

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### *APPLICATION NUMBER:*

**205832Orig1s013**

*Trade Name:* OFEV Capsules

*Generic or Proper Name:* nintedanib

*Sponsor:* Boehringer Ingelheim Pharmaceuticals Inc.

*Approval Date:* March 9, 2020

*Indication:* Treatment for chronic fibrosing interstitial lung diseases with a progressive phenotype.

# CENTER FOR DRUG EVALUATION AND RESEARCH

## 205832Orig1s013

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**APPROVAL LETTER**



NDA 205832/S-013

## **SUPPLEMENT APPROVAL**

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

Attention: Lorraine W. Sachs, M.S., RAC  
Senior Associate Director

Dear Ms. Sachs:

Please refer to your supplemental new drug application (sNDA) dated September 9, 2019, received September 9, 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 the addition of a new indication: treatment for chronic fibrosing interstitial lung diseases with a progressive phenotype.

### **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**

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

### **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.<sup>1</sup> Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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<sup>1</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

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*.<sup>2</sup>

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.

We are waiving the pediatric study requirement for ages 0 to <6 years because there is evidence strongly suggesting that the drug product would be ineffective and/or unsafe in this pediatric group, such that the risk-benefit profile in this age group would not favor nintedanib use.

We are deferring submission of your pediatric study for ages 6 to 18 years for this application because this product is ready for approval for use in adults and the pediatric study have not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act/FDCA are required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act/FDCA. This required study is listed below.

3807-1      Conduct a randomized double-blind placebo-controlled trial of  $\geq 24$  weeks in pediatric patients ages 6 to less than 18 years with fibrosing interstitial lung disease with a progressive phenotype. The objective of this trial will

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<sup>2</sup> 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>.

be to characterize the pharmacokinetics and safety in this population, as well as collect efficacy data.

Final Protocol Submission:	06/2020
Study Completion:	06/2023
Final Report Submission:	03/2024

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.<sup>3</sup>

Submit the protocol(s) to your IND 129333, with a cross-reference letter to this NDA. Reports of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

### **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*.<sup>4</sup>

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<sup>3</sup> See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019)*.

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

<sup>4</sup> 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>.

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at [FDA.gov](http://FDA.gov).<sup>5</sup> Information and Instructions for completing the form can be found at [FDA.gov](http://FDA.gov).<sup>6</sup> For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see [FDA.gov](http://FDA.gov).<sup>7</sup>

## **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 Insert

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<sup>5</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

<sup>6</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

<sup>7</sup> <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.**  
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/s/  
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BANU A KARIMI SHAH

03/09/2020 10:17:56 AM

signing with the delegated authority of Dr. Sally Seymour, Division Director, DPARP

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

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**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<sup>®</sup> (nintedanib) capsules, for oral use  
Initial U.S. Approval: 2014

### RECENT MAJOR CHANGES

Indications and Usage (1)	3/2020
Dosage and Administration, Testing Prior to OFEV Administration (2.1)	9/2019
Warnings and Precautions (5)	3/2020

### INDICATIONS AND USAGE

OFEV is a kinase inhibitor indicated for:

- Treatment of idiopathic pulmonary fibrosis (IPF). (1.1)
- Treatment of chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype (1.2)
- Slowing the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD). (1.3)

### 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 ( $\geq 5\%$ ) 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](http://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: 3/2020

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- 1.2 Chronic Fibrosing Interstitial Lung Diseases with a Progressive Phenotype
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## 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 Chronic Fibrosing Interstitial Lung Diseases with a Progressive Phenotype

OFEV is indicated for the treatment of chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype [see *Clinical Studies (14.2)*].

#### 1.3 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 (Study 1, Study 2, and Study 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 chronic fibrosing ILDs with a progressive phenotype study (Study 5), the majority (95%) of patients with ALT and/or AST elevations had elevations less than 5 times ULN and the majority (94%) 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 (Study 1, Study 2, and Study 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 chronic fibrosing ILDs with a progressive phenotype study (Study 5), diarrhea was reported in 67% versus 24% of patients treated with OFEV and placebo, respectively [see *Adverse Reactions (6.1)*]. Diarrhea led to permanent dose reduction in 16% of patients treated with OFEV compared to less than 1% of placebo-treated patients. Diarrhea led to discontinuation of OFEV in 6% 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 to 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 dose reduction or 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 (Study 1, Study 2, and Study 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 chronic fibrosing ILDs with a progressive phenotype study (Study 5), nausea was reported in 29% versus 9% and vomiting was reported in 18% versus 5% 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 (Study 1, Study 2, and Study 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 chronic fibrosing ILDs with a progressive phenotype study (Study 5), nausea led to discontinuation of OFEV in less than 1% 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 (Study 1, Study 2, and Study 3), arterial thromboembolic events were reported in 2.5% of patients treated with OFEV and less than 1% 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 less than 1% of placebo-treated patients. In the chronic fibrosing ILDs with a progressive phenotype study (Study 5), arterial thromboembolic events were reported in less than 1% of patients in both treatment arms. Myocardial infarction was observed in less than 1% of patients in both treatment arms. 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 (Study 1, Study 2, and Study 3), bleeding events were reported in 10% of patients treated with OFEV and in 7% of patients treated with placebo. In the chronic fibrosing ILDs with a progressive phenotype study (Study 5), bleeding events were reported in 11% of patients treated with OFEV and in 13% 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 clinical trials, epistaxis was the most frequent bleeding event reported.

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 (Study 1, Study 2, and Study 3), gastrointestinal perforation was reported in less than 1% of patients treated with OFEV, compared to 0 cases in the placebo-treated patients. In the chronic fibrosing ILDs with a progressive phenotype study (Study 5), gastrointestinal perforation was not reported in any patients in any treatment arm. 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, 332 patients with chronic fibrosing ILDs with a progressive phenotype, 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 (Study 2 and Study 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  $\geq 5\%$  of OFEV-treated Patients and More Commonly Than Placebo in Study 1, Study 2, and Study 3**

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

<sup>a</sup> Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain and abdominal tenderness.

<sup>b</sup> 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.

<sup>c</sup> 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%). Alopecia was also reported in more patients treated with OFEV than placebo (0.8% vs. 0.4%).

#### *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%), and in 15 (28%) versus 7 (14%) patients 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)*].

#### Chronic Fibrosing Interstitial Lung Diseases with a Progressive Phenotype

OFEV was studied in a phase 3, double-blind, placebo-controlled trial (Study 5) in which 663 patients with chronic fibrosing ILDs with a progressive phenotype were randomized to receive OFEV 150 mg twice daily (n=332) or placebo (n=331) for at least 52 weeks. At 52 weeks, the median duration of exposure was 12 months for patients in both treatment arms. Subjects ranged in age from 27 to 87 years (median age of 67 years). The majority of patients were Caucasian (74%) or Asian (25%). Most patients were male (54%).

The most frequent serious adverse event reported in patients treated with OFEV, more than placebo, was pneumonia (4% vs. 3%). Adverse events leading to death were reported in 3% of patients treated with OFEV and in 5% of patients treated with placebo. No pattern was identified in the adverse events leading to death.

Adverse reactions leading to permanent dose reductions were reported in 33% 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 (16%).

Adverse reactions leading to discontinuation were reported in 20% of OFEV-treated patients and 10% of placebo-treated patients. The most frequent adverse reaction that led to discontinuation in OFEV-treated patients was diarrhea (6%).

The safety profile in patients with chronic fibrosing ILDs with a progressive phenotype treated with OFEV was consistent with that observed in IPF patients. In addition, the following adverse events were reported in OFEV more than placebo in chronic progressive fibrosing ILD: nasopharyngitis (13% vs. 12%), upper respiratory tract infection (7% vs 6%), urinary tract infection (6% vs. 4%), fatigue (10% vs. 6%), and back pain (6% vs. 5%).

#### 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  $\geq 5\%$  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 <sup>a</sup>	18%	11%
Liver enzyme elevation <sup>b</sup>	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 <sup>c</sup>	5%	2%

<sup>a</sup> Includes abdominal pain, abdominal pain upper, abdominal pain lower, and esophageal pain.

<sup>b</sup> Includes alanine aminotransferase increased, gamma-glutamyltransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, blood alkaline phosphatase increased, transaminase increased, and hepatic function abnormal.

<sup>c</sup> Includes hypertension, blood pressure increased, and hypertensive crisis.

In addition, alopecia was reported in patients treated with OFEV, more than placebo (1.4% vs. 1.0%).

## 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 sternbrae (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 (Study 1, Study 2, and Study 3), 61% were 65 and over, while 16% were 75 and over. In the chronic fibrosing ILDs with a progressive phenotype clinical study (Study 5), 61% were 65 and over, while 19% were 75 and older. In SSc-ILD (Study 4), 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.

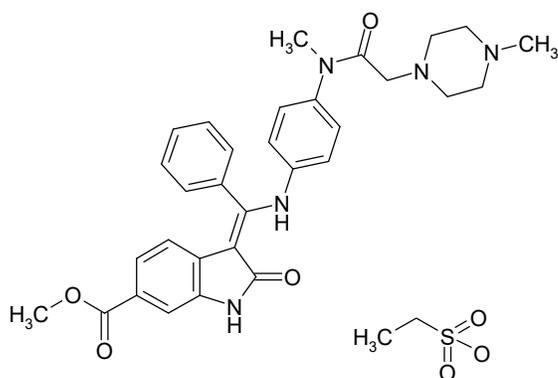
## 10 OVERDOSAGE

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)  $\alpha$  and  $\beta$ , 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 FLT-3 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 chronic fibrosing ILDs with a progressive phenotype, 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 CYP3A4 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 [<sup>14</sup>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  $AUC_{0-inf}$  (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  $AUC_{0-inf}$  (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 H<sub>2</sub> 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 [NCT00514683]) and two phase 3 studies (Study 2 [NCT01335464] and Study 3 [NCT01335477]). These were randomized, double-blind, placebo-controlled studies comparing treatment with OFEV 150 mg twice daily to placebo for 52 weeks.

Study 2 and Study 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 Study 2 and Study 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<sub>1</sub>/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 Study 1, Study 2, and Study 3<sup>a</sup>**

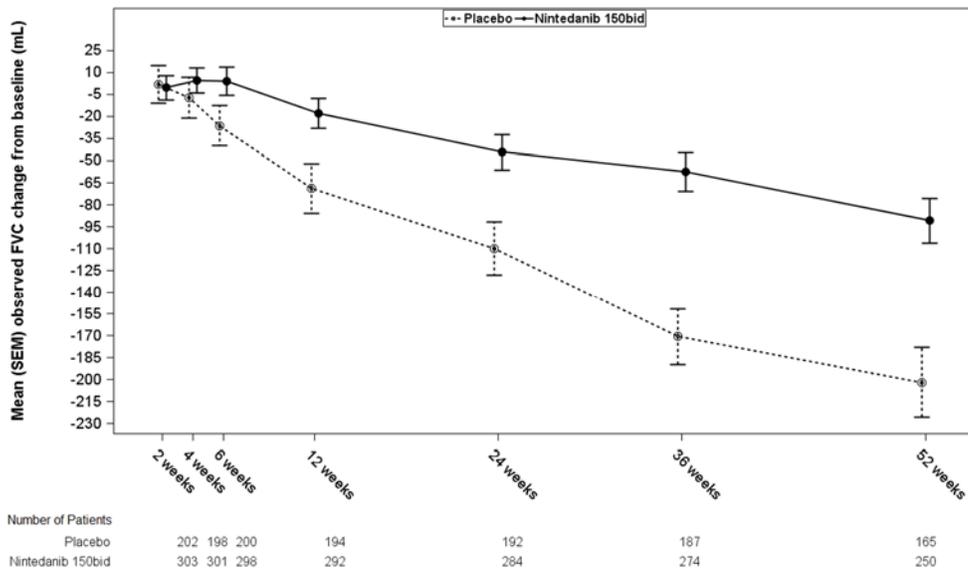
	Study 1		Study 2		Study 3	
	OFEV 150 mg twice daily	Placebo	OFEV 150 mg twice daily	Placebo	OFEV 150 mg twice daily	Placebo
Number of analyzed patients	84	83	309	204	329	219
Rate <sup>a</sup> of decline over 52 weeks	-60	-191	-115	-240	-114	-207
Comparison vs placebo Difference <sup>b</sup>	131		125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

<sup>a</sup>Randomized set in Study 1; treated set in Study 2 and Study 3

<sup>b</sup>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 Study 1 and Study 3.

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

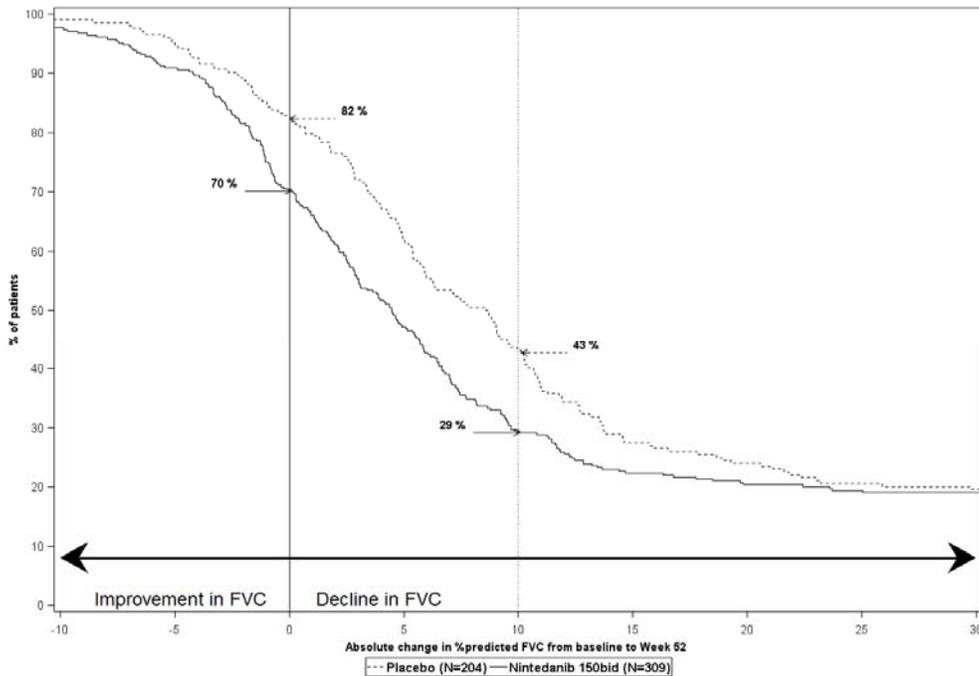


bid = twice daily

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  $\geq 0\%$  decline or  $\geq 10\%$  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

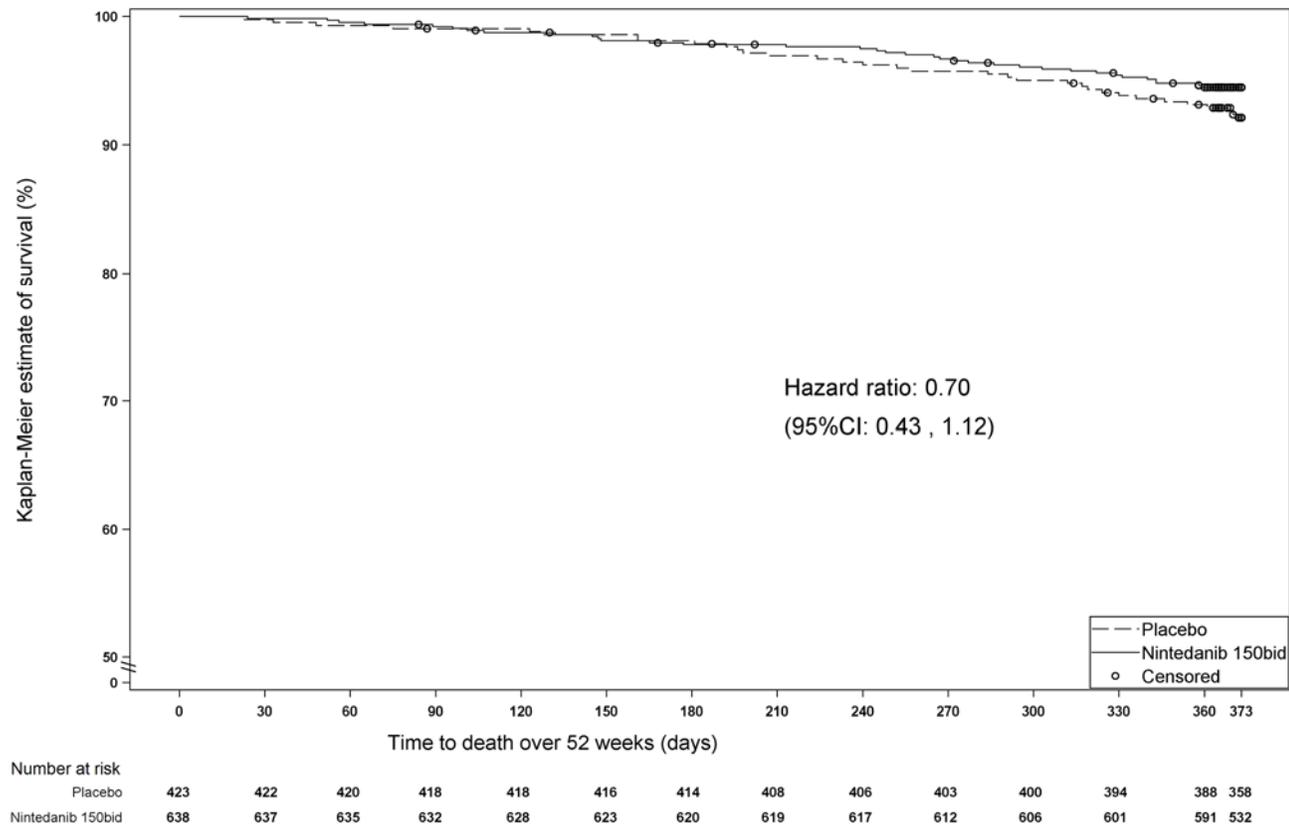
### Time to First Acute IPF Exacerbation

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 Study 2 and Study 3. In Study 1 (investigator-reported) and Study 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 Study 2 and Study 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: Study 2 and Study 3**



bid = twice daily

### 14.2 Chronic Fibrosing Interstitial Lung Diseases with a Progressive Phenotype

The clinical efficacy of OFEV has been studied in patients with chronic fibrosing ILDs with a progressive phenotype in a randomized, double-blind, placebo-controlled phase 3 trial (Study 5 [NCT02999178]). A total of 663 patients were randomized in a 1:1 ratio to receive either OFEV 150 mg twice daily or matching placebo for at least 52 weeks. Randomization was stratified based on high resolution computed tomography (HRCT) fibrotic pattern as assessed by central readers: 412 patients with UIP-like HRCT pattern and 251 patients with other HRCT fibrotic patterns were randomized. There were 2 co-primary populations defined for the analyses in this trial: all patients (the overall population) and patients with HRCT with UIP-like HRCT fibrotic pattern.

The primary endpoint was the annual rate of decline in FVC (in mL) over 52 weeks. Other endpoints included time to first acute ILD exacerbation and time to death.

Patients with a clinical diagnosis of a chronic fibrosing ILD were selected if they had relevant fibrosis (greater than 10% fibrotic features) on HRCT and presented with clinical signs of progression (defined as FVC decline  $\geq 10\%$ , FVC decline  $\geq 5\%$  and  $<10\%$  with worsening symptoms or imaging, or worsening symptoms and worsening imaging all in the 24 months prior to screening). Patients were required to have an FVC greater than or equal to 45% of predicted and a DLCO 30% to less than 80% of predicted. Patients were required to have progressed despite management deemed appropriate in clinical practice by investigators for the patient’s relevant ILD.

Patients with IPF, relevant airways obstruction (i.e., pre-bronchodilator FEV1/FVC less than 0.7), or significant pulmonary hypertension 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. Patients were also excluded if they received other investigational therapy, previous treatment with nintedanib or pirfenidone, azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, oral corticosteroids greater than 20 mg/day, or the combination of oral corticosteroids + azathioprine + n-acetylcysteine within 4 weeks of randomization, cyclophosphamide within 8 weeks prior to randomization, or rituximab within 6 months.

