decline (mL/Year)	-93 (14)	-52 (14)	-94 (13)	-51 (14)
Nintedanib vs. Placebo				
Difference (SE)		41 (19)		43 (19)
95% CI		3, 79		5, 80
p-value		0.035		0.026

Abbreviations: N: sample size in Treated Set; SE: standard error; CI: confidence interval
Source: FDA Statistical Reviewer

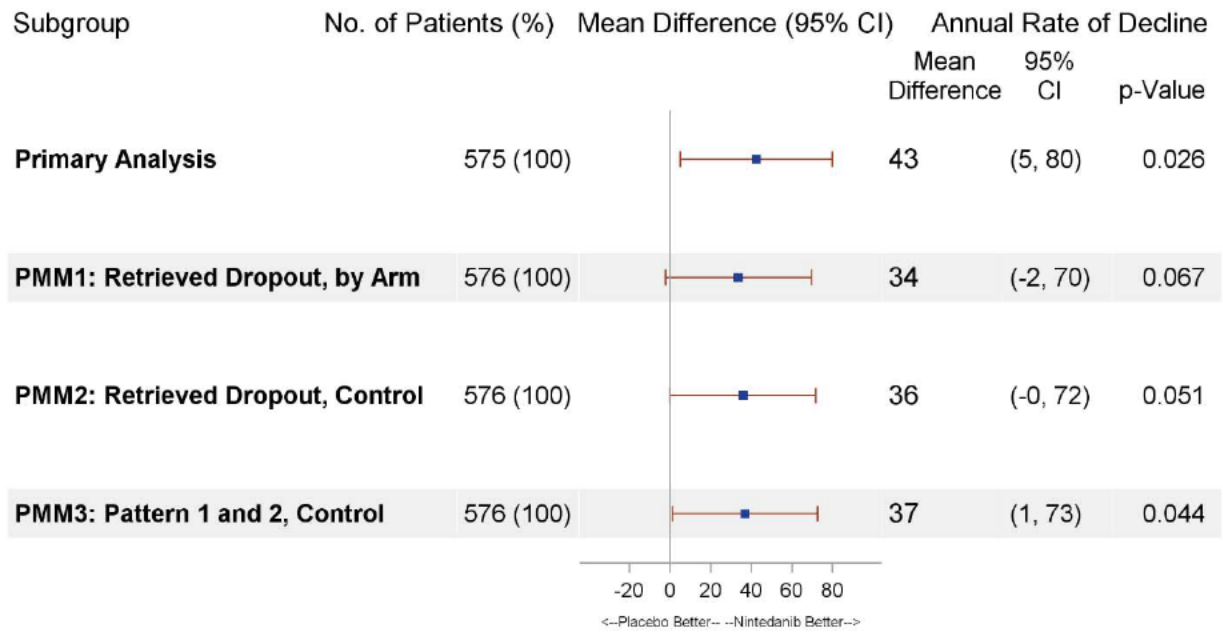
The original PMM analysis results are displayed in Table 22 side-by-side with the analyses performed on the expanded dataset. While there was no significant treatment effect in any of the three original PMM analyses, post hoc analyses on the expanded dataset failed on PMM1 (p-value = 0.067) and just failed on PMM2 (p-value = 0.051), but showed statistical significance on PMM3 (p-value = 0.044). Of note, among the three pattern mixture models, PMM1 gives an estimator which is more aligned with the treatment policy estimand effect size estimate in that: missing data for patients who were alive were imputed using retrieved dropout data from the same treatment arm; missing data for patients who were deceased were imputed using the worse half of the retrieved dropout data from the placebo arm. Figure 14 displays the PMM approach estimated effect sizes and their associated confidence intervals based on the expanded dataset.

Table 22. Pattern Mixture Modeling Approaches Pre-planned (over 52 weeks, Treated Set) vs. Post hoc (52 Weeks + 28 Days for missing data, Expanded Set)

	Pre-planned 52 Weeks			Post hoc (52 Weeks + 28 Days)		
	Mean Difference (mL/Year)	95% CI (mL/Year)	P-value	Mean Difference (mL/Year)	95% CI (mL/Year)	P-value
Nintedanib vs. Placebo						
PMM1: Retrieved Dropout, by Arm	30	-6, 66	0.105	34	-2, 70	0.067
PMM2: Retrieved Dropout, Control	33	-3, 69	0.074	36	-0, 72	0.051
PMM3: Pattern 1 and 2, Control	34	-2, 70	0.064	37	1, 73	0.044

Abbreviations: N: sample size in Treated Set; SE: standard error; CI: confidence interval
Source: FDA Statistical Reviewer

Figure 14. Forest-plot for Rate of Decline in FVC [mL/Year] over the 52 Weeks + 28 Days for missing Data Sensitivity Analyses (Expanded Set)



Abbreviations: No.: Number; PMM: pattern mixture model; CI: confidence interval
Source: FDA Statistical Reviewer following the Applicant's proposed analyses

Table 23 summarizes the tipping point analysis results based on the expanded dataset. Again, the body of the table provides p-values for the comparisons for the nintedanib group to the

placebo group for the corresponding shifts. The blue boxed cell in the table, corresponds to shifts of 0 in both arms, which is analogous to the primary analysis under the missing at random assumption. The pink shaded region shows shifts which are sufficient to "tip" the rate of decline conclusion; that is, the results are no longer statistically significant at 0.05 level. The blue shaded region shows cases where significance was maintained. The red boxes correspond to a relative shift of 45 mL/year in favor of placebo. Based on the expanded dataset, we saw a treatment effect of about 43 mL/year, if the dropouts in nintedanib are assumed to progress at the rate seen in placebo, then nintedanib will still have a significant effect in the overall trial.

Table 23. Annual Rate of Decline in FVC in mL over the 52 Weeks + 28 Days for missing Data, Tipping Point Analysis (Expanded Set)

p-values		Shift in Placebo (Change in mL/Year)											
		-60	-45	-30	-15	0	15	30	60	75	90	105	120
Shift in Nintedanib (Change in mL/Year)	-120	0.049	0.052	0.055	0.059	0.062	0.066	0.069	0.073	0.077	0.082	0.086	0.091
	-105	0.044	0.047	0.050	0.052	0.056	0.059	0.062	0.066	0.070	0.074	0.078	0.082
	-90	0.039	0.042	0.044	0.047	0.050	0.053	0.056	0.059	0.063	0.066	0.070	0.074
	-75	0.035	0.037	0.039	0.042	0.044	0.047	0.050	0.053	0.056	0.059	0.063	0.067
	-60	0.031	0.033	0.035	0.037	0.039	0.042	0.045	0.047	0.050	0.053	0.056	0.060
	-45	0.027	0.029	0.031	0.033	0.035	0.037	0.040	0.042	0.045	0.048	0.050	0.054
	-30	0.024	0.026	0.027	0.029	0.031	0.033	0.035	0.038	0.040	0.042	0.045	0.048
	-15	0.021	0.023	0.024	0.026	0.028	0.029	0.031	0.033	0.036	0.038	0.040	0.043
	0	0.019	0.020	0.021	0.023	0.024	0.026	0.028	0.030	0.032	0.034	0.036	0.038

Abbreviation: mL: milliliter.
Each cell contains p-value.

While we typically consider post hoc analysis exploratory as they lack the statistical rigor of a pre-planned analysis for providing confirmatory evidence, in this unique study design setting, there were 28 patients who were on study treatment at Week 52 but missed the pre-defined week 52 efficacy assessment window. In all subsequent pre-planned imputation based sensitivity analyses, this portion of patients (~1/3 of the total missing) were treated as if they had outcome similar to either patients off treatment or patients on placebo, this is a relatively harsh penalty for the study drug. With the expanded week 52 window approach, proposed by the Applicant, post sNDA submission, FVC data for 24 of the 28 patients were used in the analyses, rather than imputation of these data as missing. From this perspective, this post hoc analysis does have its merits to support the primary analysis and avoid reliance on imputations for missing data assumptions.

8.4. Conclusions and Recommendations

8.4.1. Statistical Review Conclusion and Recommendation

Based on the study statistical analysis plan: the primary analysis result was statistically significant; the pattern mixture sensitivity analyses assuming certain missing not at random assumptions showed a lack of robustness in the primary analysis result and the tipping point analysis exploring a broader space of assumptions did not provide a clear robustness of the primary analysis result and necessitated a further clinical interpretation. Results from secondary endpoints were not supportive.

Applying the primary and sensitivity analyses to the expanded dataset, we found: treatment effect was slightly larger (43 mL/Year from the expanded dataset vs. 41 mL/Year from the 52 Week data); among the three PMM approaches, the PMM1 approach, an estimator of treatment effect relatively better aligned with the treatment policy estimand, failed significance test with a p-value of 0.067; the PMM2 approach just failed significance test with a p-value of 0.051 and the PMM3 sensitivity analysis was significant with a p-value of 0.044; the tipping point analysis results support robustness of the primary analysis result.

All the above sensitivity analyses were aligned to a certain degree with estimating the treatment policy estimand. Although all three PMM analyses on the expanded dataset lean toward supporting the primary analysis compared to those on the original dataset, we still see failures to obtain statistical significance in two of the three sensitivity analyses, after using data in a post hoc sensitivity analysis.

Another limitation in strength of efficacy is regarding long term treatment effect, the assessment of which was not powered by the study design and exploratory analyses of which showed mixed results.

In summary, the primary statistical reviewer considers the program had limitations in both study design and analyses; the totality of evidence provided by the clinical development program is yet to demonstrate the expected substantial evidence of efficacy in supporting the treatment policy estimand in general. There could be ways to mitigate the limitations, for example, a subsequent study to address the above limitations, or a refinement of the study estimand and patient population to patients who can tolerate the drug.

In this complex disease setting, this primary statistical reviewer defers the approval decision making to the clinical colleagues.

It is the statistical team leader's view that although the treatment effect seen in the primary endpoint is small and not consistently supported by accepted sensitivity analyses, the statistically significant difference was demonstrated with FDA-recommended treatment policy strategy to handle intercurrent event of treatment discontinuation and to include off-treatment data in the analysis and could support a demonstration of efficacy sufficient for approval. In

addition, this lung function benefit was supported by several post hoc but not data-dredging analyses using the expanded dataset including non-missing post-Week 52 within 4 weeks.

It is the view of the acting director of Biometrics 2 that while the data from this clinical trial does not, on its own, provide substantial evidence of a treatment effect, when considered with the results from studies in related indication of IPF for which nintedanib is approved, a treatment effect in SSc-ILD appears real and can support approval for the sought indication.

8.4.2. Clinical Review Conclusion and Recommendation

The Applicant conducted a single clinical study in SSc-ILD, Study 1199.214, which demonstrated a statistically significant lower adjusted annual rate of decline in FVC with nintedanib (-42 mL/year) compared with placebo (-93 mL/year) over 52 weeks (treatment difference 40.9 mL/year) based on the pre-specified analysis of the primary endpoint. The adjusted annual rate of decline in FVC in percent predicted over 52 weeks was also lower in the nintedanib group (-2.6%/year) than in the placebo group (-1.4%/year), with a treatment difference of 1.2%/year. The observed decrease in annual rate of FVC decline was not supported by improvement in the secondary endpoints, including other measures of pulmonary involvement such as SGRQ, FACIT-dyspnea score, and DL_{CO}, measures of systemic sclerosis disease activity such as mRSS or number of digital ulcers, or measures of physical function including HAQ-DI.

In evaluating the clinical significance of the treatment effect of a lower rate of decline in FVC by 40.9 mL/year, the clinical team considered the prior experience with nintedanib in a distinct but related chronic progressive fibrosing lung disease, IPF. In the IPF program, supported by three randomized controlled studies, nintedanib has demonstrated a consistent reduction in the rate of decline in FVC, the primary endpoint in the SSc-ILD study. The IPF program was large enough to also demonstrate that decline in FVC results in clinical benefit, including a mortality benefit. FVC is used in clinical practice to monitor and guide treatment decisions regarding the management of restrictive lung disease, including IPF and SSc-ILD. This additional contextual information supports the use of FVC as a clinically meaningful primary endpoint in SSc-ILD to support traditional approval of nintedanib in SSc-ILD.