The majority of patients were Caucasian (74%) or Asian (25%). Patients were mostly male (54%) and had a mean age of 66 years and a mean FVC percent predicted of 69%, and 49% were never-smokers. The underlying clinical ILD diagnoses in groups represented in the trial were hypersensitivity pneumonitis (26%), autoimmune ILDs (26%), idiopathic nonspecific interstitial pneumonia (19%), unclassifiable idiopathic interstitial pneumonia (17%), and other ILDs (12%).

#### Annual Rate of Decline in FVC

There was a statistically significant reduction in the annual rate of decline in FVC (in mL) over 52 weeks in patients receiving OFEV compared to patients receiving placebo. The annual rate of decline in FVC (in mL) over 52 weeks was significantly reduced by 107 mL in patients receiving OFEV compared to patients receiving placebo. Results in the subpopulations of patients with HRCT with UIP-like fibrotic pattern and patients with other fibrotic patterns (Other HRCT) are included with the overall population in Table 4.

**Table 4 Annual Rate of Decline in FVC (mL) in Study 5**

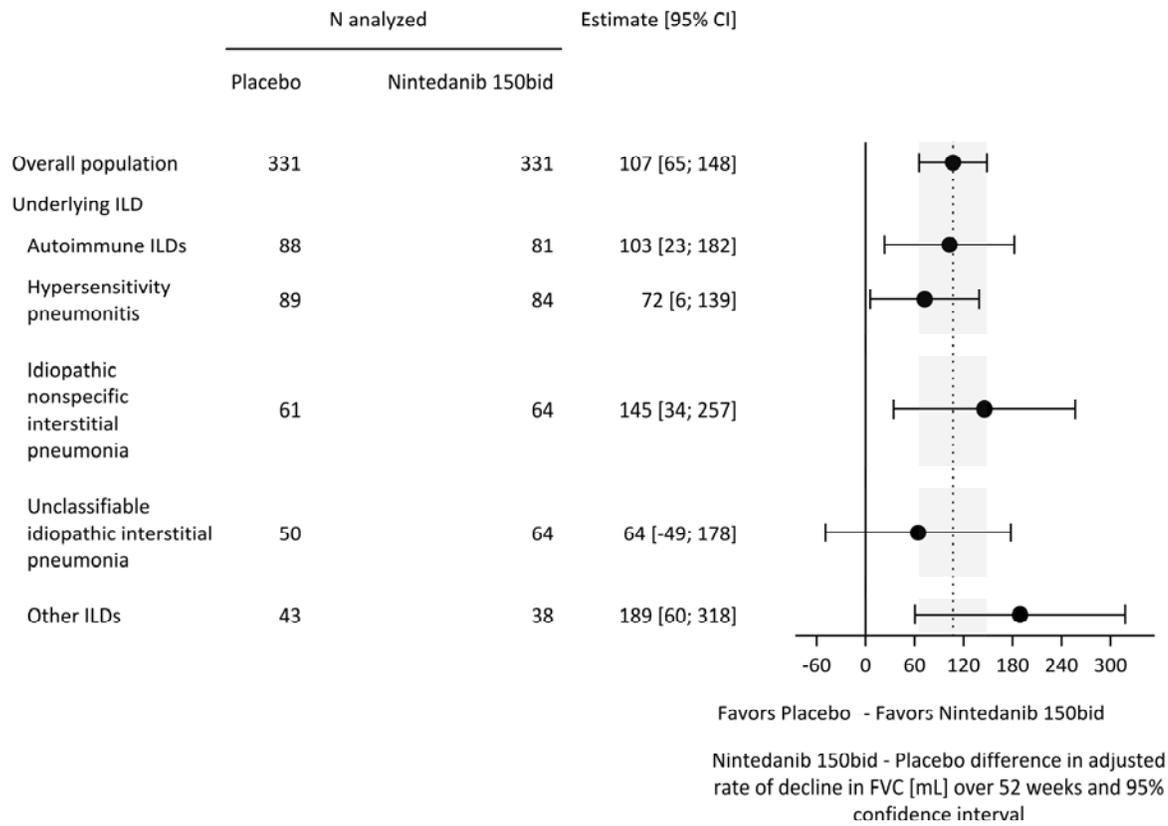
	Overall		UIP-like Subpopulation		Other HRCT Subpopulation	
	OFEV	Placebo	OFEV	Placebo	OFEV	Placebo
Number of analyzed patients	331	331	206	206	125	125
Adjusted annual rate of decline over 52 weeks	-81	-188	-83	-211	-79	-154
Comparison vs placebo difference <sup>a</sup>	107		128		75*	
95% CI	(65, 148)		(71, 186)		(16, 135)*	

<sup>a</sup>Comparison based on the Other HRCT subpopulation was not included in the multiple testing procedure. Values shown here are for descriptive purposes.

<sup>a</sup>Based on a random coefficient regression model with fixed categorical effects of treatment, HRCT pattern, fixed continuous effects of time, baseline FVC (mL), and including treatment by time and baseline by time interactions

A post-hoc exploratory analysis by ILD diagnosis was performed and is shown in Figure 4. Treatment response across ILD diagnoses was consistent for FVC.

**Figure 4 Annual Rate of Decline in FVC (mL) over 52 Weeks based on Underlying ILD Diagnosis in Study 5\***

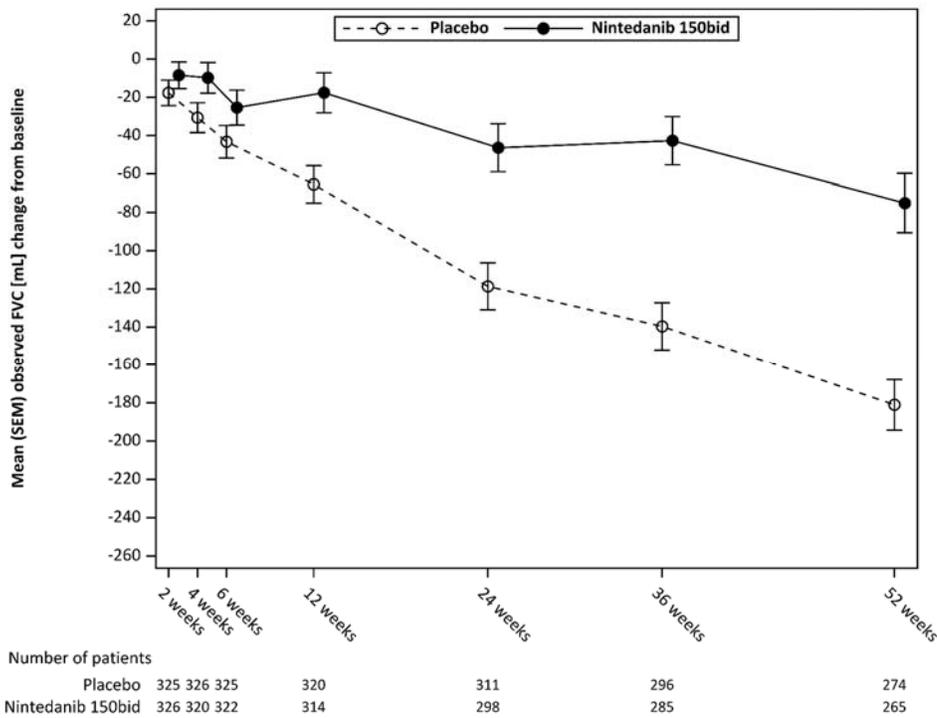


ILD = interstitial lung disease; Autoimmune ILDs: includes rheumatoid arthritis-associated ILD, mixed connective tissue disease, systemic sclerosis-associated ILD, and other terms; Other ILDs: includes fibrosing ILDs not categorized under autoimmune ILDs, hypersensitivity pneumonitis, idiopathic nonspecific interstitial pneumonia, or unclassifiable idiopathic interstitial pneumonia. The three most common ILDs in this category are exposure-related ILD, sarcoidosis, and pleuro-parenchymal fibroelastosis.

\*These results are from a post-hoc exploratory analysis. Values shown here are for descriptive purposes.

Figure 5 shows the change in FVC from baseline over time in the treatment groups. When the mean observed FVC change from baseline was plotted over time, the curves diverged at all timepoints through Week 52.

**Figure 5 Mean (SEM) Observed FVC Change from Baseline (mL) Over 52 Weeks in Study 5**

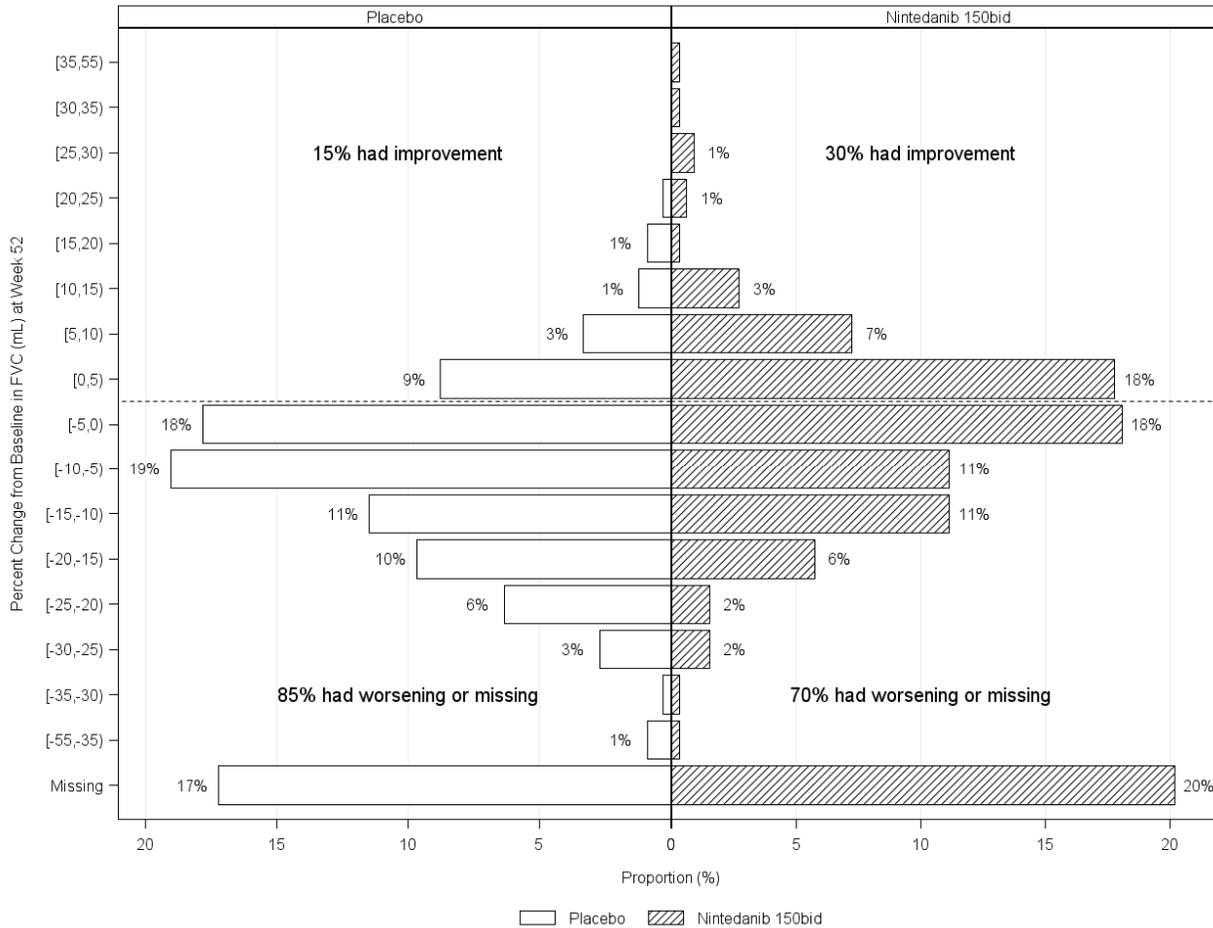


bid = twice daily

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 5. 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 5)<sup>a</sup>**



<sup>a</sup> 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

**Time to First Acute ILD Exacerbation**

Acute ILD exacerbation was defined as unexplained worsening or development of dyspnea within 30 days, new diffuse pulmonary infiltrates on chest x-ray, and/or new HRCT parenchymal abnormalities with no pneumothorax or pleural effusion, and exclusion of alternative causes. Acute ILD exacerbations were not adjudicated.

The risk of first acute ILD exacerbation did not show a statistically significant difference between the OFEV group compared to placebo (52 week treatment period: HR 0.72, (95% CI: 0.38, 1.37); whole trial: HR 0.63 (95% CI: 0.37, 1.07)).

**Survival**

Survival was evaluated for OFEV compared to placebo in Study 5 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 (52 week treatment period: HR 0.94 (95% CI: 0.47, 1.86); whole trial: HR 0.78 (95% CI: 0.50, 1.21)).

### 14.3 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 [NCT02597933]). 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<sub>1</sub>/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 5.

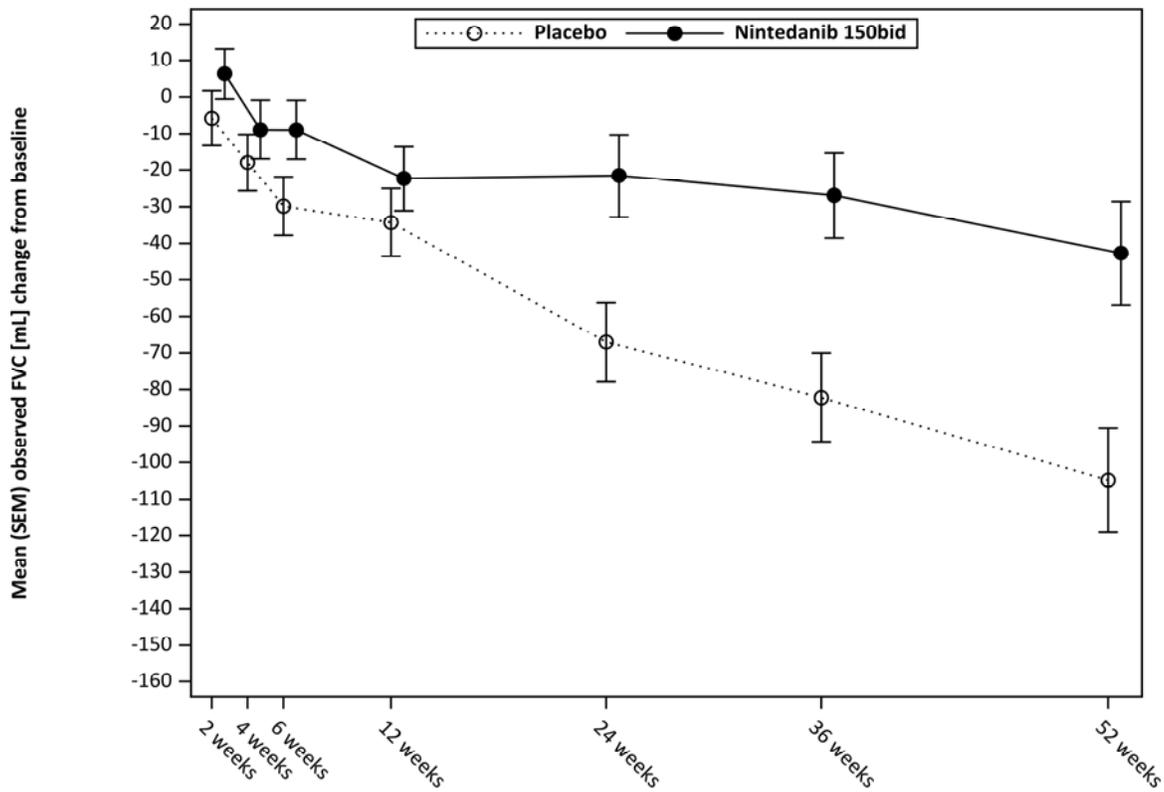
**Table 5 Annual Rate of Decline in FVC (mL) in Study 4**

	<b>OFEV 150 mg twice daily</b>	<b>Placebo</b>
Number of analyzed patients	287	288
Adjusted rate of decline over 52 weeks	-52	-93
Comparison vs placebo Difference <sup>a</sup>	41	
95% CI	(3, 79)	

<sup>a</sup>Based on a random coefficient regression model, adjusted for gender, height, age, ATA status, FVC at baseline, FVC at baseline-by-time

Figure 7 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 7 Mean (SEM) Observed FVC Change from Baseline (mL) Over Time in Study 4**



Number of patients

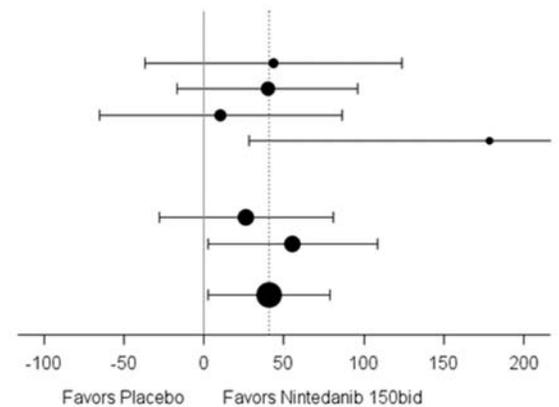
Placebo	283	281	280	283	280	268	257
Nintedanib 150bid	283	281	273	278	265	262	241

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 8).

**Figure 8 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	
<b>Region</b>					
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]
<b>Mycophenolate use at baseline</b>					
Yes	140	-67	138	-40	26 [-28; 81]
No	148	-119	149	-64	55 [2; 109]
<b>ALL</b>	288	-93	287	-52	41 [3; 79]

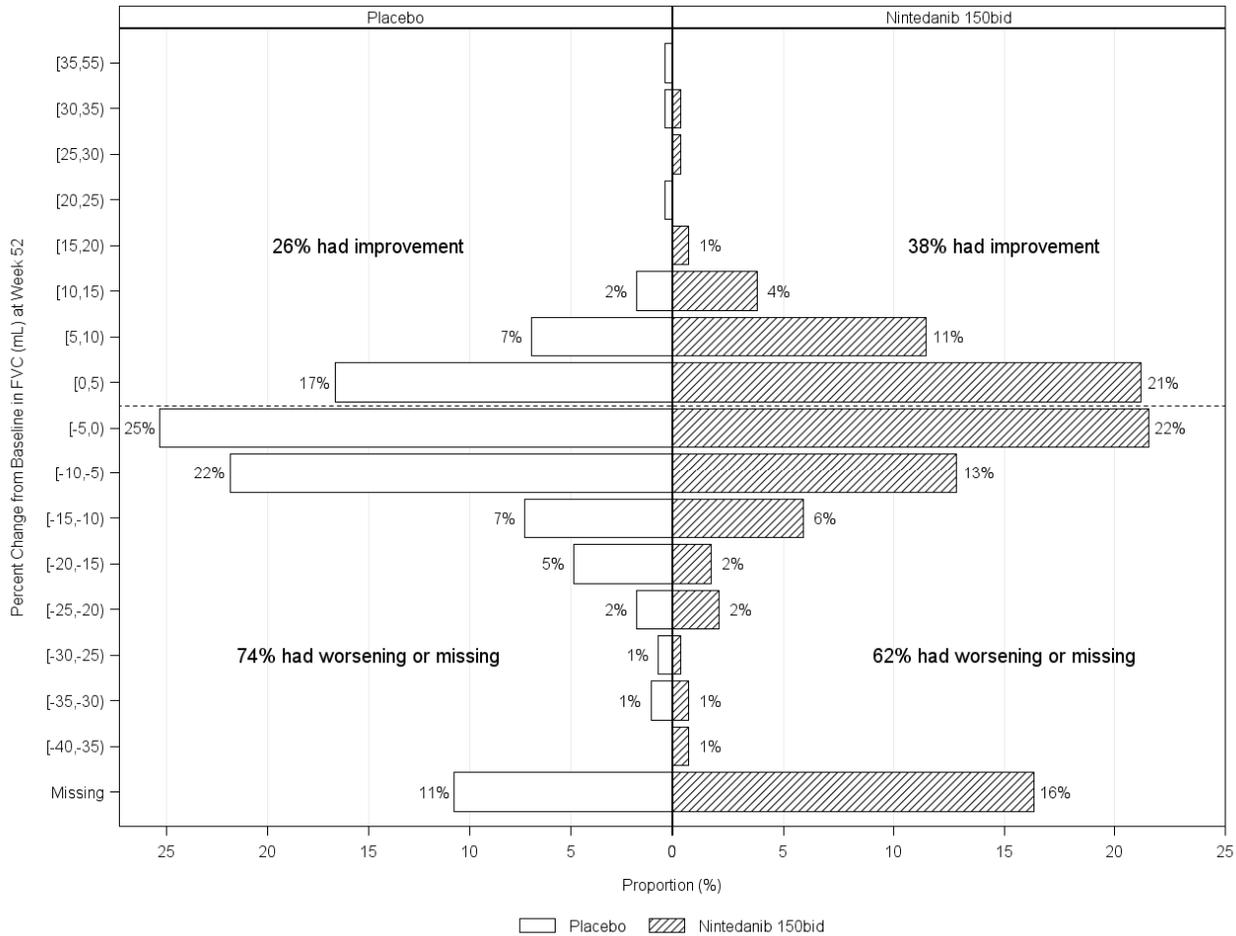


Nintedanib 150bid - Placebo difference in adjusted rate of decline in FVC [mL/yr] and 95% confidence interval

Percent Change from Baseline in Forced Vital Capacity

Figure 9 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 9 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)<sup>a</sup>**



<sup>a</sup> 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)*].

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IT6996KB272020

**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 also use 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).
  - to treat people with a chronic (long lasting) interstitial lung disease in which lung fibrosis continues to worsen (progress).
  - 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](http://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](http://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

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This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: March 2020

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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.**  
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/s/  
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BANU A KARIMI SHAH

03/09/2020 10:17:56 AM

signing with the delegated authority of Dr. Sally Seymour, Division Director, DPARP

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205832Orig1s013**

**MULTI-DISCIPLINE REVIEW**

**Summary Review**

**Office Director**

**Cross Discipline Team Leader Review**

**Clinical Review**

**Non-Clinical Review**

**Statistical Review**

**Clinical Pharmacology Review**

MEMORANDUM

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

DATE: March 12, 2020

TO: File for NDA 205832

THROUGH: Yongman Kim, Ph.D.

FROM: Yu Wang, Ph.D.

SUBJECT: Statistical Primary Review

APPLICATION/DRUG: Supplemental NDA 205832 S013/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 chronic fibrosing interstitial lung disease with a progressive phenotype (PF-ILD). The program consisted of a single study, Study 1199.247, a double-blind, randomized, placebo controlled trial evaluating efficacy and safety of oral nintedanib treatment for at least 52 weeks in patients with PF-ILD.

This study demonstrated a statistically significant improvement in the primary endpoint with support from secondary endpoints (time to first exacerbation and time to death). Specifically, the rate of decline in FVC over 52-weeks (primary endpoint) demonstrated statistically significant improvement in nintedanib-treated patients compared to placebo (107 mL, 95% CI: 65 to 149 mL; p-value<0.0001). The magnitude of this effect was similar to or better than that seen in nintedanib's idiopathic pulmonary fibrosis (IPF) or systemic sclerosis associated interstitial lung disease (SSc-ILD) programs. Although secondary time-to-event endpoints (exacerbations, death) were not statistically significant, numerical trends were favorable (HR 0.72 [95% CI: 0.38 to 1.37] and HR 0.94 [95% CI: 0.47 to 1.86], respectively). Sensitivity analyses on the primary endpoint, including a tipping point analysis, demonstrated robust results, lending further support for efficacy. Subgroup analyses were performed based on patient demographics and underlying ILD diagnoses. The subgroup analyses did not reveal noteworthy differences between subgroup treatment responses or compared to the overall population.

In the context of nintedanib in treating fibrosing lung diseases, the totality of evidence demonstrated by Study 1199.247 supports the approval of nintedanib for the treatment of PF-ILD.

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/s/  
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YU WANG  
03/12/2020 10:30:33 AM

YONGMAN KIM  
03/12/2020 10:33:40 AM

sNDA Multi-disciplinary Review and Evaluation  
 NDA 205832/S-013  
 Ofev (nintedanib) Capsules

### NDA/BLA Multi-Disciplinary Review and Evaluation

<b>Application Type</b>	Supplemental NDA
<b>Application Number(s)</b>	NDA 205832/S-013
<b>Priority or Standard</b>	Priority
<b>Submit Date(s)</b>	September 9, 2019
<b>Received Date(s)</b>	September 9, 2019
<b>PDUFA Goal Date</b>	March 9, 2020
<b>Division/Office</b>	DPARP/ODE II
<b>Review Completion Date</b>	March 9, 2020
<b>Established/Proper Name</b>	Nintedanib
<b>(Proposed) Trade Name</b>	Ofev
<b>Pharmacologic Class</b>	Kinase inhibitor
<b>Code name</b>	
<b>Applicant</b>	Boehringer Ingelheim Pharmaceuticals Inc.
<b>Dosage form</b>	Capsule
<b>Applicant proposed Dosing Regimen</b>	150mg tablet oral twice daily, dose reduction to 100mg oral twice daily
<b>Applicant Proposed Indication(s)/Population(s)</b>	Treatment of chronic fibrosing interstitial lung diseases with a progressive phenotype
<b>Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication</b>	
<b>Recommendation on Regulatory Action</b>	Approval
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	Treatment of chronic fibrosing interstitial lung diseases with a progressive phenotype
<b>Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)</b>	
<b>Recommended Dosing Regimen</b>	Same as Applicant proposed

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<b>Clinical Reviewer</b>	Khalid Puthawala, MD
<b>Clinical Team Leader</b>	Robert Lim, MD
<b>Statistical Reviewer</b>	Yu (Jade) Wang, PhD
<b>Statistical Team Leader</b>	Yongman Kim, PhD
<b>Cross-Disciplinary Team Leader</b>	Robert Lim, MD
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<b>OPDP</b>	
<b>OSI</b>	
<b>OSE/DEPI</b>	
<b>OSE/DMEPA</b>	
<b>OSE/DRISK</b>	
<b>Other</b>	

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
Clinical Pharmacology Reviewer	Lei He, PhD	OTS/OCP/DIIP	Section: 6	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
	<b>Signature: Lei He -S</b> <small>Digitally signed by Lei He -S            DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lei He -S, 0.9.2342.19200300.100.1.1=2001209362            Date: 2020.03.03 10:25:43 -05'00'</small>			
Clinical Pharmacology Team Leader	Bhawana (Bavna) Saluja, PhD	OTS/OCP/DIIP	Section: 6	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
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Clinical Reviewer	Khalid Puthawala	OND/ODE2/DPARP	Sections: 1, 2, 3, 7, 8	<b>Select one:</b> <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	<b>Signature: Khalid Puthawala -S</b> <small>Digitally signed by Khalid Puthawala -S            DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002317280, cn=Khalid Puthawala -S            Date: 2020.03.03 10:03:01 -05'00'</small>			

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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Robert Lim, MD	OND/ODE2/DPARP	Sections: All	<b>Select one:</b> <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	<b>Signature:</b> Robert H. Lim -S <small>Digitally signed by Robert H. Lim -S            DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Robert H. Lim -S, 0.9.2342.19200300.100.1.1=2000596695            Date: 2020.03.03 14:45:32 -05'00'</small>			
Acting Deputy Division Director (Clinical, designated signatory authority)	Banu Karimi-Shah, MD	OND/ODE2/DAPRP	Sections: All	<b>Select one:</b> <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	<b>Signature:</b> Banu A. Karimi-shah -S <small>Digitally signed by Banu A. Karimi-shah -S            DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300406057, cn=Banu A. Karimi-shah -S            Date: 2020.03.09 08:17:37 -04'00'</small>			
Statistical Reviewer	Yu (Jade) Wang, PhD	Office of Biostatistics/ Division of Biometrics II	Sections: 8.1, 8.3, 19.4	<b>Select one:</b> <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	<b>Signature:</b> Yu Wang -S <small>Digitally signed by Yu Wang -S            DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yu Wang -S, 0.9.2342.19200300.100.1.1=2001185097            Date: 2020.03.03 10:36:36 -05'00'</small>			
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	<b>Signature:</b> Yongman Kim -S <small>Digitally signed by Yongman Kim -S            DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yongman Kim -S, 0.9.2342.19200300.100.1.1=1300218531            Date: 2020.03.03 11:03:57 -05'00'</small>			

## Glossary

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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

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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**

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### **1.1. Product Introduction**

The Applicant, Boehringer Ingelheim (BI), has submitted a supplemental New Drug Application (sNDA) for nintedanib oral tablets for the treatment of chronic fibrosing interstitial lung disease (ILD) with a progressive phenotype at a dose of 150mg twice daily. Nintedanib (tradename OFEV) is a small molecule receptor and non-receptor tyrosine kinase inhibitor (including but not limited to platelet-derived growth factor receptor, fibroblast growth factor receptor, vascular endothelial growth factor receptor, and Fms-like tyrosine kinases). It is approved for the treatment of idiopathic pulmonary fibrosis (IPF) and systemic sclerosis interstitial lung disease (SSc-ILD), both of which are chronic fibrosing ILDs. The approved dosage and regimen for both of these indications is 150mg oral twice daily, identical to the proposed dosage and regimen.

### **1.2. Conclusions on the Substantial Evidence of Effectiveness**

Based on the clinical safety and efficacy data submitted, the recommended regulatory action is Approval for nintedanib 150mg oral twice daily for the treatment of chronic fibrosing ILDs with a progressive phenotype, with progression defined based on worsening spirometry, symptoms, and/or radiography.

To support this application, the Applicant completed study 1199.247 (study 247), a phase 3, randomized, placebo-controlled, 2-part (part A: fixed 52 weeks treatment period, part B: variable duration) efficacy/safety study in patients with chronic progressive fibrosing ILDs with a progressive phenotype (also referred to as progressive fibrosing interstitial lung disease [PF-ILD]), excluding IPF. PF-ILD represents multiple different ILDs (e.g., chronic hypersensitivity pneumonitis, rheumatoid arthritis ILD, idiopathic non-specific interstitial pneumonitis) grouped together based on shared characteristics (pulmonary fibrosis and rapid progression). The primary endpoint was rate of decline over 52 weeks in FVC, which has been used as a primary endpoint for other ILD approvals (IPF and SSc-ILD). Secondary endpoints included time-to-first exacerbation and mortality. The study population was a grouping of patients from a variety of fibrosing ILDs (e.g. connective tissue disease ILD, chronic hypersensitivity pneumonitis) with rapidly progressive disease (based on pulmonary function, symptoms, and/or radiography) who had failed conventional treatment.

This study demonstrated a statistically significant improvement in the primary endpoint with support from secondary endpoints (time to first exacerbation and time to death). Specifically, the rate of decline in FVC over 52-weeks (primary endpoint) demonstrated statistically

significant improvement in nintedanib-treated patients compared to placebo (107 mL, 95% CI: 65 to 149 mL; p-value<0.0001). The magnitude of this effect was similar to or better than that seen in nintedanib's IPF or SSc-ILD programs. Although secondary time-to-event endpoints (exacerbations, death) were not statistically significant, numerical trends were favorable (HR 0.72 [95%CI: 0.38 to 1.37] and HR 0.94 [95%CI: 0.47 to 1.86], respectively). Sensitivity analyses on the primary endpoint, including a tipping point analysis, demonstrated robust results, lending further support for efficacy.

Given that the study population represented multiple different ILDs (e.g., grouped together based on shared characteristics [fibrosis and progression]), subgroup analyses were performed based on patient demographics and underlying ILD diagnoses. The subgroup analyses did not reveal noteworthy differences between subgroup treatment responses or compared to the overall population.

In evaluating the evidence of effectiveness of nintedanib in chronic fibrosing ILDs with a progressive phenotype, the review team considered the totality of the data in the context of nintedanib experience in a distinct but related fibrosing lung disease, IPF, for which nintedanib is approved. The results from study 247 in conjunction with support from nintedanib's previously characterized benefit in IPF patients provided substantial evidence of effectiveness.

With regard to safety, the submitted study was adequate for evaluation and the overall safety results in study 247 were consistent with nintedanib's known labeled safety profile. There were no concerning imbalances between treatment arms in regard to deaths or serious adverse events (SAEs). Tolerability of nintedanib (mainly due to gastrointestinal and hepatobiliary AEs) in study 247 was similar to nintedanib's known safety profile based on common AEs and AEs leading to treatment discontinuation. Similar to efficacy, disease-based subgroup analyses for deaths or SAEs did not reveal concerning findings. Focused analyses of hepatobiliary, gastrointestinal, and pneumonia-related AEs also did not raise new concerns.

In conclusion, the submitted study supports the recommended action of Approval.

### 1.3. Benefit-Risk Assessment

#### Benefit-Risk Summary and Assessment

Chronic fibrosing interstitial lung disease with a progressive phenotype, the Applicant's proposed indication, can also be referred to as progressive fibrosing interstitial lung disease (PF-ILD). PF-ILD is a recently introduced term which groups together patients with fibrotic interstitial lung disease (ILD), caused by a variety of underlying etiologies, but with the shared characteristics of pulmonary fibrosis and rapid progression, with progression defined based on worsening spirometry, symptoms, and/or radiography.

There are no approved therapies for PF-ILD as a group, or for the individual ILDs included in the grouping (except systemic sclerosis ILD [SSc-ILD], recently approved Sept 2019). Nintedanib is approved for IPF and SSc-ILD, and the Applicant has submitted a supplemental NDA for nintedanib for the treatment of chronic fibrosing ILDs with a progressive phenotype. To support this application, the Applicant performed a single randomized, double-blinded, placebo-control trial in approximately 600 PF-ILD patients refractory to off-label treatments for the individual ILDs (no approved treatments). Based on the review of this study, the review team recommends approval of nintedanib for the proposed new indication.

In the single submitted study, nintedanib treatment resulted in statistically significant improvement versus placebo in rate of decline in FVC over 52 weeks, the primary endpoint. Efficacy was further supported by favorable point estimates for time to first exacerbation or death, time to death, time to first exacerbation; although these did not reach statistical significance. The safety results from the submitted study did not reveal new safety concerns beyond the existing known safety profile of nintedanib in IPF and SSc-ILD. Efficacy and safety across various subgroups were consistent with the overall findings.

Results from this single study in conjunction with the previously demonstrated efficacy in IPF, a distinct but related ILD, provide substantial evidence for efficacy. No new safety concerns were identified that would offset the demonstrated efficacy. The review team recommends Approval of nintedanib for the treatment of chronic fibrosing ILDs with a progressive phenotype.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<a href="#">Analysis of Condition</a>	<ul style="list-style-type: none"> <li>Chronic fibrosing ILDs with a progressive phenotype, also referred to as progressive fibrosing ILD (PF-ILD), represents interstitial lung disease (ILD), caused by a variety of underlying etiologies, but with the shared characteristics of pulmonary fibrosis and rapid respiratory worsening (i.e. progression).</li> <li>PF-ILD is a serious condition with a poor prognosis, similar to idiopathic pulmonary fibrosis (IPF)</li> <li>Many of the diseases that comprise PF-ILD (e.g. hypersensitivity pneumonitis or CTD-ILD) have pathogenesis better characterized than IPF</li> <li>PF-ILD represents a grouping of multiple different ILDs with different etiologies but with some common clinical characteristics. As such they may share a common end pathway which could be a potential target for therapy.</li> <li>The various underlying ILDs that make up PF-ILD are not common and the subset with rapid progression and fibrosis are even less common</li> </ul>	<p>PF-ILD is a serious debilitating condition with a poor prognosis. While the different ILDs that comprise PF-ILD have different etiologies, to be included in PF-ILD, patients must have pulmonary fibrosis and rapid respiratory progression. Given the shared clinical characteristics, there may be a shared common end pathway, which could be a target for therapy. As the individual ILDs that make up PF-ILD are uncommon, conducting a sufficiently powered clinical trial for each individual disease would likely raise practical issues.</p>
<a href="#">Current Treatment Options</a>	<ul style="list-style-type: none"> <li>There is no approved pharmacologic treatment for PF-ILD</li> <li>Corticosteroids and immunosuppressives are generally tried off-label for the variety of ILDs that comprise PF-ILD</li> <li>Nintedanib is approved for IPF and for systemic sclerosis ILD (SSc-ILD)</li> </ul>	<p>There are no approved therapies for PF-ILD or for the majority of ILDs that comprise the PF-ILD grouping.</p>
<a href="#">Benefit</a>	<ul style="list-style-type: none"> <li>The Applicant has demonstrated efficacy for nintedanib in PF-ILD patients based on statistically significant improvements in rate of decline in FVC over 52 weeks and supportive trends from other meaningful endpoints (time-to-exacerbation, time-to-death)</li> <li>Nintedanib treatment resulted in benefit (in FVC) in demographic and disease-based subgroup analyses as well, confirming that benefit was</li> </ul>	<p>Nintedanib provides clinically relevant treatment benefit in PF-ILD patients. Clinical data demonstrated that nintedanib was superior to placebo. The benefit in patients with PF-ILD are supported by efficacy results in patients with other fibrotic diseases (IPF, SSc-</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	not confined to a smaller population.	ILD). Together, these data provide substantial evidence of the efficacy of nintedanib in PF-ILD.
<a href="#">Risk and Risk Management</a>	<ul style="list-style-type: none"> <li>The safety profile for nintedanib in PF-ILD patients did not demonstrate any new concerning safety signals beyond that seen with nintedanib in IPF or SSc-ILD.</li> <li>No REMS is proposed</li> </ul>	<p>No safety findings were identified in the clinical development program that outweigh the potential benefit.</p> <p>Labeling and routine pharmacovigilance alone are recommended</p>

### 1.4. Patient Experience Data

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

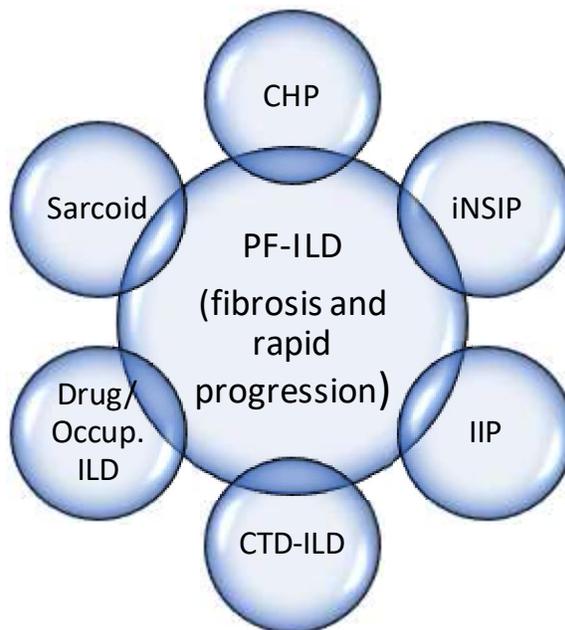
<input checked="" type="checkbox"/>	<b>The patient experience data that were submitted as part of the application include:</b>	Section of review where discussed, if applicable
<input checked="" type="checkbox"/>	Clinical outcome assessment (COA) data, such as	
X	<input type="checkbox"/> Patient reported outcome (PRO)	Section 8.1.2, Main secondary endpoints
	<input type="checkbox"/> Observer reported outcome (ObsRO)	
	<input type="checkbox"/> Clinician reported outcome (ClinRO)	
	<input type="checkbox"/> Performance outcome (PerfO)	
	<input type="checkbox"/> Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	<input type="checkbox"/> Patient-focused drug development or other stakeholder meeting summary reports	
	<input type="checkbox"/> Observational survey studies designed to capture patient experience data	
	<input type="checkbox"/> Natural history studies	
	<input type="checkbox"/> Patient preference studies (e.g., submitted studies or scientific publications)	
	<input type="checkbox"/> Other: (Please specify):	
<input type="checkbox"/>	<b>Patient experience data that were not submitted in the application, but were considered in this review:</b>	
	<input type="checkbox"/> Input informed from participation in meetings with patient stakeholders	
	<input type="checkbox"/> Patient-focused drug development or other stakeholder meeting summary reports	
	<input type="checkbox"/> Observational survey studies designed to capture patient experience data	
	<input type="checkbox"/> Other: (Please specify):	
<input type="checkbox"/>	<b>Patient experience data was not submitted as part of this application.</b>	

## 2 Therapeutic Context

### 2.1. Analysis of Condition

Chronic fibrosing interstitial lung diseases with a progressive phenotype, the Applicant's proposed indication, can also be referred to as progressive fibrosing interstitial lung disease (PF-ILD). PF-ILD is a recently termed entity which represents ILDs from a variety of etiologies that share the common characteristics of fibrosis and rapid progression (Harari et al. 2018). PF-ILD is comprised of multiple ILDs, including diagnoses such as fibrotic chronic hypersensitivity pneumonitis (CHP), connective tissue disease-associated ILD (CTD-ILD) (e.g. rheumatoid arthritis-related ILD), fibrotic chronic sarcoidosis, idiopathic nonspecific interstitial pneumonia (iNSIP), unclassifiable idiopathic interstitial pneumonia (uIIP), and exposure-related ILDs. Only the subset of patients with both fibrosis and rapid progression are included in PF-ILD. This is represented in Figure 1.