While the treatment difference observed in the SSc-ILD study was less than that in the nintedanib IPF program, which ranged from 94-131 mL/year, as compared to 40.9 mL/year in Study 1199.214 due to faster rate of decline in IPF (-191 to -240 mL/year in IPF placebo group vs. -93 mL/year in SSc-ILD placebo group), the relative difference in FVC decline comparing nintedanib to placebo was similar between the IPF and SSc-ILD programs (49% and 44%, respectively). Thus, it is reasonable to expect that the observed relative reduction in the annual rate of decline in FVC in SSc-ILD may also result in treatment effect on long-term clinical outcomes. However, given the slower rate of progression in SSc-ILD, as compared with IPF, demonstrating a clinical benefit on endpoints, such as mortality, will require a longer and larger clinical program in SSc-ILD which the Division considered to be challenging to design and execute due to the rarity of the condition. The effect of nintedanib on the lung function and

clinical outcomes has been demonstrated in IPF using study design comparable to the one supporting the SSc-ILD application. Based on the prior experience in IPF, and in the context of SSc-ILD being a rare disease, the clinical team concludes that this single study in SSc-ILD is supported by the available data from nintedanib IPF program to provide substantial evidence of efficacy to support a regulatory action.

The safety of nintedanib in SSc-ILD is generally consistent with the established safety profile of nintedanib in IPF which includes risks of gastrointestinal disorders and liver toxicity. Deaths and SAEs were balanced between the treatment groups. In the SSc-ILD population, there were an increased number of serious infections, driven by an increase in pneumonia in the nintedanib treatment group. There were more AEs leading to drug decrease and discontinuation in the nintedanib group which were mostly due to gastrointestinal events, consistent with the known safety profile of nintedanib. While infectious and gastrointestinal side effects need to be considered in patients with SSc-ILD who may be at increased risk of these events due to underlying disease and other concomitant treatments, these risks are also associated with available standard of care treatments. These risks can be adequately managed through labeling.

In summary, SSc-ILD is a rare and serious disease associated with high morbidity and mortality. It is also a disease with high unmet need for new therapies. Based on the totality of the data, including the decrease in adjusted annual rate of decline in FVC with nintedanib treatment observed in Study 1199.214, and the demonstration that a decrease in FVC decline of a similar relative magnitude compared to placebo results in clinical response in IPF, the clinical team recommends approval of nintedanib to slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease.

9 Advisory Committee Meeting and Other External Consultations

Given the modest treatment effect on FVC and the lack of support from key secondary endpoints (i.e. endpoints that directly measure clinical benefit), the benefit-risk of nintedanib for the treatment of SSc-ILD was discussed on July 25, 2019 at an Arthritis Advisory Committee that also included relevant pulmonary and statistical experts. The following is a summary of the committee discussion:

Questions to the Committee:

1. DISCUSSION: Discuss the efficacy of nintedanib for treatment of patients with systemic sclerosis interstitial lung disease (SSc-ILD).
a. Discuss the clinical meaningfulness of the changes in forced vital capacity (FVC) with nintedanib treatment in the population studied.

Committee Discussion: The committee members agreed that nintedanib's place in therapy is not clear with regards to disease course and in the sequence of treatment with other agents. The members also agreed that the study's primary efficacy endpoint

was met but noted that the study data is not robust to answer questions on long-term use. The committee members had mixed opinions on forced vital capacity (FVC) as an indicator of disease progression and lung function; some members commented that FVC is an important key component of pulmonary function tests while others weighed in on additional indicators (such as high-resolution CT scans to guide decision-making). Several committee members noted that changes in FVC are meaningful, especially in the context of a chronic, progressive disease.

2. DISCUSSION: Discuss the FVC data from the following subgroups and the implications for use of nintedanib in patients in the US.
a. US and Canada subgroup compared to the overall study population
b. Patients on background mycophenolate versus no background mycophenolate treatment

Committee Discussion: The committee members agreed that while the subgroup analysis is underpowered, there were interesting trends in the data. One member noted that overall positive results were driven by data from the non-US and Canada subgroup and no background mycophenolate subgroup. Other members expressed dissatisfaction with the relatively sparse dataset for these subgroups.

3. VOTE: Do the data provide substantial evidence of the efficacy of nintedanib for the treatment of systemic sclerosis interstitial lung disease?
a. If no, what further data are needed?

Vote Result: Yes: 10 No: 7 Abstain: 0

Committee Discussion: The majority of committee members voted "Yes", that the data provide substantial evidence of the efficacy of nintedanib for the treatment of systemic sclerosis interstitial lung disease. These members noted that the primary endpoint was met, there are no alternative treatment options for fibrotic disease, and SSc-ILD is a rare disease with tremendous unmet need. Several members who voted "Yes" expressed their hesitation in voting the way they did because of the lack of robustness of the data but recognized that there are challenges in conducting trials in this population. The committee members who voted "No" argued that it is worrisome that FVC was used as a surrogate marker, that there was no benefit seen in the secondary outcomes, and the data do not provide "substantial" evidence of efficacy. Some committee members recommended additional trials to assess effects of long-term use and to evaluate more patient-oriented outcomes.

4. VOTE: Is the safety profile of nintedanib adequate to support approval of nintedanib for the treatment of systemic sclerosis interstitial lung disease?
a. If no, what further data are needed?

Vote Result: Yes: 14 No: 2 Abstain: 1

Committee Discussion: The majority of committee members voted "Yes", that the safety profile of nintedanib is adequate to support approval of nintedanib for the treatment of SSc-ILD. These

members noted that the safety profile is known and in line with what's on the current approved label. Some committee members expressed concern at the extent of gastrointestinal side effects seen, and agreed that it may be difficult to piece out the underlying cause in these patients who already have significant gastrointestinal disruption from their disease state and are on other drugs that may cause similar adverse events. It was also noted that the risk of pneumonia may be hard to interpret given that many patients were on concomitant immunosuppressants. Some members commented that the discussion on acceptable or tolerated level of adverse events should be held between physicians and patients. The committee members who voted "No" noted that the adverse events may precipitate other issues and the magnitude of side effects seems to offset the benefit. The committee member who abstained noted that the safety profile of nintedanib may not be as manageable as discussed.

5. VOTE: Is the benefit-risk profile adequate to support approval of nintedanib at the proposed dose of 150 mg twice daily for the treatment of systemic sclerosis interstitial lung disease?
a. If no, what further data are needed?

Vote Result: Yes: 10 No: 7 Abstain: 0

Committee Discussion: The majority of committee members voted "Yes", that the benefit-risk profile is adequate to support approval of nintedanib at the proposed dose of 150 mg twice daily for the treatment of systemic sclerosis interstitial lung disease. They agreed that nintedanib provides a viable option for a disease that has a great unmet need and poor outlook. The committee members who voted "No" noted that the benefit-risk profile is not adequate to support approval of nintedanib because the magnitude and level of evidence for efficacy were small and the side effect profile remains concerning. The committee members noted the need for trials with longer term follow-up and more information on which subgroups of patients will benefit from use of this medication. There was also a recommendation for a trial using a lower dose, such as 100 mg twice daily.

10 Pediatrics

A pediatric assessment was not required as the product received orphan designation.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The label was reviewed by various disciplines of this Division, OPDP, and DMPP. Various changes to different sections of the label were done to reflect the data accurately and better communicate the findings to health care providers. Major issues with the originally-proposed labeling (version submitted March 7, 2019) are as follows:

Prescribing information

- Indications and Usage: Revised indication from the originally proposed "Treatment of systemic sclerosis-associated interstitial lung disease" to "To slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease." This indication more accurately reflects the demonstrated efficacy of the clinical trial in SSc-ILD.

- Warnings and Precautions embryo-fetal toxicity: explanation for addition of barrier method for women on hormonal contraception added as follows in italics: "*As the impact of nintedanib on the effectiveness of hormonal contraception is unknown, a*dvise women using hormonal contraceptives to add a barrier method."

- Section 5.2: Elevated Liver Enzymes and Drug-Induced Liver Injury text revised to clarify that cases of DILI were observed in clinical and post-marketing periods, however fatal events were only reported in post-marketing period. In addition, the description of AST/ALT abnormalities was revised to present proportions of patients in each treatment group with transaminase elevations ≥ 3x ULN to more clearly communicate to prescribers the proportions of patients with elevated transaminases in Study 4.

- Section 5.7: The text was revised to state that no cases of gastrointestinal perforation were reported in patients treated with OFEV or in placebo. There was one event identified by SMQ analysis of GI perforation with PT anal abscess. Review of the narrative confirmed the AE of anal abscess without GI perforation.

- Section 6.1: Revised to clarify in SSc-ILD that planned treatment duration was at least 52 weeks, however not all patients completed 52 weeks of treatment.

  The most frequent serious adverse events reported in patients treated with OFEV, more than placebo and adverse reactions leading to discontinuation were both revised to include interstitial lung disease as this information is relevant to prescribers.

  Revised common Adverse Drug Reactions Table to include fatigue, pyrexia, back pain, dizziness, skin ulcer, headache which also occurred in >= 5% of OFEV treated patients and more commonly than placebo.

- Section 12, Mechanism of Action: The Division did not agree with (b) (4) (b) (4) based on

the information in the submission. [redacted] label was revised from "IPF efficacy IPF" to "efficacy in ILD."

- Section 14.2: For ease of interpretation of the data, [redacted] was changed to a butterfly plot to better convey the data to prescribers.

  The Division deleted inclusion of [redacted].

  To provide further context for the interpretation of the primary analysis, the following were included:

  - Data from subgroup efficacy analyses of patients in the United States and Canada vs. other regions and the rest of the world and the subgroup of patients taking mycophenolate mofetil (MMF) at baseline compared to those not taking MMF, which could be relevant to prescribers in the US given that many patients could be on concomitant MMF.

  - In addition, as proposed by the Applicant, data from the secondary endpoint of mRSS, as a disease-specific measure, and analyses on survival were also presented to further contextualize the interpretation of the primary analyses.

Patient Labeling

Revisions to patient labeling were made to align with the revised prescribing information, including the addition of the new indication and the need for barrier contraception in women using hormonal contraception. Additional minor revisions were made for clarity.

12 Risk Evaluation and Mitigation Strategies (REMS)

The safety profile of nintedanib in SSc-ILD is generally similar to the known safety profile in IPF. Therefore, a REMS is not recommended based on the submitted data. The information necessary to use nintedanib safely and effectively in SSc-ILD will be provided through prescribing information and patient labeling.

13 Postmarketing Requirements and Commitment

The Applicant has agreed to conduct the drug-drug interaction study outlined below as a post-marketing requirement. The study has already been initiated as of November 2018. The Applicant has proposed the timelines for study completion and final report submission as outlined below:

Draft Protocol Submission:	**Title:** A Phase I trial to investigate the effect of nintedanib on the pharmacokinetics of a combination of ethinylestradiol and levonorgestrel in female patients with Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD) **BI Trial Number:** 1199-0340 **Document Number:** c21847264-03 **Version Number:** 3 **Date of CTP:** April 29, 2019 **Submitted to NDA 205832/S-012 (SEQ 0100) on June 03, 2019**
Final Protocol Submission:	04/2019 (no further update of CTP planned)
Study/Trial Completion:	12/2019
Final Report Submission:	04/2020

14 Division Director (or designated signatory authority) Comments

Nintedanib is a small molecule, oral capsule, kinase inhibitor, that is currently approved for the treatment of idiopathic pulmonary fibrosis (IPF). In this supplemental NDA, Boehringer Ingelheim (BI) proposes a new indication for nintedanib in the treatment of systemic sclerosis-associated interstitial lung disease (SSc-ILD). The proposed dosage form and dosing regimen are the same as those approved for the treatment of IPF, a dose of 150 mg twice daily, allowing for dose reductions and dosing interruptions for adverse events.

The Applicant submitted the results of a single clinical trial to support the proposed indication – Study 1199.214. Study 1199.214, was a double blind, randomized, placebo-controlled, parallel-group design to evaluate the efficacy and safety of oral nintedanib in patients with SSc-ILD. In Study 1199.214, patients were randomized 1:1 to nintedanib 150 mg by mouth twice daily or matching placebo. The primary endpoint was the annual rate of decline in FVC in mL over 52 weeks. Key secondary endpoints included absolute change in modified Rodnan Skin Score (mRSS) at Week 52 and absolute change in Saint George's Respiratory Questionnaire (SGRQ), a patient reported outcome (PRO) at Week 52. Additional secondary endpoints included time to death, Health Assessment Questionnaire Disability Index (HAQ-DI), and Functional Assessment of Chronic Illness Therapy (FACIT) dyspnea scale.