**Figure 1: Phenotypic overlap of various ILDs**



*Abbreviations: ILD – interstitial lung disease; CTD – connective tissue disease; IIP – idiopathic interstitial pneumonitis; iNSIP – idiopathic non-specific interstitial pneumonitis; CHP – chronic hypersensitivity pneumonitis*  
*Caption: Subsets of patients within a variety of respiratory diseases have a rapidly progressive fibrotic phenotype; this does not characterize all of the patients for that given disease (e.g. many sarcoidosis patients will not have rapidly progressive pulmonary fibrosis, but a small portion will). A grouping of those rapidly progressive fibrotic patients has been recently termed progressive fibrosing ILD (PF-ILD).*

The majority of patients with these ILDs of varying etiology (e.g. sarcoidosis, hypersensitivity

pneumonitis) do not have rapid progression, however, a subset from each have rapidly progressive disease behavior and associated fibrosis (similar to idiopathic pulmonary fibrosis [IPF]), and that is the subset of patients from each condition included in PF-ILD. It is also worth noting that at initial ILD diagnosis, a patient may not exhibit progressive respiratory worsening and fibrosing characteristics, and these can develop over time. Additionally, once the defining PF-ILD characteristics are present (fibrosis and rapid progression), the prognosis, no matter the underlying ILD diagnosis, is generally poor, similar to IPF (Wijsenbeek M et al. 2019).

In order to identify patients who may have PF-ILD, one proposed algorithm includes first diagnosing the definitive underlying ILD and then pharmacologic treatment (if available) or expectant management, depending on the clinical scenario. These patients would then continue to be followed for signs of disease progression using various modalities including clinical assessments, pulmonary function testing, and high resolution CT (HRCT) (Cottin et al. 2018). If disease progression is documented, then the patient would fall into the PF-ILD category.

The underlying ILDs that constitute the PF-ILD grouping have varying etiologies/triggers and would likely have a heterogeneous response to any single pharmaceutical treatment. However, for the subset of patients with these underlying ILDs who develop rapid progression and fibrosis (i.e., PF-ILD), it is possible that the pathway that lead to these shared characteristics is a common one. As such, studying them as a group is reasonable. Additionally, as these various underlying ILDs are not common and the subset with rapid progression and fibrosis are even less common, conducting a sufficiently powered clinical trial for each individual disease would likely raise practical issues.

## **2.2. Analysis of Current Treatment Options**

There are no approved therapies for PF-ILD, however, nintedanib and pirfenidone are approved for IPF, a similar rapidly progressive pulmonary fibrotic ILD. There are no approved therapies for the individual ILDs that constitute PF-ILD, i.e., there are no approved therapies for sarcoid, chronic hypersensitivity pneumonitis, idiopathic non-specific interstitial pneumonitis (iNSIP), or CTD-ILD, regardless of disease behavior. The single exception to this is the recent (September 2019) approval of nintedanib for SSc-ILD, which is part of the CTD-ILD category, recognizing that SScILD patients grouped into PF-ILD have rapidly progressive disease and constitute a small subset of SSc-ILD, largely considered a slower chronic progressive ILD.

In general, immunosuppressive therapies are used off-label in these conditions with oral corticosteroid therapy generally used as a common starting point. For example, sarcoidosis pharmacotherapy begins with oral corticosteroids, moving to methotrexate as second-line drug treatment for refractory disease (Schutt et al. 2010). Alternatives to methotrexate are also immunosuppressive or cytotoxic agents such as azathioprine, leflunomide, mycophenolate mofetil (MMF), cyclophosphamide, TNF-alpha antagonists, rituximab, and other investigational or off-label treatments (Paramothayan et al. 2006). Similarly, refractory CHP (refractory to antigen removal) treatment includes prednisone, azathioprine, and mycophenolate mofetil (Vasakova et al. 2017). Treatment of idiopathic NSIP begins with oral corticosteroids subsequently moving to azathioprine, MMF, cyclophosphamide, and/or rituximab (Belloli et al. 2016). Treatment of RA-ILD can start with an oral prednisone trial moving to azathioprine or MMF, with salvage trials of cyclophosphamide in light of its toxicity profile.

### **3 Regulatory Background**

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#### **3.1. U.S. Regulatory Actions and Marketing History**

Nintedanib has been marketed in the US since 2014 for the treatment of IPF (NDA 205832). It was also approved to slow the rate of decline in pulmonary function in patients with SSc-ILD in September 2019.

#### **3.2. Summary of Presubmission/Submission Regulatory Activity**

There were multiple regulatory interactions related to this sNDA.

A pre-IND meeting for IND 129333 was held May 23, 2016 in which the following points were discussed:

- No additional nonclinical studies were required
- The Agency noted that the design and conduct of the study as proposed by the Applicant was generally reasonable
  - The Agency agreed on the study design (placebo control, 12 month duration) and the dosing regimen (nintedanib 150mg po bid)
  - The Agency agreed with the primary endpoint (annual rate of decline in FVC over 52 weeks)
  - The Applicant's proposal of how to identify the study population was acceptable
  - The Agency recommended against the composite main secondary endpoint of time to progression or death, as it would likely be driven by the lung function component which was already included in the primary endpoint
  - The Agency recommended capturing hospitalization and exacerbations as key secondary endpoints
- The Agency noted that a single study may be acceptable if the efficacy was robust, given the established efficacy of nintedanib in IPF.
- The Agency noted that it would be important to evaluate the benefit-risk in both subgroups (UIP and HRCT Other, "across the spectrum of HRCT") in supportive analyses, not just the two co-primary populations
- The proposed safety database was acceptable. The Applicant was advised to consider continuing therapy in early enrollers to close of study to accumulate additional event data (exacerbations, deaths)
- The sample size calculation was acceptable
- The Agency agreed with the proposed concomitant medication handling for treating ILDs
- Inclusion of PRO results in section 14 was unlikely, but would be a review issue
- A two dimensional tipping point analysis was recommended by the Agency's statisticians

A written response was sent to the Applicant in regard to their July 26, 2018 meeting request package in which the following points were discussed:

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- The Agency's statisticians recommended selection of tipping point shift parameters that include scenarios where there is no treatment effect
- The proposed indication statement appeared to be in line with academic consensus, however final wording of the indication would remain a review issue

Breakthrough therapy designation was granted for nintedanib's PF-ILD development prior to this review, in October 2019.

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

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### **4.1. Office of Scientific Investigations (OSI)**

No clinical site inspections were deemed necessary.

### **4.2. Product Quality**

No significant issues were noted from the product quality standpoint given that the product used in this supplement was identical to the approved product.

### **4.3. Clinical Microbiology**

Not applicable.

### **4.4. Devices and Companion Diagnostic Issues**

Not applicable.

## **5 Nonclinical Pharmacology/Toxicology**

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### **5.1. Executive Summary**

No non-clinical data were submitted with this sNDA.

## 6 Clinical Pharmacology

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### 6.1. Executive Summary

Nintedanib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs). OFEV (nintedanib, 150 mg and 100 mg capsules) is approved for the treatment of IPF and slowing the date of decline in pulmonary function in patients with SSc-ILD. The approved dosing regimen is 150 mg twice daily approximately 12 hours apart taken with food. The recommended dosage in patients with mild hepatic impairment (Child Pugh A) is 100 mg twice daily approximately 12 hours apart taken with food.

The Applicant, Boehringer Ingelheim, has submitted Supplement 13 to NDA 205832 (OFEV (nintedanib)) seeking approval for nintedanib for the treatment of PF-ILD. The proposed dosage form and dosing regimen are the same as those approved for the treatment of IPF and SSc-ILD. The current efficacy supplement includes a single Phase 3 clinical study in subjects with PF-ILD (Study 1199.247). Nintedanib pharmacokinetics (PK) in patients with PF-ILD is generally comparable to IPF and SSc-ILD.

### Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology data for NDA 205832 Supplement 13 and finds the data acceptable.

### 6.2. Summary of Clinical Pharmacology Assessment

#### 6.2.1. Pharmacology and Clinical Pharmacokinetics

OFEV (nintedanib) is approved for the treatment of IPF and SSc-ILD. Refer to the approved labeling of OFEV regarding nintedanib's PK in subjects with IPF and SSc-ILD.

Study 1199.247 (INBUILD) is a Phase 3, randomized (1:1), placebo-controlled, double-blind, parallel design trial to investigate the efficacy and safety of 150 mg twice daily nintedanib over 52 weeks compared with placebo in patients with PF-ILD (n=663). PK blood samples were collected on Days 29 (one pre-dose sample) and Day 169 (at trough, 8-20 hours post-drug administration). Nintedanib plasma concentration was determined using a validated LC/MS/MS assay (Bioanalytical validation report U10-1387, reviewed in original NDA submission, refer to Clinical Pharmacology NDA review archived on September 03, 2014). The observed trough plasma concentrations of nintedanib in patients with PF-ILD from Trial 1199.247 are generally comparable to those observed in patients with IPF and SSc-ILD (Table 1 and Figure 2).

Exploratory exposure-response analysis for efficacy endpoint (annual rate of decline in forced vital capacity (FVC)) and safety (liver enzyme elevations) of nintedanib in patients with PF-ILD

has also been performed using the data from Study 1199.247. Since only one dosing regimen (i.e., 150 mg twice daily) was evaluated in patients with PF-ILD, the exposure-response analysis is considered of limited utility and therefore, no conclusions were derived from the relationship between PK parameters and efficacy/safety measures.

Table 1. Descriptive statistics of dose-normalized steady-state nintedanib trough plasma concentration ( $C_{pre,ss,norm}$ ) following multiple-dose oral administration of nintedanib 150 mg twice daily in patients with PF-ILD, SSc-ILD and IPF

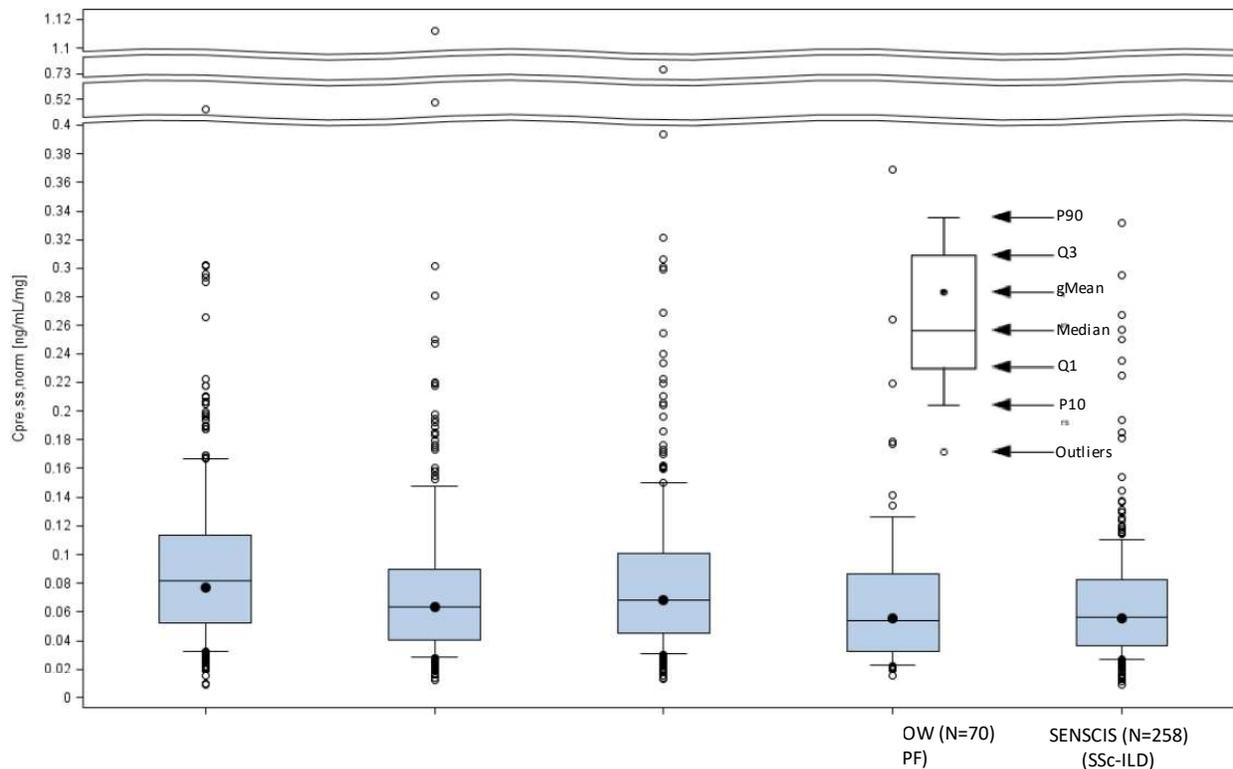
Nintedanib			$C_{pre,ss,norm}$ [ng/mL/mg]			
Population	Study	Starting dose*	N	gMean	gCV%	gMean ratio to 1199.247
Patients with PF-ILD	1199.247 (b) (6)	150 mg bid	311	0.0767	71.9	---
Patients with IPF	1199.32 (b) (6)	150 mg bid	250	0.0635	(72.4)	0.83
Patients with IPF	1199.34 (b) (6)	150 mg bid	274	0.0687	(71.3)	0.90
Patients with IPF	1199.30 (b) (6)	150 mg bid	70	0.0558	(76.0)	0.73
Patients with SSc-ILD	1199.214 (b) (6)	150 mg bid	258	0.0555	(65.4)	0.72

\* patients started with a dose of 150 mg bid but could be dose reduced to 100 mg bid based on tolerability but were also allowed to re-escalate to 150 mg bid within 4 weeks if deemed clinically appropriate

\*\*  $C_{pre,ss,norm}$  values were calculated by normalization with the dose taken at the respective PK visit and by taking the gMean value over all available PK visits (if applicable)

(Source: Table 3.2:1 of Summary of Clinical Pharmacology Studies for NDA205832-S13)

Figure 2. Box-plot comparing dose-normalized steady-state trough plasma concentrations (C<sub>pre,ss,norm</sub>) of nintedanib following multiple dose oral administration twice daily in patients with IPF, SSc-ILD and PF-ILD



Note: INBUILD, INPULSIS, TOMORROW, SENSICIS refer to the trial names in corresponding indications.  
(Source: Adapted from Figure 3.2:1 of Summary of Clinical Pharmacology Studies for NDA205832-S13)

## 6.2.2. General Dosing and Therapeutic Individualization

### General Dosing

The proposed dosage form and dosing regimen are the same as the approved dosing regimen for IPF and SSc-ILD, i.e., 150 mg twice daily approximately 12 hours apart taken with food.

### Therapeutic Individualization

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

### Outstanding Issues

None

## 7 Sources of Clinical Data and Review Strategy

### 7.1. Table of Clinical Studies

A single study, study 1199.247, was submitted by the Applicant in support of this submission (Table 2):

**Table 2: Study 1199.247 Characteristics**

Study	Design	Duration	Treatment <sup>^</sup>	N	Population	Primary Endpoint
1199.247 <i>FPFV February 2017</i> <i>LPLV April 2019</i>	Randomized, double-blinded, placebo-controlled, two-part, parallel group study	52 wks (part A) Variable (part B)	Placebo Nintedanib 150 mg oral twice daily	632	PF-ILD patients*	Rate of decline in FVC over 52 weeks
Abbreviations: FPFV – first patient first visit; LPLV – last patient last visit, PF-ILD – progressive fibrosing interstitial lung disease, FVC – forced vital capacity *Patients with at least 10% fibrosis on HRCT having the following criteria in the 24 months prior to screening were eligible: a decline in FVC ≥ 10%, a decline in FVC ≥ 5% and either worsening symptoms or worsening radiography, or worsening symptoms and worsening radiography. There were no specific inclusion or exclusion criteria related to underlying diagnoses, except the exclusion of IPF. <sup>^</sup> No immunosuppressive medications were allowed for the first 6 months of the treatment period in part A; if patients were using disallowed medications, they were discontinued if medically appropriate; enrolling patients must have “failed” prior clinically appropriate immunosuppressive therapy (per investigator) prior to enrollment						

## 7.2. Review Strategy

Support for safety and efficacy of nintedanib in chronic fibrosing ILDs with a progressive phenotype, also referred to in this review as progressive fibrosing ILD (PF-ILD), is based on the single trial described in Table 2. As noted, trial 1199.247 (study 247) was a two part study (A and B) assessing rate of decline in FVC over 52-weeks. Part A included a 52-week placebo controlled treatment period. Following the initial 52-week treatment period (part A), the study continued to follow all patients in a blinded controlled fashion until the last patient enrolled completed the last visit (variable duration portion, part B); however, the focus for this review is on the 52 week treatment period (part A); results from the whole trial (parts A + B) are discussed when appropriate.

Efficacy analyses were performed by FDA Biostatisticians to confirm the results shown in support of the Applicant's primary and secondary endpoints. Safety analyses were performed by the clinical reviewer to verify Applicant analyses or initiate other related safety analyses, using JMP Software. Safety and efficacy results focus on the treated set of patients (TS), all randomized patients receiving at least one dose of study drug (100% of the randomized patients).

As this product is approved for two related, but distinct, ILDs (i.e., IPF and SSc-ILD), data from nintedanib's IPF and SSc-ILD phase 3 programs (studies 1199.32, 1199.34, and 1199.214) are included in the discussion when appropriate to provide context and supportive evidence.