The main efficacy analysis was assessed at Week 52, but patients could remain on treatment up to a maximum of 100 weeks to collect follow-up safety and efficacy information. Patients were evaluated for safety assessments at Weeks 2, 4, 6, 12, 24, 36, 52, 68, 84, and 100. A follow-up visit was scheduled 28 days after the End of Treatment Visit. Patients who experienced clinically significant deterioration of SSc could receive rescue therapy. Permitted medications for management of deterioration include prednisone > 10 mg/day, azathioprine, cyclophosphamide, cyclosporine A, hydroxychloroquine, colchicine, D-penicillamine, sulfasalazine, rituximab, tocilizumab, abatacept, leflunomide, tacrolimus, tofacitinib, and potassium para-aminobenzoate. Patients who permanently discontinued study medication were asked to return for future visits as planned; patients who declined further follow-up visits were asked for vital status assessment at 52 weeks and 100 weeks after their randomization, or at the time the last full visit would have been scheduled, whichever occurred earlier.

The study was conducted as planned. A total of 576 patients, predominantly females (75%), were randomized and treated, 288 in each treatment arm. In addition to SSc-ILD, patients had a history of other SSc manifestations including pulmonary hypertension (9%), digital ulcers (39%), diarrhea/malabsorption/bacterial overgrowth (18%), esophageal dysphagia/reflux (74%), synovitis (24%), friction rubs (9%), and Raynaud phenomenon (97%), which were similar by treatment group. At baseline, 48% of the patients received treatment with mycophenolate and 7% received methotrexate. Use of mycophenolate and methotrexate was similar by treatment group. Approximately half of the patients were enrolled at sites in Europe, 25% were enrolled in Canada and the United States, and 23% in Asia. Overall, the patient demographic characteristics were balanced and representative of the intended patient population.

Of the 576 patients, 94% completed visits up to Week 52, the study primary endpoint; the nintedanib group had a numerically higher study withdrawal rate (8%) compared with the placebo group (5%). Treatment discontinuations occurred in 15% of patients: the nintedanib group had a numerically higher treatment discontinuation rate (19%) compared with the placebo group (11%). The most common reason for study withdrawal was adverse event.

The primary endpoint was the annual rate of decline in FVC in mL over 52 weeks (with measurements at Week 2, 6, 12, 24, 36 and 52). The adjusted annual rate of decline in FVC over 52 weeks was lower in the nintedanib group (-52 mL/year) than in the placebo group (-93 mL/year), with a treatment difference of 41 mL/year. The annual rate of decline in FVC in percent predicted over the 52-week treatment period was also compared between the two treatment groups. The adjusted annual rate of decline in FVC in percent predicted over 52 weeks was lower in the nintedanib group (-2.6%/year) than in the placebo group (-1.4%/year), with a treatment difference of 1.2%/year.

The results from the key secondary endpoints, absolute change in modified Rodnan Skin Score (mRSS) and absolute change in Saint George's Respiratory Questionnaire (SGRQ) at Week 52, were not statistically significantly different between treatment and placebo-treated patients. The results did not demonstrate differences in other secondary endpoints, including FACIT-dyspnea score and DL_{CO} at Week 52. Additionally, there were no differences in other disease-related secondary endpoints, including, number of digital ulcers, or HAQ-DI. Of note, none of these other secondary outcomes has been validated in SSc. Overall mortality and causes of death were also similar between treatment groups and expected for this patient population.

Subgroup Analyses: MMF vs. non MMF, US/Canada vs. rest of the world (ROW)
To evaluate the influence of stable background immunosuppressive therapy to study treatment, the protocol pre-specified subgroup analyses also included mycophenolate mofetil/sodium use at baseline. A less robust treatment effect was observed in adjusted annual rate of decline in FVC in the subgroups of patients on mycophenolate mofetil at baseline (treatment difference 27 mL/year) and patients from the U.S. and Canada (treatment difference 10 mL/year) with widely overlapping confidence intervals due to small subgroup sample size, limiting definitive conclusions. However, this information is relevant to prescribers in the US and warrants inclusion in product labeling to further contextualize the interpretation of the primary analysis.

Efficacy Considerations

Study 1199.214 demonstrated a statistically significant but small treatment effect on reducing the annual rate of decline in forced vital capacity (FVC) compared to placebo over 52 weeks.

Considerations regarding Missing Data

Pre-specified sensitivity analyses

To assess the robustness of the primary analysis, the FDA review team conducted sensitivity analyses to address missing data resulting from study discontinuation. Multiple sensitivity analyses to missing data assumptions were performed for the primary endpoint, including a series of analyses that utilized the Pattern Mixture Model (PMM) approach with multiple imputation. A tipping point analysis was then performed post-hoc to evaluate how robust the primary analysis results were across varying missing data assumptions, a more comprehensive range over scenarios assumed in the PMM analyses. While the results for the primary endpoint were statistically significant based on the pre-specified analysis, the sensitivity analyses showed loss of statistical significance

Post-hoc analyses of the expanded data set

Of note the pre-specified analysis of the primary endpoint use the window of FVC assessment of Week 52+8 days. Based on this analysis, 47/288 (16%) of patients on nintedanib and 31/288 (11%) on placebo had missing data at Week 52. However, of these 28 patients (16 in the nintedanib group and 12 in the placebo group) had FVC data at a later time point. For 24 out of these patients (14 in the nintedanib group and 10 in the placebo group), the first FVC measurement after Week 52 occurred within 28 days after the Week 52 time window. The clinical team considers this information relevant and reliable and, although not pre-specified, has requested additional exploratory analyses using this *expanded dataset*. The analyses from this dataset, as submitted by the Applicant, are presented below.

- The primary analysis on the expanded dataset showed a treatment effect of 43 mL/year (95% CI 5.04, 80.07; p-value = 0.0263) which is close to but numerically slightly larger than the 41 mL/year (95% CI 2.88, 79.01; p-value = 0.0350) seen in the primary analysis suggesting that the trajectory of change in the additional 24 patients who contributed to the expanded dataset was similar to that of the population used in the primary analysis.
- The repeated PMM approaches with multiple imputation analyses on the expanded dataset are shown in Table 22 and appear to support the primary analysis.
- Tipping point analysis on the expanded dataset: To lose the statistically significant treatment effect seen in the primary analysis would require those nintedanib patients with missing data to suffer an additional -90 mL/year FVC loss while placebo patients with missing data suffer no additional loss in the annual rate of decline until week 52. This scenario is implausible given the results of the primary endpoint analysis

While we typically consider post hoc analysis exploratory as they lack the statistical rigor of a pre-planned analysis for providing confirmatory evidence, in this unique study design setting, there were 28 patients who were on study treatment at Week 52 but missed the pre-defined week 52 efficacy assessment window. In all subsequent pre-planned imputation based sensitivity analyses, this portion of patients (~1/3 of the total missing) were treated as if they had outcome similar to either patients off treatment or patients on placebo, this is a relatively harsh penalty for the study drug. With the expanded Week 52 window approach, actual rather than imputed FVC data for 24 of the 28 patients were used in the analyses minimizing reliance on assumptions for imputed data for these patients. From this perspective, this post hoc

analysis is considered reasonable from clinical perspective and thus supportive of the primary analyses.

Applying the primary and sensitivity analyses to the expanded dataset, we found: treatment effect was largely the same (43 mL/Year from the expanded dataset vs. 41 mL/Year from the 52 Week data); among the three PMM approaches, the PMM1 approach, an estimator of treatment effect relatively better aligned with the treatment policy estimand, failed significance test with a p-value of 0.067; the PMM2 approach just failed significance test with a p-value of 0.051 possibly due to simulational variability from multiple imputation and the PMM3 sensitivity analysis was significant with a p-value of 0.044; the tipping point analysis results supported robustness of the primary analysis result.

The clinical team considers, and I agree, that these additional analyses, while not prespecified, reflect clinically relevant and reliable data collected in the controlled setting of a clinical study and, as part of the totality of the evidence, are supportive of the efficacy of nintedanib in SSc-ILD.

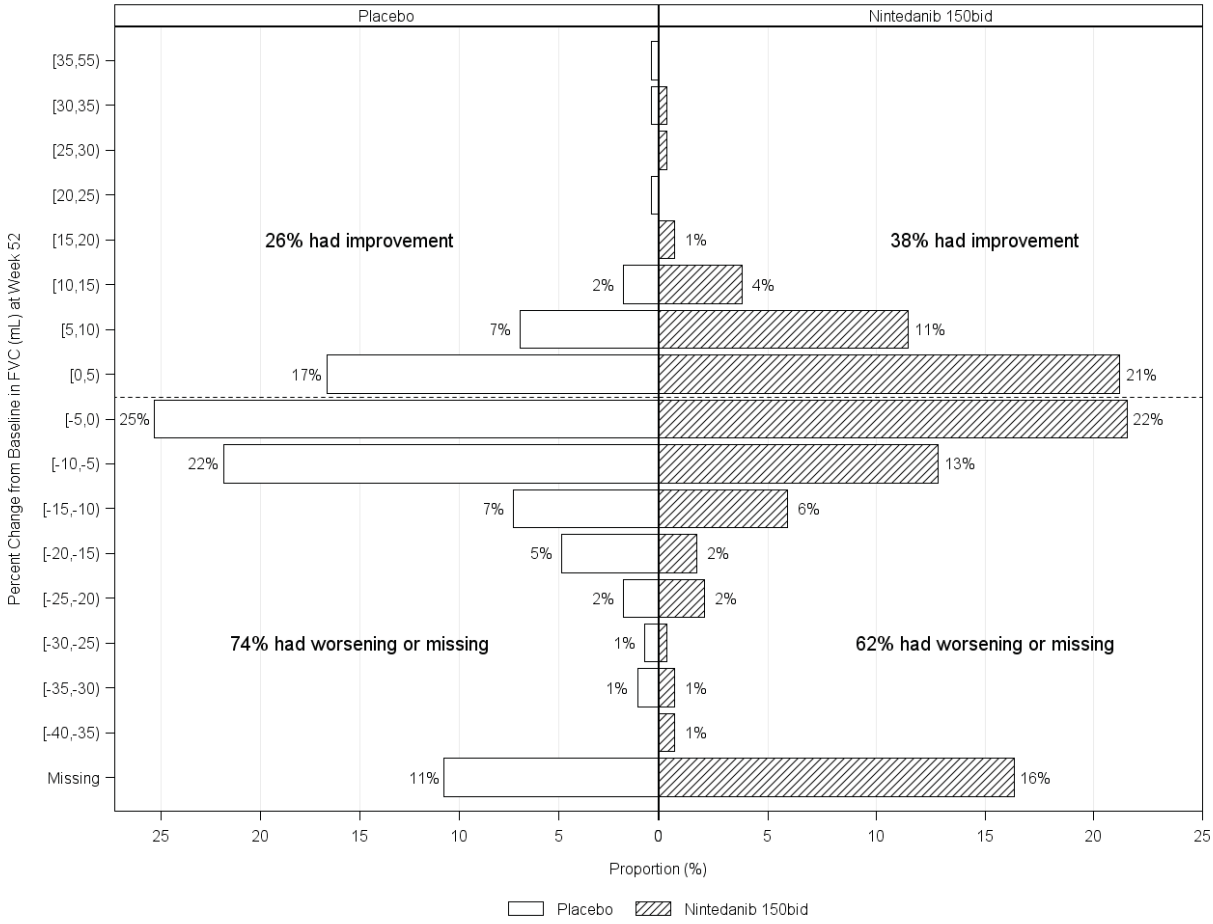
Responder Analyses
Given the uncertainty on what difference in FVC is considered clinically important in SSc-ILD, the FDA review team conducted responder analyses on relative decline in FVC using various thresholds for response such as "relative decline ≤10% (or 5%) from baseline at Week 52". In the FDA analyses, patients with missing data at Week 52 were categorized as non-responders. These endpoints are summarized in Table 12.

The proportion of responders with 5% threshold (relative decline ≤5%) was numerically higher in the nintedanib group (59%) than in the placebo group (52%), favoring nintedanib over placebo; the odds ratio was 1.37 (95% CI 0.98, 1.89; nominal p-value = 0.066). The proportion of responders with 10% threshold (relative decline ≤10%) was numerically lower in the nintedanib group (72%) than in the placebo group (74%), not favoring nintedanib over placebo; the odds ratio was 0.93 (95% CI 0.65, 1.35; nominal p-value = 0.704). Responder analyses using absolute decline in FVC percent predicted showed a similar pattern with the analyses using relative decline in FVC.

Figure 15 further illustrates the responder analyses showing that a higher proportion of patients worsened (i.e. had negative CFB) on placebo vs. nintedanib and a higher proportion improved (i.e. had a positive CFB) on nintedanib vs placebo. If one were to use a cutpoint of 0 mL change from baseline at Week 52:

- 38% of patients on nintedanib had an improvement in FVC vs. 26% on placebo,
- 62% of patients on nintedanib had a worsening or missing data vs. 74% on placebo.

Figure 15. Butterfly Plot of Percent Change from Baseline in FVC in mL at Week 52 (Treated Set)



Patients classified as having missing FVC data at Week 52 are those with no FVC assessment between Day 310 and Day 373
bid = twice daily
Source: NDA 205832/S12

Safety:

In Study 1199.214, adverse events in the nintedanib group were consistent with those known for nintedanib including diarrhea, nausea, vomiting, and liver abnormalities. Deaths and serious adverse events (SAEs) were balanced between the treatment groups. A greater proportion of patients in the nintedanib group developed SAEs of pneumonia (8 vs. 1). There were more AEs leading to drug decrease and discontinuation in the nintedanib group which were mostly due to gastrointestinal events. In addition, more patients in the nintedanib group experienced weight loss as compared to the placebo group.

Benefit-Risk Assessment

The primary statistical reviewer has identified limitations in both study design and analyses; and expressed concerns that the evidence provided by the clinical development program in SSc-ILD has not demonstrated expected substantial evidence of efficacy in supporting the treatment policy estimand in general. Dr. Wang has also suggested ways to mitigate the limitations, for example, a subsequent study to address the above limitations, or a refinement of the study estimand and patient population to patients who can tolerate the drug The acting director of Biometrics 2 further noted that while the data from the clinical trial in SSc-ILD does not, on its own, provide substantial evidence of a treatment effect, when considered with the results from studies in related indication of IPF for which nintedanib is approved, a treatment effect in SSc-ILD appears real and can support approval for the sought indication.

The clinical team and I acknowledge these considerations and recommendations. We also consider additional factors in our determination on the benefit-risk of nintedanib in SSc-ILD, as discussed below. Further, we considered the discussion and input from the Arthritis Advisory Committee and Medical Policy and Program Review Council which are summarized elsewhere in this document.

Analysis of SSc-ILD and Available Therapies

Systemic sclerosis (SSc) is a rare, multisystem, connective tissue disease involving the skin, underlying tissues, blood vessels, and major organs that affects approximately 100,000 people in the United States.[20] It is characterized by microvascular damage and fibrosis of the skin and of various internal organs, including the lung, heart, kidneys and the gastrointestinal tract. SSc is a serious disease associated with increased morbidity and mortality with a 10-year survival rate less than 70% from the time of diagnosis.[21] The primary causes of SSc-related death are pulmonary fibrosis, pulmonary arterial hypertension, heart failure, or cardiac arrhythmia. Interstitial lung disease (ILD), as detected by high resolution computed tomography (HRCT), is present in 55 to 65% of patients with SSc.[22] Severe ILD usually presents relatively early in the disease course within the first 3 years from time of diagnosis.[23] Median survival is 5 to 8 years in SSc-ILD.[24]

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[20] https://www.scleroderma.org/

[21] Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972−2002. Ann Rheum Dis 2007;66:940−4

[22] Launay D, Remy-Jardin M, Michon-Pasturel U, et al. High resolution computed tomography in fibrosing alveolitis associated with systemic sclerosis. J Rheumatol 2006;33(9):1789-801

[23] Steen VD, Medsger TA Jr. Severe Organ Involvement in Systemic Sclerosis with Diffuse Scleroderma. Arthritis Rheum 2000:43:2437−44

[24] Herzog EL, Mathur A, Tager AM, Feghali-Bostwick C, Schneider F, Varga J. Interstitial lung disease associated with systemic sclerosis and idiopathic pulmonary fibrosis: how similar and distinct? Arthritis and Rheumatology, Accepted Article, Accepted: May 08, 2014, doi:10.1002/art.38702; 2014. p. 1967-1978

Systemic sclerosis and SSc-ILD are rare conditions with high unmet medical need as there are no FDA-approved therapies. In clinical practice, patients with SSc are treated based on expert-derived recommendations for the management of organ-specific manifestations and empirically with off-label products used for other rheumatic diseases, such as cyclophosphamide. The 2017 update of European League Against Rheumatism (EULAR) recommendations for the treatment of SSc, and 2016 British Society for Rheumatology (BSR) guidelines for the treatment of SSc, recommend consideration of immunosuppressives such as cyclophosphamide and mycophenolate mofetil (MMF) for treatment of SSc-ILD.[25,26] Such therapies have inherent toxicities including cytopenias, infections, malignancies, among others.

Nintedanib in SSc-ILD

In evaluating the evidence of effectiveness of nintedanib in SSc-ILD, the Division considered the totality of the data in the context of nintedanib experience in a distinct but related chronic progressive fibrosing lung disease, IPF.

This endpoint, FVC, was selected by the Applicant based on their experience with the IPF program which used the same primary endpoint. Further analysis of data from IPF clinical development programs has demonstrated that patients with less FVC decline also demonstrated an associated decrease in mortality.[27,28] In addition, FVC has been proposed as a validated outcome measure in patients with SSc according to the principles of Outcome Measures in Rheumatologic Clinical Trials (OMERACT).[29] While FVC is a surrogate endpoint that does not directly measure how a patient feels, functions, or survives, it has been demonstrated to reliably predict clinical benefit in IPF, another fibrotic disease in which FVC is known to decline, and in which FVC is monitored clinically. The clinical benefit from altering the rate of decline in lung function in patients with IPF, as measured by FVC over 52 weeks, has been shown to be consistent in two larger clinical programs, using two different products with different mechanisms of action, nintedanib and pirfenidone.[30,31] This additional contextual information supports the use of FVC as a clinically relevant primary endpoint in SSc-ILD to support traditional approval of nintedanib in SSc-ILD. [32]

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[25] Update of EULAR recommendations for the treatment of systemic sclerosis, April 2017 https://ard.bmj.com/content/annrheumdis/early/2017/04/25/annrheumdis-2016-209909.full.pdf

[26] BSR and BHPR guideline for the treatment of systemic sclerosis, June 2016

[27] Karimi-Shah BA, Chowdhury BA, Forced vital capacity in idiopathic pulmonary fibrosis--FDA review of pirfenidone and nintedanib, N Engl J Med. 2015 Mar 26;372(13):1189-91

[28] Paterniti MO, et al, Acute Exacerbation and Decline in Forced Vital Capacity Are Associated with Increased Mortality in Idiopathic Pulmonary Fibrosis, Ann Am Thorac Soc. 2017 Sep;14(9):1395-1402

[29] Merkel P, Clements PJ, Reveille P, et al. Current status of outcome measure development for clinical trials in systemic sclerosis. J Rheumatol 2003;30:1630−47

[30] FDA-approved nintedanib labeling

[31] FDA-approved pirfenidone labeling

[32] Section 507(e)(9) of the FD&C Act

While the absolute treatment effect was larger in the nintedanib IPF program (94 to 131 mL in IPF vs. 41 mL in SSc-ILD) due to faster rate of decline in IPF (-191 to -240 mL/year in IPF placebo group vs. -93 mL/year in SSc-ILD placebo group), the relative reduction in the annual rate of decline over placebo was similar between IPF and SSc-ILD programs (49% and 44%, respectively). Thus, it is reasonable to expect that the observed relative reduction in the annual rate of decline in FVC in SSc-ILD will also result in a treatment effect on long-term clinical outcomes. However, given the slower rate of progression in SSc-ILD, as compared with IPF, demonstrating a clinical benefit on endpoints, such as mortality, will require a longer and larger clinical program in SSc-ILD which the Division considered to be challenging to design and execute due to the rarity of the condition. In assessing the need and feasibility of additional data, the Division considered several factors in this specific case. The adverse event profile of nintedanib will likely result in a significant proportion of patients needing to interrupt or discontinue therapy due to adverse events, which has the potential to result in a significant amount of missing data in a long-term clinical trial and respectively compromise the interpretability of such a study. Additional considerations included the practicality of enrolling patients in a long-term study given that nintedanib is available on the market, along with other standard of care therapies. Lastly, conducting a large and long study in SSc-ILD could divert resources and patients from other development programs in this therapeutic area which is in high need for treatment options. Based on the above considerations, the Division considered that requiring additional studies is not warranted or justified in this case.

The data supporting this submission are derived from a single study. However, the effect of nintedanib on the lung function and clinical outcomes has been also demonstrated in IPF using study design similar to the one supporting the SSc-ILD application. With this prior experience, and in this context of a SSc-IL being a rare disease, the Division and the acting director of Biometrics 2 considered that the data from the single study in SSc-ILD is supported by the available data from nintedanib IPF program to provide substantial evidence of efficacy to support approval.

The safety of nintedanib in SSc-ILD is consistent with the established safety profile of nintedanib in IPF. Gastrointestinal side effects need to be considered in patients with SSc-ILD who may also have gastrointestinal involvement from the disease. In addition to the established safety risks, in the SSc-ILD population, there were increased number of serious infections, driven by an increase in pneumonia in the nintedanib treatment group.

Action

The recommendations of the various review team members are noted. Based on evaluation of the totality of the evidence, the unmet medical need which exists in SSc-ILD, the regulatory action for this supplemental NDA is *Approval.* This determination also considered the discussion and input from the Arthritis Advisory Committee and the FDA Medical Policy and Program Review Council. The study results in this application posed many challenges to interpretation and judgement, and it was also challenging that no other secondary endpoints or measures of disease showed clinical improvement, with respect to the secondary endpoints.

This, along with the modest treatment effect on the decline in lung function, the Division considered that the most appropriate indication should be “slowing the rate of decline in pulmonary function in systemic sclerosis-associated interstitial lung disease.” This indication most accurately describes the results of the clinical development program.

The labeling will include the more narrow indication statement, the primary efficacy results for Study 1199.214, subgroup analyses of patients on MMF vs. no MMF and US/Canada and ROW. The labeling will also include a responder analysis on the prespecified patient population to 52 weeks. Labeling has been agreed upon between the Applicant and the Division.

One postmarketing study is required for a drug-drug interaction trial to assess the pharmacokinetics, safety, and tolerability for the co-administration of a combined oral contraceptive (containing ethinyl estradiol and levonorgestrel) with Ofev 150 mg twice daily.

15 Appendices

15.1. References

1) Karimi-Shah BA, Chowdhury BA, Forced vital capacity in idiopathic pulmonary fibrosis--FDA review of pirfenidone and nintedanib, N Engl J Med. 2015 Mar 26;372(13):1189-91
2) Paterniti MO, et al, Acute Exacerbation and Decline in Forced Vital Capacity Are Associated with Increased Mortality in Idiopathic Pulmonary Fibrosis, Ann Am Thorac Soc. 2017 Sep;14(9):1395-1402
3) Merkel P, Clements PJ, Reveille P, et al. Current status of outcome measure development for clinical trials in systemic sclerosis. J Rheumatol 2003;30:1630−47.
4) FDA-approved nintedanib labeling
5) Section 507(e)(9) of the FD&C Act
6) Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972−2002. Ann Rheum Dis 2007;66:940−4
7) Launay D, Remy-Jardin M, Michon-Pasturel U, et al. High resolution computed tomography in fibrosing alveolitis associated with systemic sclerosis. J Rheumatol 2006;33(9):1789-801
8) Steen VD, Medsger TA Jr. Severe Organ Involvement in Systemic Sclerosis with Diffuse Scleroderma. Arthritis Rheum 2000:43:2437−44
9) Herzog EL, Mathur A, Tager AM, Feghali-Bostwick C, Schneider F, Varga J. Interstitial lung disease associated with systemic sclerosis and idiopathic pulmonary fibrosis: how similar and distinct? Arthritis and Rheumatology, Accepted Article, Accepted: May 08, 2014, doi:10.1002/art.38702; 2014. p. 1967-1978
10) Update of EULAR recommendations for the treatment of systemic sclerosis, April 2017. https://ard.bmj.com/content/annrheumdis/early/2017/04/25/annrheumdis-2016-209909.full.pdf
11) BSR and BHPR guideline for the treatment of systemic sclerosis, June 2016 https://academic.oup.com/rheumatology/article/55/10/1906/2196591
12) Rubin D. Multiple Imputation for Nonresponse in Surveys, John Wiley & Sons, 1987
13) Steen VD, Medsger TA Jr. Improvement in skin thickening in systemic sclerosis associated with improved survival. Arthritis Rheum 2001:44:2828−35
14) Khanna D, Furst DE, Hays RD, et al. Minimally important difference in diffuse systemic sclerosis: results from the D-penicillamine study. Ann Rheum Dis 2006;65:1325−9
15) https://www.scleroderma.org/
16) FDA-approved pirfenidone labeling

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study 1199.214

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified: 1437. This number includes 43 investigators who did not participate in the study and 29 investigators who were associated with sites that did not initiate.		
Number of investigators who are Applicant employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: There was 1 investigator who disclosed that spouse is a (b) (6) employee. Significant payments of other sorts: There were 5 investigators who disclosed significant payments of other sorts. Proprietary interest in the product tested held by investigator: none Significant equity interest held by investigator in Study: none Sponsor of covered study: none		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 78		
Is an attachment provided with the reason:	Yes X	No ☐ (Request explanation from Applicant)

15.3. Nonclinical Pharmacology/Toxicology

See Section 5 above.