## 8 Statistical and Clinical and Evaluation

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### 8.1. Review of Relevant Individual Trials Used to Support Efficacy

#### 8.1.1. Study 1199.247 Protocol

##### Study Title

A double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of nintedanib over 52 weeks in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD)

##### Study dates:

February 23, 2017 to June 3, 2019 [Database lock 1 (DBL1) for main analysis]

Last patient last visit prior to DBL1: April 23, 2019

The trial continued after DBL1 for 565 patients (Database lock 2 [DBL2] September 3, 2019)

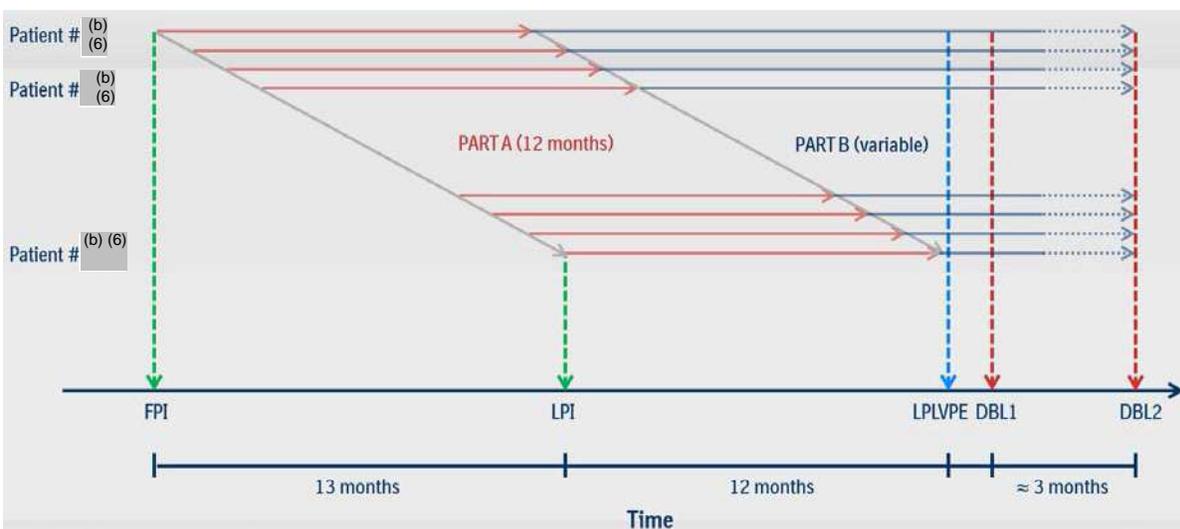
For additional information, see Figure 3

##### Study Design

Study 1199.247 (study 247) was a two part (A and B), multicenter, international, randomized, placebo-controlled, double-blind, parallel-group study comparing nintedanib 150 mg bid to placebo over a 52 week treatment period (part A). After completion of the 52-week treatment period (part A), patients continued to part B, where they continued on blinded treatment until at least the last patient to enroll in part A completed the 52-week treatment period. This resulted in a variable duration of treatment for patients in part B (Figure 3). This study was designed to investigate the efficacy and safety of nintedanib in patients with chronic fibrosing interstitial lung disease (ILD) with a progressive phenotype also referred to as progressive fibrosing ILD (PF-ILD) hereafter.

Patients were randomized (1:1) after screening to receive either nintedanib 150 mg twice daily or placebo. Randomization was stratified based on usual interstitial pneumonia (UIP) pattern and HRCT Other (2:1) as determined by central review of high resolution CT (HRCT) images according to prespecified protocol criteria (see *Study Population* section below). It was planned to have approximately 400 UIP patients and 200 HRCT Other patients.

**Figure 3: Study Timeline**



Abbreviations: DBL- database lock, FPI- first patient in, LPI- last patient in, LPLVPE - last patient last visit primary endpoint  
Source: Study 247 CSR Figure 9.1:2, p. 56

Database lock 1 (DBL1) occurred approximately 1-month after the last randomized patient completed part A, at 52 weeks/12 months (LPLVPE). Efficacy and safety analyses were performed using data from part A and combined data from part A and B (referred to hereafter as whole trial). Database lock 2 (DBL2), also shown in Figure 3, was scheduled for approximately 3 months after DBL1 (DBL1 June 3, 2019, DBL2 September 3, 2019).

The visit schedule consisted of visits 1 through 9 occurring over 1 year. After signing informed consent during visit 1, patient eligibility was assessed. Within the next several weeks of screening, HRCT images (not more than 12 months old) were assessed by central review for eligibility and stratification group, and washout of unapproved medications, if applicable, occurred. After this screening period (maximum screening period 12 weeks), patients were randomized at visit 2 to enter the trial. All patients discontinuing study treatment were asked to remain in the trial, complete regularly scheduled visits, and complete assessments.

Part A of the trial (52 weeks) included visits 2 through 9. Time between visits ranged from 2 to 16 weeks (Table 3). Visits in part B were all 16 weeks apart. Safety related laboratory testing was performed as needed for parts A and B. An end of trial visit for part A (EOTA) and a follow-up (FU) visit were performed only for premature trial discontinuation with the FU visit 4 weeks after EOTA. Schedule of Assessments shown in Table 3.

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**Table 3: Schedule of Assessments During 52-week Treatment Period (part A)**

Visit		1	2	3	4	5	6	6a	7	7a	8	8a	9	EOT <sup>1</sup>	FU <sup>1</sup>	
	Screening*	Treatment <sup>#</sup>														FU
Weeks of treatment		0	2	4	6	12	18	24	30	36	44	52			+4	
Day	Before or at the latest at Visit 1	≥4 days before Visit 2	1	15	29	43	85	127	169	211	253	309	365		+28	
Time window			±3	±3	±3	±3	±7	±7	±7	±7	±7	±7			+7	
Informed consent	X*															
HRCT sent to central review <sup>2</sup>	X															
Demographics		X														
Medical history		X	X													
Adverse events, concomitant medication		X	X	X	X	X	X		X		X		X	X	X	
In-/exclusion criteria		X	X													
Physical examination, vital signs		X	X	X	X	X	X		X		X		X	X	X	
Safety laboratory (blood and urine)		X <sup>3</sup>	X	X	X	X	X	X <sup>4</sup>	X	X <sup>4</sup>	X	X <sup>4</sup>	X	X	X	
Pregnancy test <sup>5</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK sample <sup>6</sup>					X				X							
Serum and plasma biomarker samples <sup>7</sup>			X				X		X		X		X	X		
RNA sample <sup>7</sup>			X						X				X	X		
Serum banking samples (optional) <sup>7,8</sup>			X				X		X		X		X	X		
DNA banking sample (optional) <sup>8</sup>			X													
HCRU assessments			X	X	X	X	X		X		X		X	X		
Non-elective hospitalization				X	X	X	X		X		X		X	X	X	
Spirometry (FVC) <sup>9</sup>		X	X	X	X	X	X		X		X		X	X	X	
SpO <sub>2</sub> (earlobe or forehead, resting)			X						X				X	X		
DLCO <sup>9</sup>		X	X						X				X	X		
HRCT (optional) <sup>10</sup>			X						X				X	X <sup>11</sup>		
Resting 12-lead ECG <sup>12</sup>		X	X						X				X	X		
Questionnaires: K-BILD, L-PF Symptoms & Impact, EQ-5D, PF-IQOLS <sup>13</sup>			X				X		X		X		X	X		
Review questionnaires for completeness			X				X		X		X		X	X		
Acute ILD Exacerbations				X	X	X	X		X		X		X	X	X	
Randomisation			X													
IRT call/notification	X <sup>14</sup>		X		X		X		X		X		X	(X)		

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Administer 1 <sup>st</sup> trial medication at the clinic			X											
Dispense trial medication			X		X		X		X		X			
Collect trial drug					X		X		X		X	X		
Compliance/drug accountability				X <sup>17</sup>	X	X <sup>17</sup>	X		X		X	X	X	
Trial medication termination													X	
Vital status assessment <sup>15</sup>											X			
Conclude patient participation														X <sup>16</sup>

- \* Informed consent had to be signed before any procedure related to the trial. When it was signed before Visit 1, e.g. to allow shipment of images for central review, all AEs and concomitant treatments occurring after the informed consent had to be recorded. The screening period (informed consent to Visit 2) was not to exceed 12 weeks. Upon obtaining informed consent, the patient was instructed on the medication wash-out and other restrictions needed.
  - # In case of dose changes (reduction or re-escalation) additional visits had to be included. In case of premature discontinuation of trial medication, the patient was expected to attend all visits (Part A and Part B visits) as originally planned until the end of the trial (except for the laboratory visits 6a, 7a, 8a).
  - 1 EOT A was to be done in cases of premature trial medication discontinuation during Part A of the trial with a Follow-up (FU) Visit 4 weeks later. A scheduled visit (Visit 3 to Visit 9) could be skipped if EOT A or Follow-up Visit occurred within 4 weeks prior to scheduled visits (clarified with global CTP amendment 2).
  - 2 Review of HRCT for meeting the HRCT criteria for fibrosing lung disease, for extent of ILD in the lung (10% or more), and for HRCT pattern. HRCT images not older than 12 months were to be sent to central review. If the patient did not have a HRCT within 12 months of Visit 1 or the available HRCT scan failed to meet the required image acquisition specifications, a new HRCT could be performed for the purposes of participation in the trial, provided the patient met all other inclusion and no exclusion criteria.
  - 3 The safety laboratory analysis of Visit 1 had to be repeated if screening was longer than 6 weeks.
  - 4 Intermediate laboratory tests (a-Visits) were to be done as needed for additional safety monitoring at the discretion of the investigator.
  - 5 β-HCG was analysed at Visit 2 only (at the central laboratory). Urine dipstick pregnancy tests were provided by the central laboratory and were to be performed in all women of childbearing potential every 4 to 6 weeks, i.e. at least at every visit and if necessary, additionally at home or at a local laboratory/doctor. If a urine test was not acceptable to local authorities, a blood test could be done at a local laboratory. Documentation was to be done in the patient's notes.
  - 6 PK samples were taken at Visits 4 and 7 just before drug administration. Date and exact clock times of drug administration and blood sampling had to be recorded on the eCRF. Patients were provided (Visits 3 and 6) with a PK-card to support the record of the exact clock times of medication intake 3 days preceding PK sampling.
  - 7 Biomarker samples were taken just before drug administration.
  - 8 DNA and serum banking samples were taken from eligible patients who signed a separate informed consent at Visit 2. Participation was voluntary and was not a prerequisite for participation in the trial. DNA samples could be taken at Visit 2 or any subsequent visit.
  - 9 Order of lung function measurements: 1. FVC followed by patient rest; 2. DLCO. Measurements were to be performed at approximately the same time each visit, reference time at Visit 2.
  - 10 HRCT scan was done at baseline, 24 and 52 weeks in patients who agreed as part of the informed consent. Participation was voluntary and was not a prerequisite for participating in the trial. Baseline scan was not performed in patients where eligibility scan was performed during screening.
  - 11 If EOT took place before Visit 7, HRCT was not to be performed at EOT.
  - 12 Resting ECG was recorded (if possible prior to blood draw) at Visit 2 prior to randomisation (only if abnormal at Visit 1).
  - 13 Self-reported outcomes/questionnaires had to be done by patients in a quiet place prior to other visit procedure. Order of questionnaires: 1. K-BILD, 2. L-PF Symptoms and Impact, 3. EQ-5D, 4. PF-IQOLS.
  - 14 IRT was to be notified at the latest at Visit 1 but could be notified upon informed consent signature.
  - 15 Vital status at 52 weeks (Visit 9) was to be available for all randomised patients. Consent for a vital status call at 52 weeks in case of premature discontinuation of trial participation was requested for all patients as part of the informed consent.
  - 16 Conclusion of participation was only applicable for patients who withdrew consent for trial participation.
  - 17 Compliance/drug accountability only in case of dose reduction or increase.
- Source: Study 247 CSR Table 9.5.1:1, p. 79

### **Study Population**

Planned enrollment was for 600 patients with PF-ILD as defined by eligibility criteria noted below.

#### *Key Inclusion criteria*

1. Adults male or female over age 18 years
2. Prior ILD diagnosis with one of the following criteria for worsening within 2 years prior to screening/visit 1 despite treatment with unapproved medications (e.g. immunosuppressives) commonly used in practice (per investigator):
  - a. FVC percent predicted (FVCpp) decline of  $\geq 10\%$
  - b. FVCpp decline of  $\geq 5$  to  $< 10$  combined with worsening respiratory symptoms
  - c. FVCpp decline of  $\geq 5$  to  $< 10$  combined with increasing fibrosis on imaging
  - d. Worsening respiratory symptoms and increasing fibrotic changes on imaging (not due to congestive heart failure or other comorbidities) per investigator [determination of worsening fibrotic changes was not confirmed by centrally read imaging review]
3. HRCT (performed within 12 months of visit 1) with fibrotic lung disease extent  $> 10\%$  (central reader confirmed).
4. Stable connective tissue disease (CTD) if applicable, defined as no new medication changes within 6 weeks of visit 1
5. Pulmonary function at visit 2: FVCpp  $\geq 45\%$ , DLCOpp between 30 and 80%

#### *Key Exclusion criteria*

1. Liver function test (LFT) abnormalities (transaminases or bilirubin  $> 1.5$  x upper limit of normal (ULN)) at screening. Retesting allowed if measurement error suspected by investigator. If LFT abnormalities were noted at visit 2 (start of treatment), the investigator would decide on treatment continuation.
2. Significant hepatic (Child-Pugh A,B or C), renal (creatinine clearance  $< 30$  mL/min), or cardiovascular disease (severe hypertension, MI, or unstable angina, all within 6 months) at screening.
3. IPF diagnosis by 2011 ATS/ERS/JRS/ALAT guidelines
4. Use of various immunosuppressives for ILD treatment (azathioprine [AZA], cyclosporine [CsA], mycophenolate mofetil [MMF], corticosteroids  $> 20$ mg/day, N-acetylcysteine [NAC], cyclophosphamide [CYC], rituximab). Time period required for last dose of these drugs prior to enrollment varied (e.g. 6 months prior to visit 2 for rituximab, 8 weeks for CYC). If the patient's rheumatoid arthritis (RA) or CTD were controlled with these therapies, they were not to be considered, unless change to alternate medications was medically indicated.

5. Significant pulmonary arterial hypertension (right heart failure on echo, right heart catheterization with CI < 2 L/min/m<sup>2</sup>, use of epoprostenol or treprostinil)
6. Obstructive lung disease
7. Significant hematologic abnormalities: bleeding risk (from therapeutic dose anticoagulants or high-dose anti-platelet agents; prior CNS hemorrhage within 1 year; prior hemoptysis, hematuria, or GI bleeding; coagulation test abnormalities) or thrombotic event history (stroke, TIA).
8. Investigator discretion regarding aspects of a patient's history that may pose problems: drug or alcohol use or abuse, ability to follow trial procedures, other significant pulmonary abnormalities

Central review of HRCT images was used for stratification (2:1, UIP vs. HRCT Other subgroups). Criteria used to determine UIP were consistent with 2011 ATS/ERS guidelines and required criteria # 3 below AND any of the remaining criteria:

1. Honeycomb lung destruction with basal and peripheral predominance
2. Reticular abnormalities and traction bronchiectasis with basal and peripheral predominance
3. Absence of atypical features (nodules, consolidation) and ground glass, if present, less extensive than reticulation

Older HRCTs were not reviewed by central readers and thus, assessment of change (as relevant for inclusion criteria 2d above defining disease progression) was per investigator or outside radiologist. HRCT at screening to determine eligibility had to be no older than 12 months.

Of note, no ILD diagnoses other than IPF were excluded (appropriate as nintedanib is approved for IPF); i.e. patients with sarcoidosis, hypersensitivity pneumonitis, idiopathic nonspecific interstitial pneumonitis, and any other ILDs could be included provided inclusion/exclusion criteria were met. This is consistent with the published definition of PF-ILD (Cottin et al. 2018). Although nintedanib was recently approved (Sept 2019) for SSc-ILD, the patients enrolled with SSc-ILD in study 247 had rapidly progressive SSc-ILD and thus were a subset of the recently approved population. Additionally, as noted in the demographic section, the contribution of these patients to the study population was 6%.

#### *Subject and trial discontinuation criteria*

Patients could withdraw consent without restriction but were contacted for vital status determination at week 52 and at the end of the study.

### **Study Treatments**

Study treatments given to randomized patients were one of the following:

- Nintedanib 150 mg oral soft gelatin capsule twice daily with dose reduction (to 100mg) allowed
- Matching placebo soft gelatin capsule

Nintedanib is approved at this same dosage and route for the treatment of idiopathic pulmonary fibrosis (IPF) and SSc-ILD. Dose selection was based on the current study population having overlapping disease characteristics with the IPF patient population.

The protocol delineated specific treatment and actions to be taken for diarrhea (based on number of stools per day over baseline) and liver enzyme elevations (based on the level of AST or ALT elevation). For diarrhea that was not related to an infectious cause and considered related to study drug, the following actions were recommended based on stool frequency:

- Treatment with loperamide was to be used initially for stools < 4 per day over baseline; no change in study drug was recommended for this level of diarrhea.
- For frequency of stools of 4 to 6 per day, treatment interruption with subsequent dose reduction and later re-escalation was recommended along with loperamide.
- If stool frequency remained high or if at any time became serious despite the previous interventions, treatment discontinuation was recommended.

This approach towards the management of diarrhea is more prescriptive than in the approved label but is reasonable.

An algorithm for handling liver enzyme elevations, known to be common with nintedanib, are outlined next.

*Treatment management for liver enzyme elevations*

For liver enzyme elevations, management is summarized in Table 4.

**Table 4: Protocol recommendations for managing liver enzyme elevations**

Time point	Liver enzyme elevation level					Hepatic injury*	
	>1.5x to <3x ULN	3x to <5x ULN		5x to <8x ULN			
Visit 2	Discontinue study drug or justify continuation	Discontinue study drug					
Any other visit	Continue	Dose reduction or interruption		Interruption		Discontinue study drug	
After 2 weeks, repeat testing		If <3x ULN	If ≥ 3x ULN	If <3x ULN	≥ 3x ULN		
		Restart Dose <sup>^</sup>	Discontinue study drug	Restart reduced dose	Discontinue study drug		
Continued Monitoring		Bi-weekly x 8 weeks		Weekly x 4 weeks then bi-weekly x 8 weeks			
<i>Abbreviations: ULN – upper limit normal</i> <i>* Hepatic injury defined as AST and/or ALT ≥ 8x ULN, ≥3x ULN with bilirubin ≥ 2x ULN, ≥3x ULN with INR &gt; 1.5, ≥3x ULN with eosinophilia &gt; 5%, OR ≥3x ULN with symptoms (fatigue, nausea, vomiting, RUQ pain, fever, rash)</i> <i><sup>^</sup>if study treatment was reduced, return to initial dose; if study treatment was interrupted, restart at reduced dose</i>							

Source: Study 247 CSR Table 9.4.2.1.2:1, p. 74

The management of liver enzyme elevations was generally similar to the labeled recommendations (section 2.3 of product label ) with minor exceptions. One exception was that permanent nintedanib discontinuation is currently recommended for liver enzyme elevations > 5 X ULN, as opposed to the protocol option to follow patients with 5 - 8 X ULN with treatment interruption, and offering to restart medication if repeat testing improved. Another minor difference was that protocol based repeat testing, performed at 2 weeks, used a threshold of 3 X ULN to restart dosing as opposed to labeled recommendations which compare to the patients baseline values.

These differences in the study protocol liver enzyme management from the labeled recommendations are minor and unlikely to have impacted the overall analysis, but may have allowed an increase in dose intensity (i.e. higher milligram usage) throughout the study as slightly higher levels of abnormal enzymes (5 – 8 X ULN) were tolerated without permanent drug discontinuation as well as allowance of restarting drug prior to normalization of liver enzymes.

*Duration of allowed treatment interruption and reduction*

Maximum interruption for adverse events (AEs) thought related to study drug by investigators was 4 weeks; maximum interruption for AEs not considered related to study drug was 8 weeks. When restarting, the recommendation was for dose reduction to 100 mg twice daily for AEs thought related to study drug, and restarting at the same previous dose for AEs not considered related to study drug. Re-escalation (back to 150mg twice daily) was to occur after 4 weeks for AEs considered related to study drug (for AEs not considered related to study drug, the dose was simply restarted at the previously used dose after 8 weeks).

#### *Treatment discontinuation criteria*

The study treatment was discontinued permanently for any of the following:

- Hepatic injury (transaminases  $\geq 8 \times$  ULN or transaminases  $\geq 3 \times$  ULN and one of the following: bilirubin  $\geq 2 \times$  ULN, unexplained INR  $> 1.5$ , unexplained eosinophilia  $> 5\%$ , symptoms consistent with hepatic injury)
- Unacceptable (per investigator) AEs despite dose adjustment
- Use of restricted concomitant medication (CM)
- Pregnancy

Study treatment discontinuation was highly recommended for any of the following:

- Major surgery
- Need for full-dose anticoagulation or high-dose antiplatelet therapy
- Major thromboembolic events (stroke, deep venous thrombosis, pulmonary embolism, myocardial infarction)
- Hemorrhagic events (CNS, GI, hemoptysis, hematuria)

Treatment discontinuation, interruption, and reduction criteria are generally similar to the current label (section 2.3) with some minor differences (permanent treatment discontinuation vs. treatment interruption).