15.4. OCP Appendices (Technical documents supporting OCP recommendations)

None.

15.5. Study 1199.214 Schedule of Assessments

Visit		1	2	3	4	5	6	6a	7	7a	8	8a	9	Xa[18] (9a, 10a, 11a)	X[18] (10, 11)	12/ EOT	FU[19]
	Screening		Randomised Treatment Period[7]														FU
Weeks of treatment			0	2	4	6	12	18	24	30	36	44	52	60 + every 16wk	68 + every 16wk	100	EOT + 4wk
Day Time window	Before or at the latest at Visit 1	≥4d prior Visit 2	1	15 ±3	29 ±3	43 ±3	85 ±3	127 ±7	169 ±7	211 ±7	253 ±7	309 ±7	365 ±7	±7	±7	701 ±7	+28 +7
Informed Consent[1]	X																
Send HRCT to central review[2]	X																
Demographics		X															
Medical history		X	X														
Adverse events, conc. therapy		X	X	X	X	X	X		X		X		X		X	X	X
In-/exclusion criteria		X	X														
Questionnaires (SGRQ, FACIT-dyspnoea, SHAQ, EQ-5D-5L, patient global VAS)[3]			X						X				X			X	
Review questionnaires for completeness			X						X				X			X	
Physical examination, vital signs		X	X	X	X	X	X		X		X		X		X	X	X
Collect/review/dispense menstruation calendar	X		X	X	X	X	X		X		X		X		X	X	X

Visit		1	2	3	4	5	6	6a	7	7a	8	8a	9	Xa[18] (9a, 10a, 11a)	X[18] (10, 11)	12/ EOT	FU[19]
	Screening		Randomised Treatment Period*														FU
Weeks of treatment			0	2	4	6	12	18	24	30	36	44	52	60 + every 16wk	68 + every 16wk	100	EOT + 4wk
Day Time window	Before or at the latest at Visit 1	≥4d prior Visit 2	1	15 ±3	29 ±3	43 ±3	85 ±3	127 ±7	169 ±7	211 ±7	253 ±7	309 ±7	365 ±7	±7	±7	701 ±7	+28 +7
HCRU			X	X	X	X	X		X		X		X		X	X	
mRSS assessment			X				X		X		X		X		X	X	
Digital ulcer assessment			X				X		X		X		X		X	X	
Safety Laboratory (blood and urine)		X[4]	X	X	X	X	X	X[5]	X	X[5]	X	X[5]	X	X[5]	X	X	X
Pregnancy test[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK sample[7]					X				X								
Autoantibody assessment[8]		(X)	X						X				X				
Biomarker samples[9]			X		X				X				X				
DNA banking sample[10]			X														
SpO_2 (earlobe or forehead, resting)			X						X				X			X	
Spirometry (FVC)[11]		X	X	X	X	X	X		X		X		X		X	X	X
DLCO[11]		X	X						X				X			X	
12-lead ECG		X	X[12]						X				X			X	
Echocardiography[13]		X											X				

Visit		1	2	3	4	5	6	6a	7	7a	8	8a	9	Xa[18] (9a, 10a, 11a)	X[18] (10, 11)	12/ EOT	FU[19]
	Screening		Randomised Treatment Period*														FU
Weeks of treatment			0	2	4	6	12	18	24	30	36	44	52	60 + every 16wk	68 + every 16wk	100	EOT + 4wk
Day Time window	Before or at the latest at Visit 1	≥4d prior Visit 2	1	15 ±3	29 ±3	43 ±3	85 ±3	127 ±7	169 ±7	211 ±7	253 ±7	309 ±7	365 ±7	±7	±7	701 ±7	+28 +7
Randomization			X														
IRT call/notification	X[14]		X		X		X		X		X		X		X	(X)	
Dispense trial medication			X		X		X		X		X		X		X		
Collect trial medication					X		X		X		X		X		X	X	
Compliance/drug accountability				X[20]	X	X[20]	X		X		X		X		X	X	
Physician global VAS			X						X				X			X	
Termination of trial medication[15]																X	
Vital status assessment[16]													X			X	
Conclude subject participation[17]																	X

Footnotes:

* In case of dose change (reduction or re-escalation) additional visits have to be included (refer to Section 6.2.4).
- In case of prematurely trial medication discontinuation, the patient completes end of treatment Visit (EOT and follow-up Visit (FU) 4 weeks later), the patient should be asked to come to future visits as planned (refer to Section 6.2.3).
- EOT assessments are the same as described for Visit 12. If EOT is performed at week 52, the Flowchart for Visit 9 is valid (i.e. Biomarker samples to be drawn).

[1] Before or at the latest at Visit 1. Informed consent (IC) needs to be signed before any procedure related to the trial is performed. All adverse events (AEs) and concomitant therapies (CTs) from the day of signing informed consent have to be recorded. The screening period (informed consent to Visit 2) must not be longer than 12 weeks.

[2] Review of high resolution computer tomography (HRCT) for extent of fibrotic disease in the lung (10% or more). Central review: a historical HRCT not older than 12 months should be sent; only if the patient does not have a HRCT within 12 months at Visit 1 but meets all other inclusion and no exclusion criteria, the HRCT can be performed for the purposes of participation in the trial (except for patients in Germany).

[3] Self-reported outcome questionnaires must always be done by the patients in a quiet place prior to any other visit procedure. Order of questionnaires: 1. SGRQ, 2. FACIT-dyspnoea, 3. SHAQ, 4. EQ-5D-5L, 5. Patient's global VAS.

[4] The safety lab of Visit 1 must be repeated if screening is longer than 6 weeks.

[5] Intermediate lab tests (a-Visit) do not necessarily need to be a site visit. Cautionary note: dependent on concomitant treatment additional safety monitoring should be considered at discretion of the investigator.

[6] ß-HCG will be performed at Visit 2 only, at central lab. Urine dipstick pregnancy tests will be provided centrally and should be performed in all women of childbearing potential every 4-6 weeks: at least at every visit and if necessary, additionally at home or at a local doctor / laboratory. If urine test is not acceptable to local authorities, a blood test can be done at a local laboratory. Women of childbearing potential will be instructed accordingly.

[7] PK samples will be taken at Visits 4 and 7 just before drug administration. Date and exact clock time of drug administration and blood sampling must be recorded on the eCRF. patients will be provided (Visits 3 and 6) with a PK card to support the record of the exact clock time of medication intake three days preceding PK sampling.

[8] anti-Topoisomerase antibodies (ATA) will be assessed at Visit 2, 7, and 9 (and at V1 if historically not available); anti-RNA polymerase III antibodies ((anti-)RNA Pol III) and anti-centromere antibodies (ACA) will be assessed at Visit 2 only.

[9] Biomarker samples will be taken just before drug administration. Date and exact clock time of drug administration and blood sampling must be recorded on the eCRF.

- Samples for Protein Biomarkers will be taken at Visits 2, 4, 7, 9, just before drug administration.
- One sample for prespecified DNA analyses will be taken at Visit 2.
- Samples for RNA expression analyses will be taken at Visits 2, 7, and 9, just before drug administration.

[10] DNA (Desoxyribo Nucleid Acid) banking sample: one blood sample will be taken from those eligible patients who signed a separate informed consent at Visit 2 (or on a subsequent visit); Participation is voluntary and is no prerequisite for participation in the trial.

[11] Order of lung function measurements: same time each visit ± 90 min, reference time at Visit 2: 1. FVC followed by patients rest; 2. DLCO.

[12] ECG will be performed (if possible prior to blood draw) at Visit 2 prior randomisation (only if abnormal at Visit 1).

[13] Echocardiography will at least be performed in patients with a history of pulmonary hypertension at screening (time window Visit 1 to Visit 2) and after 1 year (time window Visit 9 to Visit 9a).

[14] IRT needs to be notified at time point of informed consent (at the latest at Visit 1) to trigger trial medication shipments; ATA status (historical) will be entered at randomisation (Visit 2) at the latest.

[15] Termination of trial medication data needs to be collected any time trial medication is permanently discontinued.

[16] Vital status at 52 weeks and at 100 weeks or at the timepoint when patient's last full visit (i.e. EOT or V9, V10, V11, V12) would have been scheduled, whatever occurs earlier should be available for all patients. Permission to contact withdrawn patients for vital status assessment should be requested by site.

[17] Trial completion:

- At the end of the follow-up Visit for patients who have completed the trial on treatment as planned.
- After early discontinuation (end of treatment [EOT]) and follow-up Visit), if a patient refuses to attend future visits as originally planned.
- At the end of Visit 12 or at the global end of the trial for patients who discontinued trial medication early but came to future visits as planned.

[18] Same scheme should be repeated as often as needed: Visit 'X' stands for Visit 10 and Visit 11; Visit 'Xa' stands for Visits 9a, 10a, and 11a.

[19] The follow-up (FU) visit should be planned for 28 days (+7 days window) after last drug intake (end of treatment [EOT]).

[20] Compliance / drug accountability only in case of dose reduction/increase

Source: Study 1199.214 protocol

15.5.1. Recommendations for Treatment Interruption or Dose Reduction

Table 24. Allowed Treatment Reduction or Interruption Periods of Nintedanib

	AEs considered drug-related	AEs not considered drug-related
Maximum interruption period	4 weeks	8 weeks
Recommended re-start	with reduced dose (100 mg bid)	with the same dose (100 mg bid or 150 mg bid)
Re-escalation	within 4 weeks to 150 mg bid	not applicable

Source: CSR 1199.214 Table 9.4.2.1:1

Table 25. Recommendations for Managing Liver Enzyme Elevations

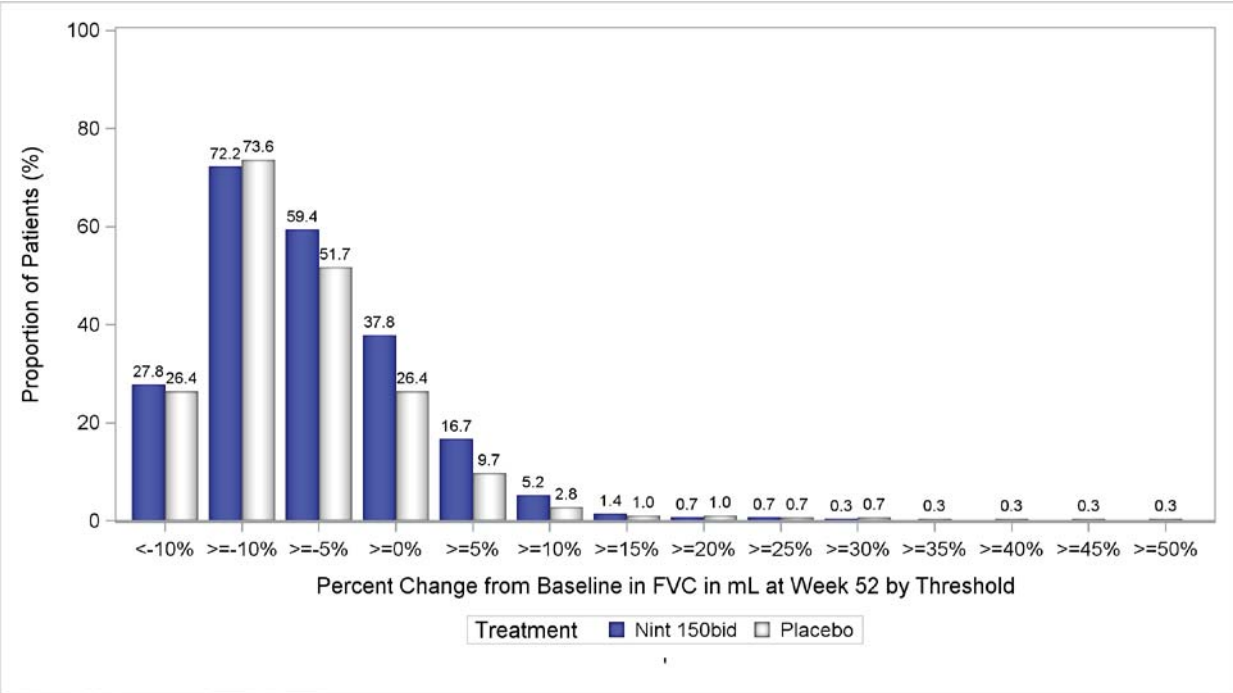
Time point	AST or ALT increase to			Signs of hepatic injury[1]
	>1.5x to <3x ULN	≥3x to <5x ULN and no signs of hepatic injury[1]	≥5x to <8x ULN and no signs of hepatic injury[1]	
Visit 2 (randomisation)	Withdrawal of trial medication or continuation to be justified[2]	Withdrawal of trial medication	Withdrawal of trial medication	Withdrawal of trial medication
Any other Visit	Continuation as planned[3]	Dose reduction or interruption[4]	Interruption of trial medication	Withdrawal of trial medication
		Close observation[5] After 2 weeks or any time later	Close observation[5] After 2 weeks or any time later	Clinical evaluation of hepatic injuriy[1]
	<3x ULN	≥3x ULN	<3x ULN	≥3x ULN
	Dose reduced: return to initial dose Interrupted: restart at reduced dose. Bi-weekly monitoring for at least 8 weeks	Permanent discontinuation Close observation[5]	Restart at reduced dose Weekly monitoring for 4 weeks, then bi-weekly for at least 8 weeks	Permanent discontinuation Close observation[5]

Source: CSR 1199.214 Table 9.4.2.1.2:1

15.6. Additional Graphical Displays

Figure 16 displays the proportions of responders at various response definitions; that is, proportions of patients whose percent change from baseline were greater than certain cutoffs, where missing data was imputed as a decline worse than 10%. For example, with cutoff of -10%, 72.2% and 73.6% of patients in the nintedanib and placebo arms respectively had 10% or less decline from baseline in FVC (mL) at Week 52, indicating that placebo is numerically favorable over nintedanib. On the other hand, with cutoff of -5%, 59.4% on nintedanib and 51.7% of patients on placebo had 5% or less decline from baseline in FVC (mL) at Week 52, indicating that nintedanib is numerically favorable over placebo. Finally, with cutoff of 0%, 37.8% and 26.4% of patients on nintedanib and placebo respectively had an improvement at Week 52 compared with baseline, indicating that nintedanib is numerically favorable over placebo. In this plot, missing data were represented in a group on the left combined with the group of >10% decline, again reflecting the assumption that missing data have worse outcome.

Figure 16. Proportions of Responders at Various Cutoffs among Treated Patients, Based on Analysis of Percent Change from Baseline in FVC in mL at Week 52 (Treated Set)



Abbreviations: mL: milliliter
Note: Missing data were considered as having a relative decline in FVC in mL of >10%.
Source: FDA Statistical Reviewer

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/s/

RACHEL GLASER
09/06/2019 01:49:16 PM

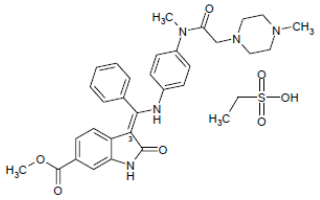
NIKOLAY P NIKOLOV
09/06/2019 01:51:39 PM
Signed under the authority, delegated by Dr. Sally Seymour, Division Director, DPARP.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205832Orig1s012

PRODUCT QUALITY REVIEW(S)

CHEMIST'S REVIEW *Review #1*	1. ORGANIZATION BRANCH 1/DPMA1/OLDP/OPQ	2. NDA NUMBER **205-832**
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road, P.O. Box 368 Ridgefield, CT 06877 Name and Title of Applicant's Responsible Official Ingeborg Arny-Cornejo, M.D., Senior Associate Director, Regulatory Affairs Tel: (203) 482-7095, FAX: (203) 791-6262 ingeborg.arny-cornejo@boehringer-ingelheim.com		4. AF NUMBER
		5. SUPPLEMENT (S) NUMBER(S) DATES(S) **S-12; SE; SDN 662; SN 0096** Letter Date: 3/7/19 Stamp Date: 3/7/19 **Due Date: 9/7/19** #Priority Review
6. NAME OF DRUG OFEV®	7. NONPROPRIETARY NAME Nintedanib	
8. SUPPLEMENT PROVIDES FOR: the addition of a new indication: "Treatment of systemic sclerosis-associated interstitial lung disease (SSc-ILD)".		
9. PROPOSED INDICATION FOR USE Treatment of Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD)	10. HOW DISPENSED RX x_ OTC ___	11. RELATED IND/NDA/DMF
12. DOSAGE FORM(S) capsule	13. POTENCY 100 mg and 150 mg	
14. CHEMICAL NAME AND STRUCTURE ethanesulfonic acid - methyl (3Z)-3-{[(4-{methyl-[(4-methylpiperazin-1-yl)acetyl]amino}phenyl)amino]-(phenyl)methylidene}-2-oxo-2,3-dihydro-1H-indole-6-carbox late 1:1  Molecular Formula: $C_{31}H_{33}N_5O_4 \cdot C_2H_6O_3S$; Molecular Weight: 649.76		15. RECORDS AND REPORTS CURRENT YES__NO REVIEWED YES__NO
16. COMMENTS: No changes are noted in Sections 3, 11, and 16 of the OFEV Prescribing Information.		
17. CONCLUSIONS AND RECOMMENDATIONS Labeling changes are acceptable from CMC standpoint.		
18. REVIEWER NAME Chong-Ho Kim, Ph.D.	SIGNATURE	DATE COMPLETED May 5, 2019

Background:

Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) is submitting this supplement to NDA 205832 for OFEV® (nintedanib) capsules for the addition of a new indication: "Treatment of systemic sclerosis-associated interstitial lung disease (SSc-ILD)".

This supplement includes changes to the labeling to update the OFEV Prescribing Information within the following sections of the HIGHLIGHTS and full PRESCRIBING INFORMATION:

- INDICATIONS AND USAGE,
- DOSAGE AND ADMINISTRATION,
- WARNINGS AND PRECAUTIONS,
- ADVERSE REACTIONS, DRUG INTERACTIONS,
- USE IN SPECIFIC POPULATIONS,
- OVERDOSAGE,
- CLINICAL PHARMACOLOGY,
- CLINICAL STUDIES, and
- PATIENT COUNSELING INFORMATION.

The Patient Information has been revised for consistency with the full Prescribing Information.

Review

1.12 Other Correspondence

1.12.14 Environmental Analysis

Boehringer Ingelheim Pharmaceuticals, Inc. is claiming an exemption from the requirements for an EA for nintedanib capsules, based upon paragraph (b) of the regulation which allows a categorical exclusion for an action on an NDA if the action increases the use of the active moiety, but the estimated expected introduction concentration (EIC) of the substance at the point of entry into the aquatic environment will be below 1 part per billion.

Estimation of the concentration of the substance at the point of entry into the aquatic environment was calculated based on the July 1998 Guidance for Industry:
Environmental Assessment of Human Drug and Biologics Applications using the equation:

EIC-Aquatic (ppb) =Ax Bx C x D where

A = kg/year produced for direct use (as active moiety)
B = 1/liters per day entering POTWs*
C = year/365 days

D = 10^9 µg/kg (conversion factor)
* 1.214 x 1011 liters per day entering publicly owned treatment works (POTWs),

The estimated concentration is based on the maximum expected annual direct usage during the peak year within the first five years in the marketplace after approval of this request (Confidential Appendix 1). This results in an estimated concentration at the point of entry into the aquatic environment below 1 ppb from this action and all previously approved submissions (Confidential Appendix 2).

Evaluation: *Acceptable*
BIPI's claim for an exemption from the requirement for an EA for nintedanib capsule is acceptable.

1.14 Labeling

1.14.1 Draft Labeling

1.14.1.3 Draft Labeling Text

Evaluation: *Acceptable*
There are no changes in Sections 3, 11, and 16.

CONCLUSION AND RECOMMENDATION

No changes are noted in Sections 3, 11, and 16 of the OFEV Prescribing Information.

Labeling changes are acceptable from CMC standpoint.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHONG HO KIM
05/14/2019 01:32:03 PM

RAMESH RAGHAVACHARI
05/14/2019 11:10:22 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205832Orig1s012

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 205-832
Supporting documents No.:	Sequence 0662
Applicant's letter date:	March 7, 2019
CDER stamp date:	March 7, 2019
Product:	OFEV (nintedanib) capsules
Indication:	Idiopathic pulmonary fibrosis (IPF, approved) Systemic sclerosis associated interstitial lung disease – (SSc- ILD, proposed)
Applicant:	Boehringer Ingelheim
Review Division:	Pulmonary, Allergy and Rheumatology Products
Reviewer:	Luqi Pei, Ph.D.
Team Leader:	Carol Galvis, Ph.D.
Division Director:	Sally Seymour, M.D.
Project Manager:	Jessica Lee, Pharm. D.

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 205-832 are owned by BI or are data for which BI has obtained a written right of reference. Any information or data necessary for approval of NDA 205-832 that BI does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 205-832.

LABELING REVIEW

Edits to Section 12.1 Mechanism of Action of the proposed label for OFEV capsules submitted on March 7, 2019 (NDA 205-832/S-012, SDN 662) are recommended. The edits are made to ensure the labeling reflects the most current thinking of the Agency. See Section IV for the recommended edits.

I. INTRODUCTION

This review evaluates the proposed revisions to Section 12.1 Mechanism of Action of the OFEV (nintedanib) label (NDA 205-832/S-012). Boehringer Ingelheim (BI) submitted an efficacy supplement to the OFEV application on March 7, 2019 (Seq. #096, SDN #662, Supplement S-012). The supplement proposed to add systemic sclerosis-associated interstitial lung disease (SSc-ILD) as a new indication of OFEV Capsules, an approved and currently marketed product. Addition of the new indication and supporting clinical data necessitates labeling revisions. The revisions relevant to the nonclinical discipline were limited to Section 12.1 Mechanism of Action.[1]

The Agency has approved 8 versions of the OFEV label, but only 2 versions were related to the nonclinical discipline. These versions were approved on October 15, 2014 and February 4, 2016, (DARRTS ID# 3643917 and 3882552, respectively). The former was the original product label. The latter was the Pregnancy and Lactation Labeling Rule (PLLR)-compliant labeling conversion. The approvals of the nonclinical sections were based on the reviews completed by Dr. Luqi Pei on August 28, 2014 and January 25, 2016 (DARRTS ID# 3618575 and 3877455, respectively).

This review consists of 4 sections. Section I provides relevant background information. Section II presents the proposed revisions to Section 12.1 of the approved Ofev label. Section III evaluates the Applicant's proposal. Section IV presents conclusion and recommendations.

II. PROPOSED LABELING REVISION

Boehringer Ingelheim proposed to revise Section 12.1 Mechanism of Action of the OFEV capsule label as below. Highlights indicate proposed changes. Underline indicates addition. Strikethrough indicates deletion.

> **12.1 Mechanism of Action**
> Nintedanib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs). Nintedanib inhibits the following RTKs: platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, vascular endothelial growth factor receptor (VEGFR) 1-3, and ~~Fms-like tyrosine kinase-3 (FLT3)~~ colony stimulating factor 1 receptor (CSF1R). In addition, nintedanib

[1] The review will not discuss other nonclinical sections (e.g., 8.1 and 13.1) of the product label because the Applicant did not propose any changes to these sections.