#### *Concomitant medication restrictions*

Because there are no approved medications for treatment of ILDs (other than IPF which was excluded, and, until recent, SSc-ILD) and because inclusion criteria were such that patients enrolled had to have failed prior attempts at off-label and unapproved treatments, the following medications were restricted for the first 6 months of the treatment period:

- azathioprine (AZA)
- cyclosporine (CsA)
- tacrolimus
- oral corticosteroids  $>20$  mg/day
- rituximab (RTX)
- cyclophosphamide (CYC)

- mycophenolate mofetil (MMF)
- investigational drugs

Patients requiring these medications, for their ILD or for underlying autoimmune disease treatment, were not to be enrolled; the intent of the study was to enroll patients failing immunosuppressive treatments, regardless of treatment target. The only exception regarding use of immunosuppressives was that methotrexate or TNF inhibitors (primarily for RA) were allowed unrestricted.

Washout periods prior to visit 2 (treatment initiation) for these restricted medications varied. AZA, CsA, tacrolimus, MMF and corticosteroids required 4 weeks washout; CYC required 8 weeks; investigational drugs required 6 half-lives or 4 weeks (the longer of the two); and, RTX required 6 months.

Because nintedanib is known to cause GI adverse effects, increase liver enzymes, and to be a substrate of p-glycoprotein and CYP3A4, medications that could cause drug-drug interactions related to these mechanisms were to be initiated with careful consideration (e.g. ketoconazole, phenytoin, carbamazepine).

#### *Treatment compliance*

Compliance was determined based on capsule counts. Patients were instructed to bring remaining capsules (and empty package material) to all visits. Treatment compliance was calculated as a percentage of capsules actually taken x 100 / capsules that should have been taken. If compliance was outside of 80-120%, counseling was given to patients.

### **Study Endpoints**

#### *Primary Endpoint*

The primary efficacy endpoint was annual rate of decline in forced vital capacity (FVC) in mL over 52 weeks.

#### *Secondary Endpoints*

The Applicant categorized their secondary endpoints as “main” and “other”, however, there was no multiplicity testing procedure applied to any non-primary endpoints.

“Main” secondary efficacy endpoints (as denoted by Applicant) were as follows:

- Absolute change from baseline in K-BILD total score at week 52
- Time to first acute ILD exacerbation or death over 52 weeks (composite)
- Time to death over 52 weeks

Additionally, the Applicant studied the following endpoints as “other secondary efficacy endpoints” and “further endpoints”:

- Time to death due to respiratory cause over 52 weeks
- Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) scores at week 52:
  - Total score
  - Impact score
  - Symptoms total score as well as individual domain scores (fatigue, dyspnea, and cough domain scores)
- Time to first non-elective hospitalization or death over 52 weeks

FVC was measured using spirometers supplied by the sponsor to all participating sites. Spirometry was performed according to ATS/ERS 2005 guidelines (daily spirometer calibration, regular pump calibration). On visit days for spirometry measurement, smoking was discouraged as well as strenuous activity 12 hours prior to testing. Use of long acting bronchodilators required a 24 hour washout prior to spirometric testing and 8 hours for short-acting bronchodilators. Central spirometry review was performed to provide feedback to the sites regarding quality of the data received.

Four patient reported outcome (PRO) questionnaires were used during study 247: King’s Brief Interstitial Lung disease questionnaire (K-BILD), Living with Pulmonary Fibrosis Symptoms and Impact questionnaire (L-PF), EuroQol 5-Dimensional quality of life Questionnaire (EQ-5D), and Pulmonary Fibrosis Impact on Quality of Life Scale (PF-IQOLS). (b) (4)

L-PF is a 44 item questionnaire with 2 modules: 1) symptoms (23 items) and 2) impacts (21 items). The symptoms module covers three symptoms (referred to as “domains”): 1) dyspnea, 2) cough, and 3) fatigue. The impacts module has a single score. Symptoms and impacts scores combined give a total L-PF score. Scores range from 0 to 100, with higher indicating greater impairment. However, L-PF does not have an established minimum clinically important difference in PF-ILD.

The K-BILD questionnaire consists of 15 items across 3 domains: breathlessness and activities, psychological, and chest symptoms. Scores range from 0 to 100, with higher scores representing better health status. The minimum clinically important difference for K-BILD has not been established for PF-ILD but may range from 4 to 8 in other disease processes (Nolan et al. 2019; Patel et al. 2013; Sinha et al. 2019).

Acute exacerbations of ILD were defined based on IPF exacerbation definitions used previously during nintedanib's IPF pivotal trials (studies 1199.32 and 1199.34) but modified slightly to apply for all ILDs:

- Previous or concurrent diagnosis of ILD
- Acute worsening or new dyspnea within last 1 month
- CT with new bilateral ground-glass changes superimposed
- Clinical worsening not explained by cardiac causes

Events that failed to meet the above criteria but were felt clinically to be an exacerbation, were labeled as 'suspected acute exacerbations' and were not counted in the efficacy endpoint calculations. Acute exacerbations were not adjudicated. In contrast, IPF exacerbations were adjudicated in both phase 3 IPF pivotal trials.

Overall, the FVC, exacerbation, and mortality related endpoints discussed above are reasonable to assess for clinically meaningful change in regard to ILD. FVC has been used previously for IPF and SSc-ILD as a primary endpoint, and exacerbations and mortality are considered highly relevant. However, with regard to PROs, there is no established PRO for IPF (the best studied ILD), SSc-ILD, or PF-ILD; while K-BILD and L-PF results will be discussed in this review the clinical significance of the results are unknown

## **Statistical Analysis Plan**

### Co-primary Populations

The Statistical Analysis Plan (SAP) defined two co-primary populations for the analyses:

- The overall population (Overall)
- Patients with HRCT with UIP-like fibrotic pattern (UIP)

Patients with other HRCT fibrotic patterns represented the complementary population (HRCT Other). The primary endpoint and secondary endpoints were analyzed in both co-primary populations as well as in the complementary population for this review.

### Analysis Sets

The following analysis sets were defined in the 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.

For Efficacy Data:

- For main efficacy analyses, data from randomization date up to week 52 were considered.

- For supportive efficacy analyses over the whole study period, all data collected after randomization 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 Analyses: The primary endpoint was analyzed in both co-primary populations as well as in the complementary population. In each population, 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, HRCT fibrotic pattern (for the analysis in the overall population only), fixed continuous effects of time and baseline FVC (mL), as well as the interaction terms of treatment group-by-time and baseline-by-time. Random effects were included for patient response for both time and intercept. 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 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, 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 model assumption for linear decline in patient level FVC 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):*

Methodology is described in detail in Appendix 19.6. While the 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, as will be explored in the tipping point analysis described below, therefore results for the PMM approaches analyses are not presented in this review.

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

To comprehensively explore the plausible space of missing data assumptions, a tipping point analysis was planned to evaluate how robust the primary analysis results were across varying missing data assumptions. 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 HRCT fibrotic pattern (only for the overall population), 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 analyses were two-dimensional, i.e., allowing assumptions about the missing outcomes on the two arms to vary independently, and including scenarios where dropouts on nintedanib have worse slopes than dropouts on placebo. These analyses included all observed data, regardless of whether measurements were made on- or off-treatment.

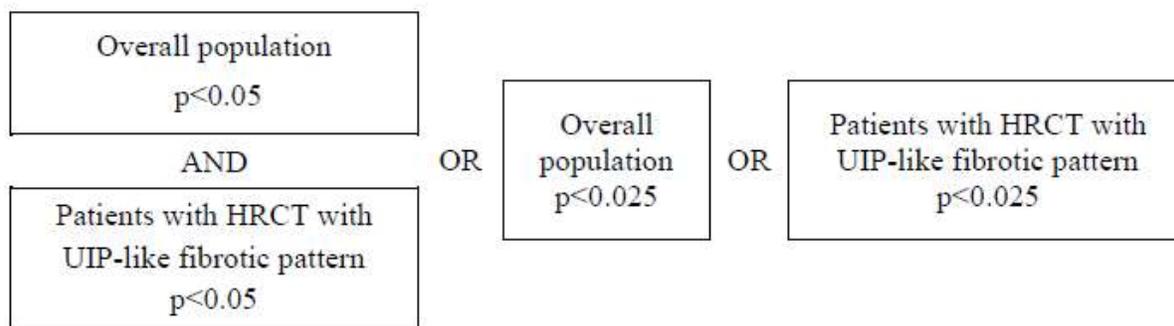
*Sensitivity to the Analysis Model:*

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

Multiplicity Control Procedure

The superiority of nintedanib treatment compared with placebo was tested for the primary endpoint in both co-primary populations. A Hochberg procedure was used in order to maintain an overall type 1 error rate of 5%. Statistical significance was to be declared if the analyses in both co-primary populations were significant at the two-sided 5% level, or if the analyses in either co-primary population were significant at the two-sided 2.5% level. No other endpoints were evaluated in a confirmatory manner.

**Figure 4. Type I error control: Hochberg procedure**



Source: Clinical Overview Figure 2.

#### Subgroup Analyses for the Primary Efficacy Endpoint

For each subgroup factor, the analysis 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 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 CI was presented using a forest plot. The subgroup analyses on the primary efficacy endpoint were conducted with interaction term in the analysis model by subgroup variable of HRCT fibrotic pattern, age, gender, race, geographical region, and ILD subtype.

#### Primary Analyses for Continuous Secondary Efficacy Endpoints

The secondary endpoints including main and other secondary endpoints were analysed in both co-primary populations. Nominal p-values are presented in this review for the main secondary endpoints.

Absolute change from baseline in the K-BILD 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, HRCT fibrotic pattern (for the analysis in the overall population only), visit, and the fixed continuous effects of baseline, as well as the interaction terms of treatment group-by-visit and baseline-by-visit interactions. 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 Living with Pulmonary Fibrosis (L-PF) symptoms dyspnea or cough domain score at Week 52: these endpoints were analyzed in the same manner as in the primary analysis of the absolute change from baseline in K-BILD at Week 52, using the same methods for handling missing data.

#### Primary Analysis for Time to Event Secondary Efficacy Endpoints

These endpoints were analysed using a stratified log-rank test (stratified by HRCT fibrotic pattern for the analysis in the overall population only). A Cox proportional hazards model stratified by the same factor was used to derive the hazard ratio (HR) and 95% CI between the 2 randomized treatment groups. Kaplan-Meier plots by treatment group were presented.

#### Primary Analysis for Binary Secondary Efficacy Endpoints

In the analysis of binary endpoints, proportions of patients with a relative decline from baseline in FVC % predicted greater than 5% or 10% were performed using a logistic regression model adjusting for baseline FVC % predicted and HRCT pattern (for analyses in the overall population only). Adjusted odds ratios together with 95% CIs were reported to quantify the effect of treatment.

#### Safety Analyses

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

#### **Protocol Amendments**

The original protocol was dated September 13, 2016. Two global amendments and 6 local amendments were issued. None of the local amendments applied to the US protocol.

Global amendment 1 occurred on December 21, 2016 before the first patient enrolled. This amendment added the primary analysis to be conducted in the HRCT Other subgroup (complementary population) as well as the two co-primary populations. Other changes were minimal.

Global amendment 2 occurred June 8, 2018. Handling of the end of trial and open-label extension transition were clarified. For consent withdrawal prior to 52 weeks, the scheduling of an end-of-trial part A (EOTA) visit and FU visit were specified. Similarly, an end-of-trial part B (EOTB) visit scheduling clarification was also added. The remaining parts of this amendment dealt with AE handling and were reasonable (AEs were to be collected after EOT within the residual effect period; AE analyses would take the drug half-life into account; potential drug induced liver injury [DILI] cases were defined as AEs of special interest). Other changes were minimal.

A note to file dated March 1, 2017 (first patient enrolled February 23, 2017) provided added information for patients who may not have received immunosuppressive therapies due to expert opinion (such as lack of perceived benefit in asbestosis related ILD) but may still be eligible for study enrollment (based on worsening spirometry, symptoms, and/or radiography), as the goal of the study was to assess patients with progressive fibrosing ILD with no available treatment options, whether they are resistant to anti-inflammatory or immunomodulatory therapy or not. This issue was raised at an investigator meeting.

It is unlikely that these protocol amendments affected study outcomes appreciably.

### 8.1.2. Study 1199.247 Results

#### **Compliance with Good Clinical Practices**

Documented approval was obtained from institutional review boards (IRBs) and independent ethics committees (IECs) prior to study initiation. All protocol modifications were made after IRB/IEC approval. The studies were conducted in accordance with good clinical practice (GCP), code of federal regulations (CFR), and the Declaration of Helsinki.

#### **Financial Disclosure**

The Applicant has adequately disclosed financial interests and arrangements with the investigators. Form 3454 is noted and verifies that no compensation is linked to study outcome. The PIs did not disclose any proprietary interest to the sponsor. See Financial Disclosure in section 16.2 for further details.

#### **Patient Disposition**

A total of 1010 patients were screened across ~150 sites in 15 countries. Of these 1010 patients, 663 patients were randomized. Most common screen failure reasons were failure to have >10% fibrosis on HRCT, and DLCO not being between 30 and 80% predicted normal at visit 2.

Overall, >90% of patients completed the first 52 weeks of the study (part A). More patients in the nintedanib arm discontinued study treatment (mostly due to AEs); otherwise, patient disposition was fairly balanced between arms. Key patient disposition information is summarized in Table 5.

**Table 5: Patient Disposition, 52 week Treatment Period, Overall Population**

	Placebo	Nintedanib
Screened	1010	
<b>Randomized</b>	331	332
<b>Completed 52 weeks of Treatment</b>	282 (85)	252 (76)
<b>Treatment discontinuation before 52 weeks</b>	49 (15)	80 (24)
Adverse event	34 (10)	65 (20)
Protocol deviation	2 (0.6)	1 (0.3)
Lost to follow-up	1 (0.3)	0
Consent withdrawal	9 (3)	11 (3)
Other	3 (1)	3 (1)
<b>Completed 52 weeks of study</b>	311 (94)	314 (95)
<b>Not completed 52 weeks of study*</b>	20 (6)	18 (5)
Death	16 (5)	17 (5)
Consent withdrawal	3 (1)	1 (0.3)
Lost to follow-up	1 (0.3)	0

Source: FDA Statistical reviewer

Note: \*the breakdown for patients who did not complete 52 weeks of study was based on patient disposition over the whole trial.

Most patients (94%) completed the 52-week treatment period (part A) of the study to provide off-treatment data despite treatment discontinuations that ranged from 15-24%. Tolerability is a known issue with nintedanib and, unsurprisingly, more patients discontinued treatment in the nintedanib arm, mostly due to AEs (65 of 80 patients). The cause of most patients in both arms not being able to complete the 52 week treatment period was death (16 of 20 placebo patients, 17 of 18 nintedanib patients), highlighting the serious nature of the disease process.

Patient disposition at 52 weeks for the UIP subpopulation and the HRCT Other subpopulation was generally similar to the overall population.

### Protocol Violations/Deviations

No protocol deviations (PD) led to exclusion of patients from the analysis. PDs for the two co-primary populations were generally similar. The most common important protocol deviations were related to eligibility criteria, study treatment and compliance, and concomitant medication usage. This is summarized in Table 6.

**Table 6: Protocol Deviations, 52 week Treatment Period, Overall Population**

Protocol deviation	Placebo (N=331)	Nintedanib (N=332)
Patients with at least 1 protocol deviation	50 (15)	41 (12)
Inclusion criteria not met	3 (1)	4 (1)
Exclusion criteria met	7 (2)	9 (3)
Patients with excluded underlying disease or condition	2 (1)	3 (1)
Forbidden previous therapy	5 (2)	6 (2)
Trial medication compliance not 80-120%	19 (6)	23 (7)
Concomitant restricted medication usage	23 (7)	9 (3)
Within 1 <sup>st</sup> 6 months*	19 (6)	7 (2)
Investigational drugs (nintedanib or pirfenidone) in 12 months	4 (1)	2 (1)
* azathioprine, cyclosporine, tacrolimus, rituximab, cyclophosphamide, mycophenolate mofetil, and oral corticosteroids >20mg/day		

Source: Study 247 CSR Table 10.3:1, p.138

Concomitant restricted medication usage accounted for nearly half of the placebo patients' violations (23 of 50 patients), mostly with use of immunomodulatory therapy. Trial medication compliance accounted for over half of the nintedanib patients' violations (23 of 41 patients). These results are not surprising as it may be expected for placebo patients to request alternate therapy (not wanting to wait 6 months in the setting of their serious disease) and for nintedanib patients to have tolerability issues, given its known safety profile.

These PDs are unlikely to have had a large impact on the overall analysis of safety and efficacy.

### Demographics

Overall, the majority of the study population was white, with a mean age of 66 years, with no gender imbalance, and with about half of patients being never smokers. Patients were from the following regions of the world: Europe (301 patients, 45%), Asia (155 patients, 23%), United States and Canada (136 patients, 21%), and the rest of the world (71 patients, 11%). Treatment arms were fairly balanced in regard to demographics. This information is summarized in Table 7.

**Table 7: Demographics, Overall Population**

Characteristic	Placebo (N=331)	Nintedanib (N=332)
<b>Age (years)</b>		
Mean (Min, Max)	66 (27,87)	65 (31,87)
<b>Gender</b>		
Male	177 (54)	179 (54)
<b>Race</b>		
White	246 (74)	242 (73)
Black	5 (2)	5 (2)
Asian	80 (24)	83 (25)
Other	0	2 (1)
<b>Region</b>		
US and Canada	69 (21)	67 (20)
US	64 (19)	61 (18)
Ex-US	262 (79)	265 (80)
Europe	147 (44)	154 (46)
Asia	76 (23)	79 (24)
Rest of World	39 (12)	32 (10)
<b>Smoking Status</b>		
Never	162 (49)	163 (49)
<b>Body Weight (kg)</b>		
Mean (SD)	77 (18)	77 (17)

Source: FDA Statistical Reviewer

When considering the UIP and HRCT Other subpopulations, demographics were generally similar with some minor differences. One difference was related to gender: there were more men in the UIP subpopulation (60%) and more women in the HRCT Other subpopulation (60%). Another difference was related to smoking status: there were more past and current smokers in the UIP subpopulation (57%). These observations are not surprising as UIP is generally considered more rapidly progressive, and male gender and smoking status have been correlated with more rapidly progressive disease (Ekstrom et al. 2014). Similarly, if we consider NSIP as representative of HRCT Other radiography (NSIP comprises one of the largest radiographic categories seen amongst ILD patients), female predilection and non-smoking status are generally associated with NSIP (Travis et al. 2008). Next, we will consider how the overall study population in study 247 compares to the IPF and SSc-ILD study populations.

Given the grouping of patients used to create the study population for study 247 and the fact that nintedanib is approved for IPF and SSc-ILD, it is important to compare (and contrast) study 247's population with the study populations in nintedanib's IPF and SSc-ILD development programs. In doing so, one finds that the demographics of the study 247 overall population

differ noticeably from the pivotal IPF and SSc-ILD studies in certain aspects. In comparison to the IPF study population, there were more never-smokers and females in study 247 (49% vs. 28% never smokers, 46% vs. 21% females). This is understandable as IPF is a disease seen more in male smokers.

Similarly, the study 247 population differed from the SSc-ILD study population in certain demographic aspects. In study 247, there were less females (46% vs. 75%) and patients were older (mean age 65 years vs. mean 54 years). This too is not surprising as SSc-ILD is generally a disease of middle age females (Bussone et al. 2011). All in all, the study population in study 247 was noticeably different than the IPF and SScILD study populations in certain key demographic aspects, and, thus, represents a different population of ILD patients. These differences provide reassurance that any treatment response noted in the further discussions are likely not due to the inadvertent inclusion of a patient population for which the efficacy of nintedanib has already been demonstrated.

### **Baseline Characteristics**

In the study 247 population, the mean time since ILD diagnosis was approximately 4 years. The majority of patients had diagnoses of either chronic hypersensitivity pneumonitis (CHP), autoimmune ILDs, or idiopathic NSIP. Baseline ILD related characteristics were balanced between arms. This information is summarized in Table 8.

**Table 8: Baseline Characteristics, ILD Diagnosis and PF-ILD Criteria, Overall population**

Characteristic	Placebo (N=331)	Nintedanib (N=332)
Time since ILD diagnosis	3.9 years	3.7 years
<b>Underlying ILD diagnosis</b>		
CHP	89 (27)	84 (25)
Idiopathic NSIP	61 (18)	64 (19)
uIIP	50 (15)	64 (19)
Autoimmune ILDs	88 (27)	82 (25)
RA-ILD	47 (14)	42 (13)
MCTD	12 (4)	7 (2)
SSc-ILD	16 (5)	23 (7)
Other autoimmune ILDs*	13 (4)	10 (3)
Other ILD^	43 (13)	38 (11)
Exposure-related ILD	18 (5)	21 (6)
Sarcoidosis	8 (2)	4 (1)
Other^	17 (5)	13 (4)
<b>Criteria for PF-ILD inclusion</b>		
FVC decline ≥10%	172 (52)	160 (48)
FVC decline ≥5%, <10% and worsening symptoms or imaging	97 (29)	110 (33)
Worsening symptoms and imaging	61 (18)	62 (19)
<p><i>Abbreviations: ILD – interstitial lung disease, NSIP – non-specific interstitial pneumonia, RA – rheumatoid arthritis, MCTD – mixed connective tissue disease, SSc – systemic sclerosis (scleroderma), CHP – hypersensitivity pneumonitis, uIIP – unclassifiable idiopathic interstitial pneumonitis, FVC – forced vital capacity</i></p> <p><i>* includes interstitial pneumonia with autoimmune features, positive anti-PL7 antibody ILD, Sjogren’s syndrome associated ILD, anti-neutrophil cytoplasmic antibody associated ILD, CTD organizing pneumonia, lupus associated ILD, microscopic polyangiitis associated ILD, undifferentiated CTD-ILD, polymyositis CTD-ILD</i></p> <p><i>^ includes ILDs from the following: desquamative interstitial pneumonitis, pleuro-parenchymal fibroelastosis, post stem cell transplant fibrosis, antisynthetase syndrome, unspecified CTD, post-Acute interstitial pneumonitis, post chemotherapy, IgG4-related lung disease, cryptogenic organizing pneumonitis, fibrosis with emphysema, respiratory bronchiolitis ILD, pulmonary alveolar proteinosis, chronic eosinophilic pneumonia, interstitial pneumonia with autoimmune features, lipoidic fibrosis, overlap NSIP with organizing pneumonia without CTD</i></p>		

Source: study 247 CSR Table 10.4.2:1, p.146; reviewer verified

In regard to disease progression and eligibility, one possible concern was that patients may have qualified for study entry based on more subjective criteria of disease progression such as symptom worsening or worsening imaging (not centrally determined) rather than objectively defined FVC criteria. However, this was not found to be the case. About half of the patients had FVC decline ≥ 10% and another ~30% of patients had FVC decline of 5-10% coupled with

worsening symptoms or imaging. This provides an objective spirometric anchoring for the rapidly progressive disease behavior associated with PF-ILD and for the study populations eligibility. While there were not imbalances in the overall population between treatment arms in regard to disease progression eligibility, whether these disease behavior criteria were balanced within the HRCT based subgroups (UIP and HRCT Other) was explored.

Given that UIP has been associated with more rapidly progressive disease than the other radiographic categories, the possibility existed that more patients in the UIP subpopulation had greater FVC decline at time of study entry. Conversely, because the HRCT Other subpopulation could have had less rapidly progressive disease, the possibility existed that that subgroup had more patients that entered the study via eligibility through more subjective bases (worsening symptoms and radiography). A reviewer analysis comparing eligibility criteria (for disease progression) between the subpopulations of UIP and HRCT Other did not reveal any concerning imbalances.

In regard to time-since-ILD-diagnosis, treatment arms were fairly balanced, and results were similar to the SSc-ILD program. However, the time-since-ILD diagnosis to screening was shorter in the IPF studies (4 years vs. ~1.5 years), likely due to eligibility criteria in study 247 requiring failure of prior treatment before enrolling.

### **Treatment Compliance and Rescue Medication Use**

Compliance was between 80 and 120% for the majority of patients in both treatment arms (>92%). Those with compliance outside this range (for the 52 week treatment period) were considered to have a major protocol deviation, however were not excluded from any efficacy or safety analyses; proportions of compliance-based protocol deviations were similar between arms (6% placebo, 7% nintedanib). There were no major differences in the subpopulations (UIP or HRCT Other).

Overall, treatment compliance was generally similar between arms and is not expected to have impacted the overall analysis. See section 8.2.2 for further details on exposure and dosing intensity.

### **Concomitant Medications**

Given the mean age of the study population (65 years) and their underlying disease process, it is not surprising that 99% of study patients were on at least 1 baseline and/or concomitant medication. The most common medications were corticosteroids, GERD/peptic ulcer disease medications, anti-inflammatory agents, and anti-propulsives.

While the treatment arms were balanced for the most commonly used medications, some less commonly used medications were differentially used. For example, anti-propulsive medication

use at baseline was low (<1%), but use during the treatment period increased noticeably and disproportionately in the nintedanib arm (42% nintedanib vs. 11% placebo); however, this is understandable in the setting of nintedanib’s known side effect profile.

Certain medications were restricted given their potential for confounding the treatment effect. In terms of restricted medications, use of azathioprine, cyclosporine, tacrolimus, rituximab, cyclophosphamide, mycophenolate mofetil, or oral corticosteroids >20 mg/day were disallowed for the first 6 months of the 52 week treatment period. There were more placebo patients who used these restricted medications over the 52 week treatment period (Table 9).

**Table 9: Restricted Medications, 52 week Treatment Period, Overall Population**

Restricted Medication	Placebo (N=331)	Nintedanib (N=332)
Number of patients with ≥1 restricted medication use	70 (21)	36 (11)
Corticosteroids*	57 (17)	33 (10)
Immunomodulatory medications for ILD <sup>^</sup>	21 (6)	9 (3)
*includes prednisone, prednisolone, methylprednisolone, hydrocortisone, meprednisone, betamethasone, deflazacort, dexamethasone		
<sup>^</sup> includes non-biologic and biologic DMARDs: MMF, azathioprine, tacrolimus, cyclosporine, rituximab, cyclophosphamide		

Source: Study 247 CSR Table 10.4.6:3, p.161

This observation of more placebo patients turning to restricted immunosuppressive medications may be supportive of nintedanib having a favorable treatment response.

The number of patients taking prohibited medications (antithrombotics) was small and balanced between treatment arms (placebo 4% vs. nintedanib 6%, not shown). Two placebo patients took nintedanib (prohibited for placebo arm) when off study treatment.

In summary, review of the concomitant medications used by patients during the 52 week treatment period (including restricted and prohibited medication use) does not reveal any concerning imbalances that would be expected to impact analyses or interpretation.

### **Efficacy Results – Primary Endpoint**

The primary endpoint of study 247 was the annual rate of decline in FVC over 52 weeks. Nintedanib-treated patients had a statistically significant improvement in decline in FVC over placebo patients in the overall population and the UIP subpopulation. For the HRCT Other subpopulation, based on the point estimate, rate of decline was also improved for nintedanib-treated patients versus placebo, with 95% CI excluding the null; however, as this comparison was not part of the prespecified statistical multiple testing strategy, this result is considered supportive evidence that nintedanib is effective in the overall population (Table 10).

**Table 10: Primary Endpoint, Rate of FVC decline over 52 weeks**

	Overall		UIP		HRCT Other	
	Placebo (N=331)	Nintedanib (N=332)	Placebo (N=206)	Nintedanib (N=206)	Placebo (N=125)	Nintedanib (N=126)
Number Analyzed	331	332	206	206	125	125
Adjusted Annual Rate of Decline, mL/Year (SE)	-188 (15)	-81 (15)	-211(20)	-83 (21)	-154 (21)	-79 (22)
Nintedanib vs. Placebo						
Difference (SE)		107 (21)		128 (29)		75 (30)
95% CI		65, 149		71, 186		16, 135
p-value		<0.0001		<0.0001		0.0137*
*not a prespecified comparison in the multiple testing procedure. P-value shown is nominal and for exploratory purposes.						

Source: FDA Statistical Reviewer

The FVC treatment effect in the overall population and in the UIP subgroup of 107 mL/year and 128mL/year, respectively, is comparable to the treatment effect seen in nintedanib’s IPF development program (94 to 131 mL/year). The FVC treatment effect in the HRCT Other subpopulation of 75 mL/year, though numerically smaller compared to the IPF studies, is larger than the treatment effect seen in nintedanib’s SScILD program (41 mL/year). Next, we will discuss these radiographically stratified pre-specified subgroups (UIP and HRCT Other).

Given that IPF radiographically manifests as UIP, that the study population was enriched for UIP radiography (2:1), and that nintedanib is approved for IPF, concern may exist that these efficacy results are driven by the inadvertent presence of IPF patients in study 247. However, several points address this concern. First, patients diagnosed with IPF were actively excluded (eligibility criteria), and the majority of patients had a non-IPF ILD diagnosis (26% of patients had CHP; 26%, autoimmune ILD ;19%, iNSIP); given that IPF is a diagnosis of exclusion, these elements combine to make IPF patient inclusion unlikely. Next, certain demographic and baseline characteristic differences between IPF trial patients and study 247 patients demonstrate the distinct nature of these two study populations. Specifically, there were more females (49% study 247 vs. 21% IPF studies), more never-smokers (49% study 247 vs. 28% IPF studies), and a longer time between enrollment and ILD diagnosis (mean 3.7 years study 247 vs. mean 1-1.7 years IPF studies) [Table 7 and Table 8]. Lastly, efficacy analyses of subgroups by ILD diagnoses

as well as analyses excluding particular diagnoses that could mistakenly “hide” IPF patients (e.g. uIIP or “other”), all showed generally similar treatment effects; these results are discussed later in the review (Figure 7). For these reasons, it is unlikely that an inclusion of IPF patients could account for the treatment effect seen in study 247.

Multiple sensitivity analyses were performed by the Applicant to test the robustness of the primary endpoint results (in regard to data handling, missing data, or analysis model used) and showed relatively consistent results. The Applicant’s additional sensitivity analyses to the linearity assumption or to mis-stratification did not reveal concerns (Refer to the Applicant’s CSR for additional sensitivity analyses results).

The FDA statistical team also performed additional sensitivity analyses, including tipping point sensitivity analyses to missing data for the primary endpoint in both the co-primary populations (See *Additional Analyses Conducted* section for Tipping Point Analysis Results). These FDA performed sensitivity analyses supported the robustness of the primary endpoint results.

In summary, the primary endpoint analyses demonstrated that nintedanib treatment resulted in lower annual rate of decline in FVC compared to placebo treatment. This effect in the UIP and HRCT Other subpopulations was consistent with the overall population. The effect does not appear to be driven by inadvertent inclusion of IPF patients or a specific ILD diagnoses. Primary endpoint results support the efficacy of this product in the studied population.

### **Efficacy Results – Secondary Endpoints and Further Endpoints**

This trial included multiple secondary and further endpoints. Per the protocol, the following were considered by the Applicant as the “main” secondary endpoints:

- Time to first acute ILD exacerbation or death over 52 weeks
- Time to death over 52 weeks
- Change from baseline in K-BILD total score at week 52

Analyses of these endpoints are included in this review. Additionally, analyses of time to first non-elective hospitalization, change from baseline in the K-BILD, and the Living with Pulmonary Fibrosis (L-PF) questionnaire scores endpoints were also included as these were thought to be potentially informative.

The overall trial multiplicity testing procedure did not control for type I error associated with testing on any of the secondary or further endpoints, limiting interpretation of these endpoint results. For these endpoints, 95% confidence intervals and associated nominal p-values are reported for descriptive purposes in this review.

#### *Time to first acute ILD exacerbation or death*

For the “main” secondary endpoint of time to first acute ILD exacerbation or death, exacerbation was defined relatively similar to IPF exacerbations. An acute ILD exacerbation was defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality with all of the following:

- Previous or concurrent diagnosis of ILD
- Acute worsening or development of dyspnea typically less than 1 month duration
- Computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with fibrosing ILD
- Deterioration not fully explained by cardiac failure or fluid overload.

Acute ILD exacerbations were not adjudicated. Exacerbations where all four of the above criteria were not met, were not included in the efficacy analysis. With regard to death, at week 52, vital status data was obtained in all patients.

For this composite endpoint, results were not statistically significant. The HR point estimate for the overall population and UIP subpopulation were  $<1$ , and the 95% CI did not exclude null. For the HRCT other subpopulation, HR point estimate was slightly  $>1$  with a 95% CI that did not exclude null. These data are summarized in Table 11.

**Table 11: Main Secondary Endpoint, Time-to-First Exacerbation or death over 52 weeks, Cox Proportional Hazard Model Analysis**

Hazard Ratio (95% CI), p-value	Overall		UIP subpopulation		HRCT Other subpopulation	
	Placebo (N=331)	Nintedanib (N=332)	Placebo (N=206)	Nintedanib (N=206)	Placebo (N=125)	Nintedanib (N=126)
Time to First Exacerbation or Death	0.8 (0.47 to 1.34), p=0.40		0.67 (0.36 to 1.24), p=0.2		1.2 (0.47 to 3.39), p=0.21	

Source: FDA Statistical Reviewer

These results are consistent with the primary endpoint results in that the magnitude of the treatment effect based on point estimates was the most favorable in the UIP subpopulation and overall population, and least in the HRCT other subpopulation.

Overall, these data are supportive of a treatment effect. However, because this endpoint was a composite and could potentially be driven by a single component, FDA also performed additional analyses of each component of the composite. These results are summarized in Table 12 and discussed individually below.

**Table 12: Time-to-Death and Time-to-First Exacerbation over 52 weeks, Cox Proportional Hazard Model Analysis**

Hazard Ratio (95% CI), p-value	Overall		UIP subpopulation		HRCT Other subpopulation	
	Placebo (N=331)	Nintedanib (N=332)	Placebo (N=206)	Nintedanib (N=206)	Placebo (N=125)	Nintedanib (N=126)
Time to First Exacerbation	0.72 (0.38 to 1.37), p=0.31		0.72 (0.33 to 1.58), p=0.42		0.70 (0.22 to 2.21), p=0.55	
Time to Death	0.94 (0.47 to 1.86), p=0.85		0.68 (0.32 to 1.47), p=0.33		5.0 (0.59 to 43.02), p=0.14	

Source: FDA Statistical Reviewer

*Time to first exacerbation*

As noted in Table 12, the HR point estimates for time to first exacerbation over 52-weeks in the overall population, UIP subpopulation, and HRCT Other subpopulation were less than 1 favoring nintedanib, though 95% CIs did not exclude null. These results suggest that nintedanib may have a positive effect in terms of exacerbation, recognizing that study 247 was not powered for exacerbations. These results are similar to the IPF program where a similar trend was observed for exacerbation.

In regard to the whole trial (52 week treatment period + variable treatment period – [parts A

and B] to database lock 2 [DBL2]), time-to-first-exacerbation results are consistent with the 52 week results, with similar favorable HR point estimates. Specifically, the HRs for time to first exacerbation for the overall population, UIP subpopulation, and HRCT other subpopulation were 0.63 [95%CI: 0.37 to 1.07], 0.69 [95%CI: 0.36, 1.32], and 0.53 [95% CI: 0.21, 1.34], respectively.

Overall, while these results are not statistically significant, the exacerbation trend is favorable for nintedanib-treated patients and supportive of the primary endpoint.

#### *Time to death*

As noted in Table 12, similar to the above discussion regarding exacerbations, the HR point estimates in the overall and UIP subpopulation for time to death over 52-weeks were less than 1 favoring nintedanib, however, 95% CIs did not exclude the null. Time to death results over the whole trial (A+B) to DBL1 and DBL2 were consistent with the 52-week results for the overall population (HR 0.7 [95%CI 0.43,1.15], HR 0.78 [95%CI 0.50, 1.21], respectively) and for the UIP subpopulation (HR 0.63 [95%CI 0.36,1.10], HR 0.66 [95%CI 0.40, 1.10], respectively). Of note, DBL2 was 3 months after DBL1. See section 8.1.1 for details.

With regard to the HRCT other subpopulation, the HR point estimate was >1 with a value of 5 (95%CI 0.59, 43.0). While this point estimate for the HRCT Other subpopulation may raise some concern, it is based on a small number of events (5 nintedanib deaths and 1 placebo death) and has an extremely wide 95% confidence interval. As such, this observation is likely due to chance. Moreover, when examining mortality data from the whole trial (parts A+B) to DBL1 and DBL2, this was no longer observed and HRs were lower. There were similar number of deaths in each group out to DBL1 (HR 1.06 [95%CI 0.37, 3.03]) and DBL2 (HR 1.27 [95%CI 0.53, 3.07]) with much narrower confidence intervals. Additionally, a review of death narratives in regard to timing of death in relation to study drug, doses prior to death, demographics, or cause of death, did not reveal any concerning overlapping features (see section 8.2.4, Table 20). Taken together, this suggests that the observed time to death over 52-weeks results for the HRCT Other subpopulation was due to stochastic processes and does not represent a safety signal.

It is worth noting that the PF-ILD mortality data is generally consistent with that observed in the IPF and SSc-ILD programs, in that while statistically significant improvements in rate of FVC decline were demonstrated, no statistically significant mortality effects was observed.

Overall, though not statistically significant, the mortality data for the overall population are generally supportive of the primary endpoint.

#### *Time to first non-elective hospitalization*

For the endpoint of time to first non-elective hospitalization, a favorable trend (HR<1) was present for nintedanib treated patients in the overall population (HR 0.93 [95%CI:0.69,1.25]) and UIP subpopulation (HR 0.82 [95% CI: 0.56, 1.20]) in the 52 week period, however, 95% CIs

did not exclude the null. For the HRCT Other subpopulation the HR was >1, with a 95% CI not excluding null (HR 1.06 [95% CI: 0.63, 1.76]). Results over the whole trial (A+B) to DBL2 were consistent with the 52-week results with HR <1 and 95% CI including null.

Overall, these time-to-event analyses show favorable trends for nintedanib treated patients supporting the primary endpoint.

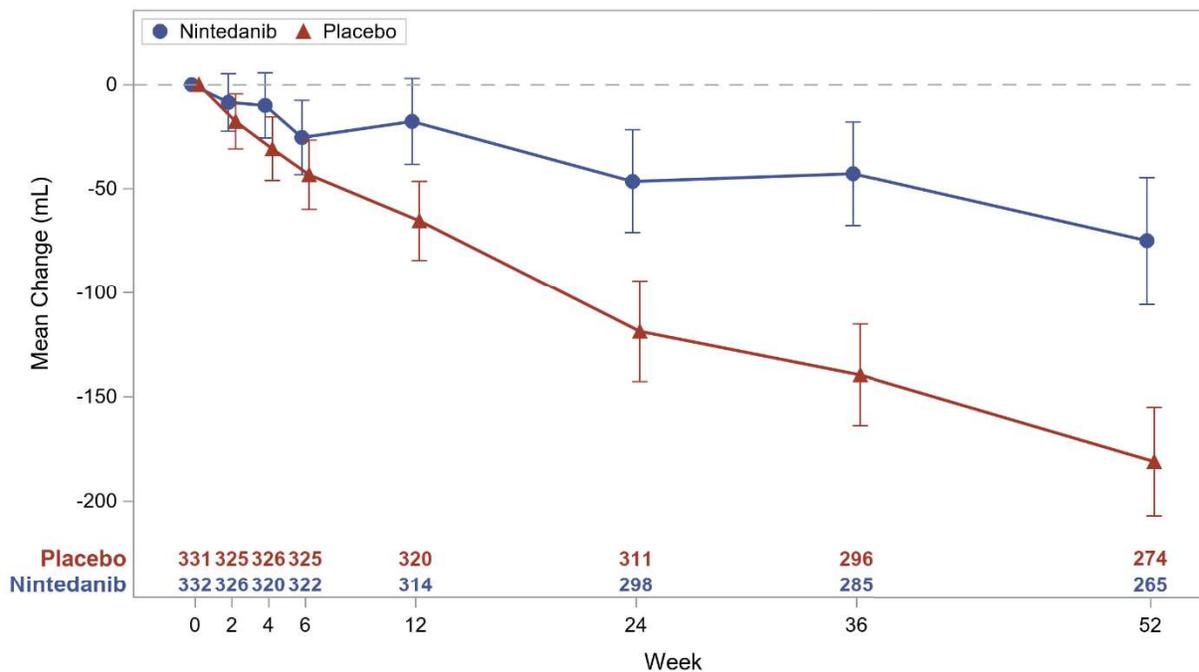
### Dose/Dose Response

Dose response was not explored in this submission. Nintedanib dosing was established in the IPF program (see Dr. Miya Paterniti’s clinical review dated Sept 3, 2014).