(b) (4)

III. EVALUATIONS OF APPLICANT'S PROPOSAL

III.1 Summary of Proposed Labeling Revisions

For the convenience and clarity of discussions, the review groups the proposed revisions to Section 12.1 Mechanism of Action of the approved nintedanib label into 3 areas:

1. Modification of nintedanib targets. Specifically, BI proposed to (b) (4) (b) (4) colony stimulating factor 1 Receptor (CSF1R).
2. (b) (4)
3. Replacement of IPF with ILD and Change in statements about tissue fibrosis pathology.

III.2 Evidence in Support of the Proposed Revisions

BI submitted 6 pharmacology reports and 18 literature articles to support the proposed labeling changes summarized above. Table 1 summarizes findings in the reports of pharmacology studies. Briefly, nintedanib inhibited release of mediators by human T cells and peripheral blood mononuclear cells (PBMC) in vitro. It inhibited the proliferation and migration of human dermal fibroblasts in vitro. It attenuated fibrotic tissue formation in murine models of pulmonary, skin, and liver fibrosis. None of the reports evaluated the binding affinity to or IC_{50s} of nintedanib on individual RTKs or nRTKs.

Table 1: Summary of Newly Submitted Pharmacology Data

Report No.	Document #	Finding
2018-i-r-ppss-report1	n00264111-01	Inhibition of release of mediators by human T cells stimulated with anti-CD3 or anti-CD3 in combination with anti-CD28 (IC_{50} = 4.9 – 77 and nmol/L) [a]
2018-i-r-ppss-report2	n00264112-01	Inhibition of release of mediators by PBMCs with anti-CD3 or anti-CD3 in combination with anti-CD28 (IC_{50} = 17 – 59 and nmol/L) [a]
Dist-GvHD-Tsk-1-Fra-	n0023966	Inhibition of proliferation and migration of cultured primary human dermal fibroblasts (PHDF) induced by PDGF and TGFβ at 100 nmol/L in vitro
		Attenuation of skin and pulmonary fibrosis in mouse models
Dist-huFibro-Bleo-2012	n00239280	Inhibition of mRNA synthesis of proteins involved in connective tissue formation in cultured PHDF in vitro
		Attenuation of skin and pulmonary fibrosis in mouse models
LWN-1	n00265037-01	Inhibition of proliferation and migration of primary human lung fibroblasts from SSc-ILD patients induced by PDGF and TGFβ at 100 – 1000 nmol/L in in vitro
Umr7355-2inem	U12-2472-01	Inhibition of liver fibrosis in a mouse model

a. Mediators measured included IFNγ, IL-2, IL-4, IL-5, IL-10, IL12p70, and IL-13.

The review discusses selected literature articles relevant to the nonclinical evaluation of the proposed labeling changes only. The review will not discuss most papers because they were clinical reports and reviews discussing organ/system manifestations of sclerosis. The review also uses a paper that published after the applicant's submission of the supplement.

Wollin et al. compared inhibition of tyrosine kinase activities by nintedanib on its targets in BA/F3 cells (a murine tumor cell line) in vitro.[2] Table 2 summarizes IC_{50} values of assay results. The left half of the table presents insensitive targets (IC_{50s} > 250 nmol/L) based on the reviewer's opinion; the right half presents highly sensitive to nintedanib inhibition (IC_{50s} = 17 – 58 nmol/L). The nintedanib IC varied greatly among the kinases (i.e., 10 – 20 folds). (b) (4)

(b) (4)

[2] Wollin et el. Antifibrotic and anti-inflammatory activity of the tyrosine kinase inhibitor nintedanib in experimental models of lung fibrosis, *JPET*, 2014;349:209-220.

Table 2: Inhibition of Tyrosine Kinase in BA/F3 Cells by Nintedanib

Assay	IC_{50} (nM)	Assay	IC_{50} (nM)
FGFR1	300 - 1000	PDGFRα	41
FGFR2	257	PDGFRβ	58
FGFR3	300 - 1000	VEGFR2	46
FGFR4	300 - 1000	VEGFR3	33
VEGFR1	300 - 1000	LCK	22
LYN	300 - 1000	FLT-3	17
SRC	811		

Huang et al. reported nintedanib (50 – 60 mg/kg, PO) decreased serum levels of M-CSF1B and VEGF in the fos-related antigen-2 (Fra2) mice (Fig. 1).[3] These mice also showed statistically significant decreases ($p < 0.05$) in fibrotic area, hydroxyproline content, and myofibroblasts in the lung (not shown). Interestingly, nintedanib at 60 mg/kg (qd), but not 50 mg/kg (bid) caused decreases in VEGF levels in these mice.

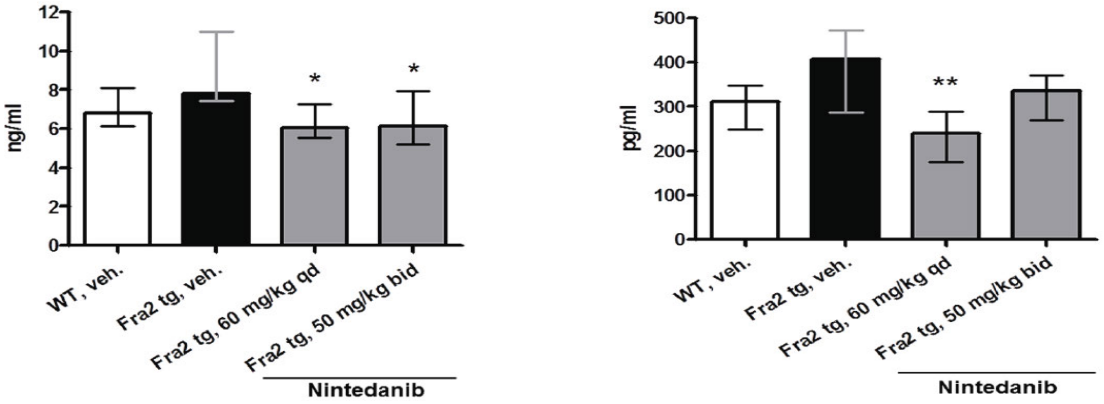


Fig 1: Nintedanib treatment decreases serum levels of M-CSF (A) and VEGF (B) in Fra2 transgenic mice. n=6 mice per group. *$0.01 \leq p < 0.05$; **$0.001 \leq p < 0.01$ versus vehicle-treated Fra2 transgenic mice. Fra2 tg, Fra2-transgenic mice; WT, vehicle-treated wild-type mice.

Huang et al. also reported that nintedanib inhibited polarization of human macrophages induced by M-CSF, IL-4, and IL-13 in vitro. Bellamri et al reported that nintedanib inhibited activation of CSF1R in human macrophages, reduced the adhesion of human macrophages, inhibited CCL2 gene expression induced by CSF1 in M0 macrophages, decreased production of IL-1b and IL-8 in M1 macrophages (pro-inflammation) and expression of M2 (pro-fibrosis) markers in vitro. [4]

[3] Huang et al. Nintedanib inhibits macrophage activation and ameliorates vascular and fibrotic manifestations in the Fra2 mouse model of systemic sclerosis. *Ann Rheum Dis* 2017;76(11):1941-1948.

[4] Bellamri et al., Alteration of human macrophage phenotypes by the anti-fibrotic drug nintedanib. Internat'l Immunopharmacol 2019;72:112-123.

III.3 Evaluation of the proposed changes

The submitted nonclinical information supports some of the proposed changes in Section 12.1 Mechanism of Action of the nintedanib label. There is sufficient information to support the addition of CSF1R as a target of nintedanib. There is insufficient information to support (b) (4), neither is there sufficient information to support (b) (4). The proposed edits to the inhibition of tyrosine kinases in pathogenesis of ILD appears acceptable, per discussions with the clinical discipline.

III.3.1 Modification of Nintedanib Targets

There is sufficient nonclinical data to support addition of CSF1R but insufficient information to support (b) (4).

1. BI proposed to add CSF1R (M-CSF receptor) to the list of nintedanib targets. Colony-stimulating factors (CSF) play an important role in the tissue fibrosis. Activation and proliferation of macrophages are associated with inflammation, which is a cause of many disease processes, including fibrosis. There are at least 3 known CSFs: M-CSF, GM-CSF, and G-CSF; and corresponding receptors (Table 4). These factors stimulate the differentiation and proliferation of individual types of white blood cells: granulocytes, macrophages, and eosinophils/macrophages. Colony-stimulating factors are glycoproteins that bind to receptor proteins on the surface of hemopoietic stem cells. The binding activates intracellular signaling pathways and result in cell proliferation and differentiation. See Metcalf's review (*Cancer Immunol Res* 2013;1(6):351-361) on the pharmacological and physiologic functions of CSFs.

Table 4: Colony Stimulating Factors

Code	Full name	Primary target	Drug name
M-CSF (CSF1)	Macrophage CSF	Macrophage (M0)	
GM-CSF (CSF2)	Granulocyte-macrophage CSF	Macrophage, eosinophil	Sargramostim
G-CSF (CSF3)	Granulocyte CSF	Neutrophil	Filgrastim

Data discussed in Section II.2 showed that nintedanib treatment resulted in decreases in serum M-CSF1B levels in Fra2 mice. M-CSF1B appears be the counterpart of M-CSF in mice. Nintedanib also inhibited function of CSF1R from human macrophages in vitro. The available data support the inclusion of CSF1R as a target of nintedanib.

2. (b) (4) Wollin et al. compared inhibition of tyrosine kinase activities by nintedanib on its targets in BA/F3 cells (a murine tumor cell line) in vitro. These results differed from what were reported in the original NDA

submission. For example, the mean IC_{50s} for VEGFR-1 was 34 ± 15 and 300 – 1000 in the original NDA and Wollin's report, respectively.[5] The exact reason for the difference is unknown, but the species difference in VEGFR-1 could be a factor. The original labeling review used data from receptors and cells of human origin while Wollin used a murine cell line. (b) (4)

III.3.2 (b) (4)

BI proposed to (b) (4) from Section 12.1 (highlight below):

(b) (4)

III.3.3 Replacing IPF with ILD

BI proposed to replace IPF with ILD and to change in pathogenesis of tissue fibrosis as shown in Table 3. The highlighted section reflects the proposed change. The review team discussed the proposed in the August 1, 2019 meeting. The team determined that the proposed wording was acceptable.

Table 3: Approved and Proposed Text for Mechanism of Action of Nintedanib

Approved	Proposed
Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these receptors and blocks the intracellular signaling which is crucial for the proliferation, migration, and transformation of fibroblasts representing essential mechanisms of the IPF pathology.	Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these kinases and blocks the intracellular signaling cascades, which have been demonstrated to be involved in the pathogenesis of fibrotic tissue remodeling in interstitial lung diseases.

[5] See the nonclinical original NDA review (p29, Table 12) completed by Dr. Luqi Pei on August 28, 2014 (DARRTS ID# 3618575).

IV. CONCLUSION AND RECOMMENDATION

Edits to the Section 12.1 of the proposed labeling are recommended. Below are recommended text and edits to the Applicant's proposal (a clean copy and track change version, respectively). The highlight in Paragraph 2 presents the recommended edits to the Applicant's proposal. Underline indicate addition while strikeout indicate deletion.

1. Nintedanib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs). Nintedanib inhibits the following RTKs: platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, vascular endothelial growth factor receptor (VEGFR) 1-3, colony stimulating factor 1 receptor (CSF1R), and Fms-like tyrosine kinase-3 (FLT3). These kinases except for FLT-3 have been implicated in pathogenesis of interstitial lung disease (ILD). Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these kinases and blocks the intracellular signaling cascades, which have been demonstrated to be involved in the pathogenesis of fibrotic tissue remodeling in ILD. Nintedanib also inhibits the following nRTKs: Lck, Lyn and Src kinases. The contribution of FLT3 and nRTK inhibition to nintedanib efficacy in ILD is unknown.

2. Nintedanib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs). Nintedanib inhibits the following RTKs: platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, vascular endothelial growth factor receptor (VEGFR) 1-3, ~~and~~ colony stimulating factor 1 receptor (CSF1R), and Fms-like tyrosine kinase-3 (FLT3). ~~In addition, Nintedanib also inhibits the following nRTKs: Lck, Lyn and Src kinases.~~ These kinases except for FLT-3 have been implicated in ~~IPF~~ pathogenesis of interstitial lung disease (ILD). Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these kinases and blocks the intracellular signaling cascades, which have been demonstrated to be involved in the pathogenesis of fibrotic tissue remodeling in ILD (b) (4). Nintedanib also inhibits the following nRTKs: Lck, Lyn and Src kinases. ~~–~~The contribution of FLT3 and nRTK inhibition to ~~IPF~~ nintedanib efficacy in ILD is unknown.

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LUQI PEI
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CAROL M GALVIS
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I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205832Orig1s012

STATISTICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 03, 2019

TO: File for NDA 205832

THROUGH: Yongman Kim, Ph.D.

FROM: Yu Wang, Ph.D.

SUBJECT: Statistical Primary Review

APPLICATION/DRUG: Supplemental NDA 205832 S012/Ofev(nintedanib)

Executive Summary

The applicant submitted a supplement to NDA 205832 for OFEV (nintedanib) capsules for the addition of a new indication, treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD). The program consisted of a single study, Study 1199.214, a double-blind, randomized, placebo controlled trial evaluating efficacy and safety of oral nintedanib treatment for at least 52 weeks in patients with SSc-ILD.

Based on the study statistical analysis plan: the primary analysis result was statistically significant; the pattern mixture sensitivity analyses assuming certain missing not at random assumptions showed a lack of robustness in the primary analysis result and the tipping point analysis exploring a broader space of assumptions did not provide a clear robustness of the primary analysis result and necessitated a further clinical interpretation. Results from secondary endpoints were not supportive.

Applying the primary and sensitivity analyses to the expanded dataset, we found: treatment effect was slightly larger (43 mL/Year from the expanded dataset vs. 41 mL/Year from the 52 Week data); among the three PMM approaches, the PMM1 approach, an estimator of treatment effect relatively better aligned with the treatment policy estimand, failed significance test with a p-value of 0.067; the PMM2 approach just failed significance test with a p-value of 0.051 possibly due to simulation variability from multiple imputation and the PMM3 sensitivity analysis was significant with a p-value of 0.044; the tipping point analysis results support robustness of the primary analysis result.

All the above sensitivity analyses were aligned to a certain degree with estimating the treatment policy estimand. Although all three PMM analyses on the expanded dataset lean toward supporting the primary analysis compared to those on the original dataset, we still see a failure to obtain statistical significance in one of the three sensitivity analyses, after using data in a post hoc sensitivity analysis.

Another limitation in strength of efficacy is regarding long term treatment effect, the assessment of which was not powered by the study design and exploratory analyses of which showed mixed results.

In summary, the primary statistical reviewer considers the program had limitations in both study design and analyses; the totality of evidence provided by the clinical development program is yet to demonstrate the expected substantial amount of evidence in supporting the treatment policy estimand in general. There are ways to mitigate the limitations, for example, a subsequent study to address the above limitations, or a refinement of the study estimand and patient population to patients who can tolerate the drug.

In this complex disease setting, this primary statistical reviewer defer the approval decision making to the clinical colleagues.

Refer to the Multi-disciplinary Review and Evaluation for additional details.

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YU WANG
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YONGMAN KIM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205832Orig1s012

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	August 21, 2019
To:	Sally Seymour, MD Acting Director **Division of Pulmonary, Allergy and Rheumatoid Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Kyle Snyder, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	OFEV (nintedanib)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 205832
Supplement Number:	S-012
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.

1 INTRODUCTION

On March 7, 2019 Boehringer Ingelheim Pharmaceuticals, Inc. submitted for the Agency's review, Supplemental New Drug Application (sNDA) 205832/S-012 for OFEV (nintedanib) capsules, for oral use. The purpose of this sNDA is to propose the addition of a new indication "Treatment of systemic sclerosis-associated interstitial lung disease (SSc-ILD)" and provide updates to the OFEV Prescribing Information (PI) and Patient Package Insert (PPI) accordingly.

OFEV (nintedanib) was originally approved on October 15, 2014 and is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) on March 25, 2019 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for OFEV (nintedanib) capsules, for oral use.

2 MATERIAL REVIEWED

- Draft OFEV (nintedanib) capsules, for oral use PPI received on March 7, 2019, revised by the Review Division throughout the review cycle, and received by DMPP on August 13, 2019.
- Draft OFEV (nintedanib) capsules, for oral use PPI received on March 7, 2019, revised by the Review Division throughout the review cycle, and received by OPDP on August 13, 2019.
- OFEV (nintedanib) capsules, for oral use PI received on March 7, 2019, revised by the Review Division throughout the review cycle, and received by DMPP on August 13, 2019.
- OFEV (nintedanib) capsules, for oral use PI received on March 7, 2019, revised by the Review Division throughout the review cycle, and received by OPDP on August 13, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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MARCIA B WILLIAMS
08/21/2019 11:55:58 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 20, 2019

To: Khalid Puthawala, Clinical Reviewer
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Jessica Lee, Regulatory Project Manager, (DPARP)

From: Kyle Snyder, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Team Leader, OPDP

Subject: OPDP Labeling Comments for OFEV® (nintedanib) capsules, for oral use

NDA: 205832/S-012

In response to DPARP's consult request dated March 25, 2019, OPDP has reviewed the proposed prescribing information (PI) and patient package insert (PPI) for OFEV® (nintedanib) capsules, for oral use. This supplement provides for a new indication for treatment of systemic sclerosis-associated interstitial lung disease.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DPARP on August 13, 2019, and are provided below.

PPI: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Kyle Snyder at (240) 402-8792 or kyle.snyder@fda.hhs.gov.

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KYLE SNYDER
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CLINICAL INSPECTION SUMMARY

Date	July 2, 2019
From	Min Lu, M.D., M.P.H., Medical Officer Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Nadia Habal, M.D., Clinical Reviewer Rachel Glaser, M.D., Clinical Team Leader Jessica Lee, Regulatory Project Manager Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
NDA	205832/S012
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Drug	Ofev (nintedanib)
NME	No
Therapeutic Classification	Kinase inhibitor
Proposed Indication	Treatment of Systemic Sclerosis Associated Interstitial Lung Disease
Consultation Request Date	April 8, 2019
Summary Goal Date	July 5, 2019
Action Goal Date	September 6, 2019
PDUFA Date	September 6, 2019

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites (Drs. Sfikakis and Highland) were selected for inspections for Study Protocol 1199.214, entitled "A double-blind, randomized, placebo-controlled trial evaluating efficacy and safety of oral nintedanib treatment for at least 52 weeks in patients with 'Systemic Sclerosis associated Interstitial Lung Disease' (SSc-ILD)." The study data derived from these clinical sites, based on the inspections, are considered reliable and the studies in support of this application appear to have been conducted adequately.

2. BACKGROUND

OFEV (nintedanib) is a kinase inhibitor approved in 2014 for the treatment of idiopathic pulmonary fibrosis (IPF). Systemic sclerosis is a rare chronic disease of unknown cause characterized by diffuse fibrosis and vascular abnormalities in the skin, joints, and internal organs (especially the esophagus, lower gastrointestinal tract, lungs, heart, and kidneys). Currently, immunosuppressive agents (mycophenolate mofetil, cyclophosphamide, methotrexate, azathioprine, and prednisone) have been used to address the organ-specific manifestations.

In this application, the sponsor submitted the results from a Phase 3 study (Protocol 1199.214) for nintedanib to support the proposed new indication for the treatment of systemic sclerosis associated interstitial lung disease (SSc-ILD).

Protocol 1199.214

This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study in patients with SSc-ILD. The primary objective of the study was to investigate the efficacy and safety of nintedanib 150 mg twice daily in patients with SSc-ILD.

The primary efficacy endpoint of the study was the annual rate of decline in forced vital capacity (FVC) in mL over 52 weeks. The key secondary efficacy endpoints included absolute change from baseline in the modified Rodnan Skin Score (mRSS) at Week 52 and absolute change from baseline in the Saint George's Respiratory Questionnaire (SGRQ) total score at Week 52.

The main inclusion criteria of the study included patients aged ≥18 years, with onset of systemic sclerosis (defined as the first non-Raynaud symptom) ≤7 years before screening; ≥10% fibrosis of the lungs, confirmed by central review of a chest high-resolution computed tomography (HRCT) scan; FVC ≥40% predicted; and hemoglobin (Hb)-corrected carbon monoxide diffusion capacity (DLco) 30 to 89% predicted.

Patients were randomized in 1:1 ratio to nintedanib 150 mg twice a day or placebo. Randomization was stratified by anti-topoisomerase antibody (ATA) status (positive or negative). The main efficacy and safety assessments were performed during the study. Individual patients stayed on blinded trial treatment until the last randomized patient reached 52 weeks of treatment, but no longer than 100 weeks. Patients were followed up for 28 days after the end of treatment. Patients could participate in an open-label extension trial (Study1199.225) at the end of the study, in which all patients received nintedanib treatment.

The study screened 819 subjects and randomized 580 subjects in 194 sites in 32 countries in Asia, Australia, Europe, North America, and South America. The first subject enrolled on November 30, 2015 and the last subjects completed the last visit in this study on November 28, 2018.

Rationale for Site Selection

Two clinical sites were selected using risk ranking from the clinical site selection tool based on high enrollment, better efficacy results for study drug, high discontinuation rate, and the number of adverse events and deaths reported at those sites.

3. RESULTS (by site):

1) Petros Sfikakis, M.D. (Site #30001, Athens, Grace)

The site screened 14 subjects and enrolled 10 subjects in Study Protocol 1199.214. Among the 10 enrolled subjects, six subjects completed the study and four subjects discontinued the study. The reason of discontinuations included three deaths (Subject (b) (6) in the placebo group died of acute myocardial infarction; Subject (b) (6) in the placebo group died of sudden death/ myocarditis; and Subject (b) (6) in the nintedanib group died of chest pain/cardiorespiratory arrest/myocarditis) and adverse events (Subject (b) (6) in the nintedanib group experienced diarrhea, dermatitis psoriasiform, and upper abdominal pain). An audit was conducted for all 10 enrolled subjects.

The inspection evaluated the following documents: source records, sponsor and monitor correspondence, screen and enrollment log, test article accountability logs, primary efficacy endpoint, adverse events reports, concomitant medication logs, protocol deviation reports, discontinuations, electronic case report forms, and informed consent forms. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. All adverse events and serious adverse events were entered into the electronic case report form (eCRF). No under-reporting of adverse events was noted.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. No significant observations were identified. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

2) Kristin Highland, M.D. (Site #10011, Cleveland, OH)

The site screened 10 subjects and enrolled nine subjects in Study Protocol 1199.214. Among the nine enrolled subjects, eight subjects completed the study and one subject (Subject (b) (6) in the placebo group) discontinued due to adverse events (diarrhea, night sweats and nausea; diagnosed with diverticulosis). An audit was conducted for all nine enrolled subjects.

The inspection included review of Institution Review Board (IRB) correspondence and approvals, monitor correspondence and monitoring records, screen and enrollment logs, investigational product accountability and storage, electronic records, review of data in electronic case report forms (eCRFs) and other source records, subject files, informed consent forms (ICFs) and all other pertinent records. The information found in the data listings were compared to the information found in the source records. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. Verification of the primary efficacy data was performed by comparing the results

of the Forced Vital Capacity (FVC) at Visit one to the FVC at Week 52/Visit 9 to the data listings. No discrepancies were identified between the source documents and the data listings. The key secondary endpoint change in modified Rodnan Skin Score was verifiable. The value for the St. George's Respiratory Questionnaire (SGRQ) were calculated by the sponsor; however values in the eCRF matched those in the source documents. For Subject (b) (6) (in the nintedanib group) the FVC was not measured at Week 52 due to a pneumothorax adverse event. The 52-week data for absolute change in the modified Rodnan Skin Score for Subject (b) (6) (in placebo group) was not submitted due to the assessment being performed by the sub-investigator when the principal investigator had performed the initial assessment. The study required the same accessor to avoid interobserver variability.

No under-reporting of adverse events was noted. Each of the AEs were assessed for severity and relationship to the study drug. All concomitant medications were well documented.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. No significant observations were identified. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

{See appended electronic signature page}

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/s/

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