### Durability of Response

To evaluate for durability of response, change from baseline in FVC was assessed throughout the 52-week treatment period (Figure 5). The difference between placebo and nintedanib groups did not appear to diminish over the 52-week treatment period, suggesting that the FVC effect is durable.

**Figure 5: FVC, Mean of observed absolute change from baseline in FVC over 52 weeks, Overall population**



Source: FDA Statistical Reviewer

### **Persistence of Effect**

Persistence of efficacy after treatment discontinuation was not separately evaluated. Thus, an analysis of spirometry or other efficacy endpoints in patients discontinuing treatment in a systematic fashion cannot be performed. A persistence of treatment effect for nintedanib is not expected based on its mechanism of action and known pharmacology.

### **Efficacy Results – PRO endpoints**

#### *Kings Brief Interstitial Lung Disease (K-BILD) questionnaire*

The K-BILD questionnaire is a self-completed health status questionnaire with 15 items across three domains (psychological, breathlessness and activities, and chest symptoms) scored from 0 to 100, with higher scores representing better health status, and increases in scores indicating improvement.

The adjusted mean for the absolute change from baseline in K-BILD scores at week 52 trended in favor of nintedanib for all populations (overall, UIP, HRCT Other) but 95% CIs included the null. Specifically, the treatment difference was +1.3, +1.5, and +1.1 points in the overall, UIP, and HRCT Other populations, respectively. Importantly, the changes in both arms were small and the treatment difference is likely not clinically relevant based on information available for K-BILD in other ILDs (MCID 4-8 [Nolan et al. 2019; Patel et al. 2013]).

The FDA Clinical Outcome Assessment (COA) team also reviewed whether the K-BILD questionnaire was acceptable for use in PF-ILD. They determined that the K-BILD was not fit-for-purpose as some of its items were not well-defined and could be impacted by factors (e.g. psychosocial factors) other than the treatment (items 3, 5, 6, 8, 12, 14,15). See review from COA reviewer Onyeka Illoh review dated January 16, 2020 for more details.

Overall, this endpoint does not provide support to the primary endpoint, and its significance is unclear.

#### *Living with Pulmonary Fibrosis (L-PF) questionnaire*

The L-PF questionnaire consists of 44 items within 2 modules (symptoms and impact). Within the symptoms module (23 items) there are three symptoms covered: dyspnea, cough, and fatigue. The impacts module (21 items) has a single score. Total scores range from 0 to 100 with higher values representing greater impairment.

As noted in Table 13, favorable trends were noted in all nintedanib treated patients for total scores and symptom domain scores of cough and dyspnea.

**Table 13: Secondary Endpoint, L-PF Scores, Change from Baseline at Week 52**

	Overall		HRCT-UIP		HRCT-Other	
	Pbo (N=331)	Nint (N=332)	Pbo (N=206)	Nint (N=206)	Pbo (N=125)	Nint (N=126)
<b>Total Score</b>						
<b>Number of Patients Analyzed</b>	315	324	196	200	119	124
<b>Adjusted mean change from baseline</b>	3.9	-0.2	3.8	-0.6	4.0	0.3
<b>Difference (95% CI)</b>	-4.1 (-6 to -2.1)		-4.4 (-6.8 to -2.0)		-3.6 (-6.8 to -0.5)	
<b>Symptom Dyspnea Domain Score</b>						
<b>Number of Patients Analyzed</b>	317	324	196	200	121	124
<b>Adjusted mean change from baseline</b>	7.9	4.3	8.3	4.1	6.9	4.1
<b>Difference, 95% CI</b>	-3.5 (-6.1 to -0.9)		-4.2 (-7.5 to -0.9)		-2.7 (-7.0 to 1.6)	
<b>Symptom Cough Domain Score</b>						
<b>Number of Patients Analyzed</b>	314	322	194	199	120	123
<b>Adjusted mean change from baseline</b>	4.3	-1.8	4.1	-3.2	4.6	-0.3
<b>Difference, 95% CI</b>	-6.1 (-9.7 to -2.5)		-7.3 (-11.9 to -2.7)		-4.3 (-10.0 to 1.4)	
Abbreviations: Nint – nintedanib, Pbo – placebo						

Source: FDA Statistical Reviewer

The adjusted mean for the absolute change from baseline in L-PF total scores at week 52 were in favor of nintedanib-treated patients in all populations (overall and both HRCT subgroups) with 95% CIs excluding the null. Symptom domain scores for cough and dyspnea also trended in favor of nintedanib treated patients, however, only for the overall population and the UIP subpopulation did the 95% CIs exclude the null.

While point estimates may have favored nintedanib, with 95% CIs excluding null for some comparisons as noted above, the clinical meaning of these data are uncertain. The MCID for L-PF is unknown and the FDA COA team found that there was insufficient support for its interpretability and clinical meaningfulness given that anchor scales that would be useful for deriving meaningful change thresholds were not administered in study 247. See review from COA reviewer Onyeka Illoh review dated January 16, 2020 for more details.

Overall, this endpoint does not provide support to the primary endpoint, and its significance is unclear.

#### Data Quality and Integrity

No issues were discovered with respect to data quality or data integrity.

## **Additional Analyses Conducted**

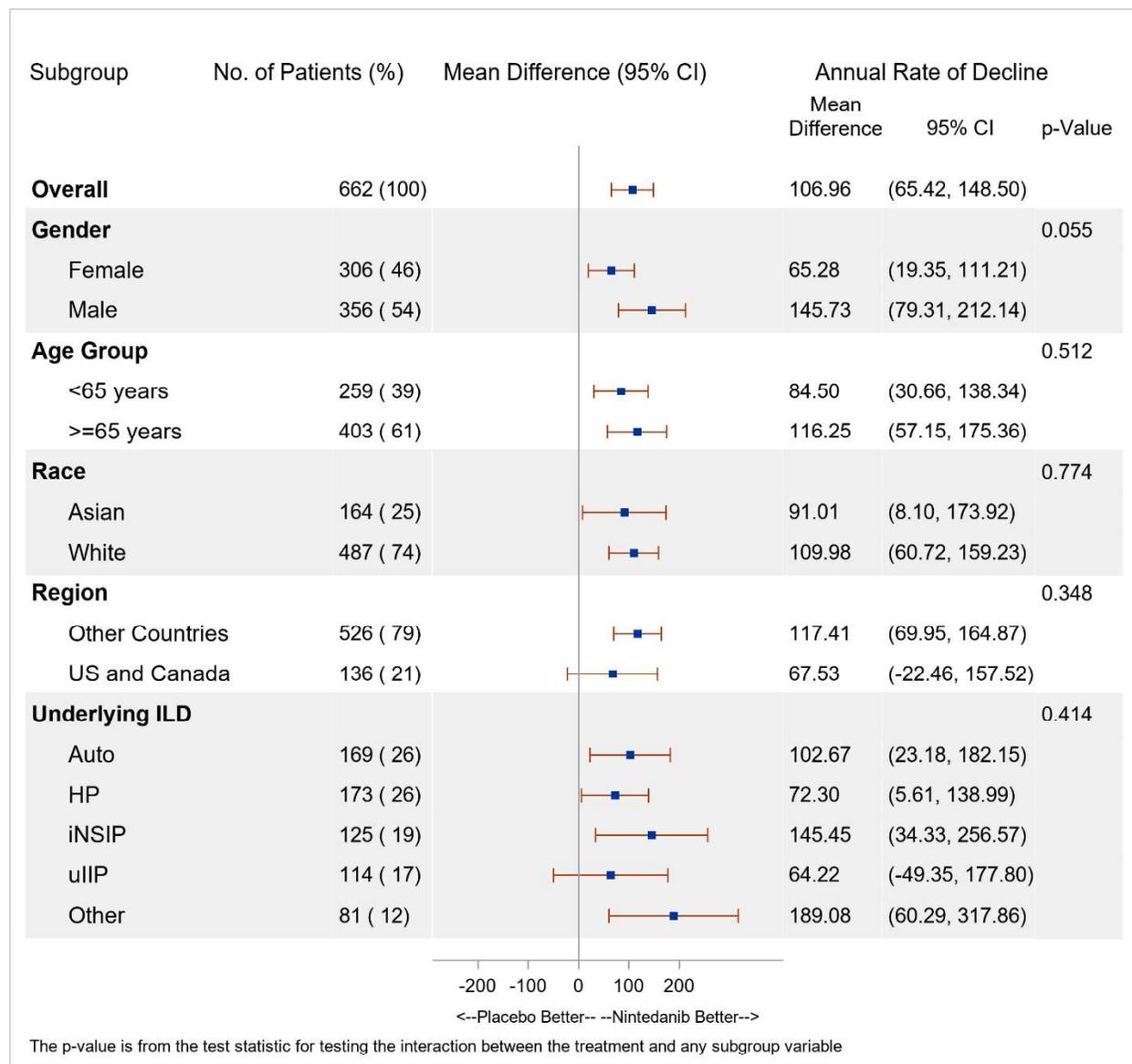
### *Subgroup Analyses*

Given the heterogeneous nature of the studied population (including multiple ILD diagnoses), assessing treatment response across subgroups was important for providing information to healthcare providers as well as informing future real-world use. In this section, subgroup analyses were only performed for the primary efficacy endpoint. This section provides the reviewer's subgroup analyses by gender, race, age, geographical region, and by ILD diagnosis.

No significant interaction was found between treatment and the pre-specified subgroups at the 5% level of statistical significance.

Subgroup analyses for the primary endpoint by demographic subgroups and by ILD diagnoses (Figure 6) were generally consistent with the overall population, except males had a slightly larger treatment effect than females. It is important to acknowledge that these analyses are limited due to the small subgroup sample sizes and that the study was not powered to detect differences in subgroups by ILD diagnosis. Thus, definitive conclusions cannot be drawn.

**Figure 6: Primary Endpoint, Subgroup Analysis, 52 week Treatment Period, Overall Population**

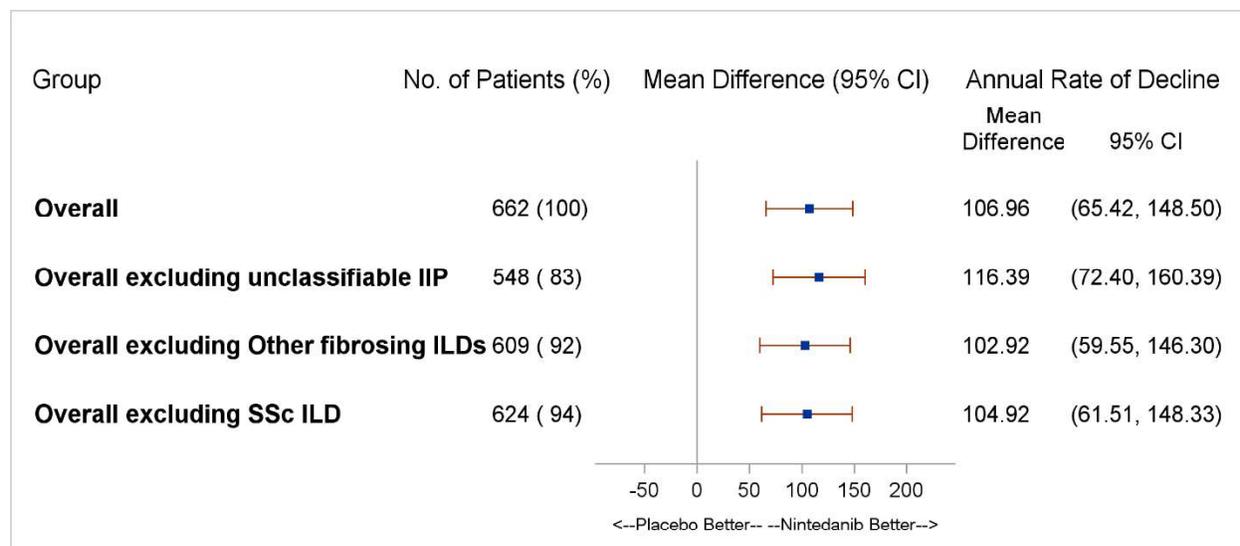


**Abbreviations:** **ILD:** Interstitial lung disease; **Auto:** Includes Rheumatoid Arthritis associated ILD, Mixed connective tissue disease, Systemic sclerosis associated ILD, and selected terms from the following: interstitial pneumonia with autoimmune features, positive anti-PL7 antibody ILD, Sjogren’s syndrome associated ILD, anti-neutrophil cytoplasmic antibody associated ILD, CTD organizing pneumonia, lupus associated ILD, microscopic polyangiitis associated ILD, undifferentiated CTD-ILD, polymyositis CTD-ILD; **HP:** Chronic hypersensitivity pneumonitis; **iNSIP:** Idiopathic nonspecific interstitial pneumonia; **uIIP:** Unclassifiable idiopathic interstitial pneumonia; **Other:** Includes Exposure-related ILD, Sarcoidosis, and selected terms from the following: desquamative interstitial pneumonitis, pleuro-parenchymal fibroelastosis, post stem cell transplant fibrosis, antisynthetase syndrome, unspecified CTD, post-Acute interstitial pneumonitis, post chemotherapy, IgG4-related lung disease, cryptogenic organizing pneumonitis, fibrosis with emphysema, respiratory bronchiolitis ILD, pulmonary alveolar proteinosis, chronic eosinophilic pneumonia, interstitial pneumonia with autoimmune features, lipoidic fibrosis, overlap NSIP with organizing pneumonia without CTD

Source: FDA Statistical Reviewer

Given that nintedanib is approved for IPF and SSc-ILD, that IPF is a diagnosis of exclusion that could have potentially been inadvertently included in uIPF or Other ILDs, and that SSc-ILD patients were included in study 247, these subgroups were selected for an exclusion-based subgroup analysis, assessing treatment response by removing individual subgroups (Figure 7). Of note, SSc-ILD patients selected in this study represent a rapidly progressive subset of the general SSc-ILD patients studied in study 214, the basis for approval for nintedanib in SSc-ILD. Regardless, no notable changes in treatment response were noted.

**Figure 7: Primary Endpoint, by Excluding Certain Subgroups, 52 week Treatment Period, Overall Population**



Source: FDA Statistical Reviewer

This exclusion-based analysis does not suggest that the observed treatment effect was driven by inadvertent inclusion of patients with IPF or SSC-ILD.

Overall, these subgroup based analyses do not suggest that the treatment response seen in the overall population was driven by a particular demographic subgroup or by a particular ILD diagnosis.

*Tipping Point Analysis*

Table 14 summarizes the primary efficacy follow-up status at Week 52 according to FVC data availability, trial medication discontinuation status, and vital status at week 52. Despite the off-treatment data retrieval plan and effort across the two arms, there were 17% of placebo patients and 20% of nintedanib patients with their week 52 FVC data missing.

**Table 14: Summary of FVC Data Availability at Week-52 (Overall Population)**

	<b>Placebo N=331</b>	<b>Nintedanib N=332</b>	<b>Total N=663</b>
	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>
<b>FVC Data Available at 52 Weeks</b>			
FVC at 52 weeks, trial drug until 52 weeks	262 (79)	241 (73)	503 (76)
FVC at 52 weeks, trial drug prematurely discontinued	12 (4)	24 (7)	36 (5)
<b>No FVC Data at 52 Weeks</b>			
No FVC at 52 weeks, alive at 52 weeks	38 (12)	50 (15)	88 (13)
No FVC at 52 weeks, died before 52 weeks	19 (6)	17 (5)	36 (5)

Source: FDA Statistical Reviewer

For each co-primary population, the results over a relatively comprehensive range of by-arm shift (S) values are summarized in Table 15 and Table 16. The header rows show the shifts applied to dropouts in the placebo group, with “200” meaning a 200 mL/year rate of increase in FVC imposed on the assumed background missing-at-random (MAR) rate of decline in placebo; similarly, the header columns show a range of shifts applied to dropouts in the nintedanib arm, with “-550” meaning an additional 550 mL/year rate of decline imposed on the assumed background MAR rate of decline in nintedanib. The body of the table provides p-values for the comparisons for the nintedanib group to the placebo group for the corresponding shifts. As the objective of a tipping point analysis is to identify the points that tipped the primary analysis conclusion, while the full analyses explored wider ranges of deltas for both the two arms, in each table, only the ranges that provide the most relevant information are included.

**Table 15: Tipping Point Analysis, Annual Rate of Decline in FVC in mL over 52 Weeks, Overall Population**

		Shift in Placebo (Change in mL/Year)				
		0	200	250	300	350
Shift in Nintedanib (Change in mL/Year)	-550	0.019	0.100	0.143	0.198	0.268
	-500	0.009	0.058	0.087	0.126	0.177
	-450	0.004	0.032	0.050	0.075	0.110
	-400	0.002	0.016	0.027	0.042	0.065
	-350	<.001	0.008	0.014	0.022	0.036
	-100	<.001	<.001	<.001	<.001	<.001
	0	<.001	<.001	<.001	<.001	<.001

Source: FDA Statistical Reviewer

**Table 16: Tipping Point Analysis, Annual Rate of Decline in FVC in mL over 52 Weeks, UIP Subpopulation**

		Shift in Placebo (Change in mL/Year)				
		0	100	150	200	250
Shift in Nintedanib (Change in mL/Year)	-550	0.037	0.082	0.118	0.166	0.226
	-500	0.021	0.050	0.074	0.108	0.153
	-450	0.011	0.029	0.044	0.067	0.099
	-400	0.006	0.016	0.025	0.040	0.061
	-350	0.003	0.008	0.014	0.022	0.036
	-100	<.001	<.001	<.001	<.001	<.001
	0	<.001	<.001	<.001	<.001	<.001

Source: FDA Statistical Reviewer

In each table, the yellow highlighted cell in each table could be used as a reference cell. This cell corresponds to shifts of 0 in placebo and a shift of -100 (a negative counter-effect for the treatment effect from primary analyses: 107 mL/year in the overall population, and 128 mL/year in the HRCT-UIP population, of roughly the same magnitude) in nintedanib, which is analogous to the situation that the dropouts in nintedanib are assumed to progress at the rate seen in placebo while the dropout in placebo are assumed to stay in trend. The p-value in this

cell stays very significant ( $<0.001$ ) meaning that nintedanib will still have a significant effect in the overall trial. 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.

Overall, the tipping point analysis suggests that the results are robust based on the lack of plausibility of the “tipping points”.

## **Integrated Review of Effectiveness**

### **8.1.3. Integrated Assessment of Effectiveness**

Nintedanib has demonstrated efficacy in patients with chronic fibrosing ILDs with a progressive phenotype with a statistically significant reduction in decline in FVC over 52 weeks (Table 10). This is further supported by favorable trends in time-to-event secondary endpoints such as time to first exacerbation and time-to-death (Table 11 and Table 12). These data from the single pivotal trial (study 247) in conjunction with established efficacy of nintedanib in IPF, a distinct but related fibrosing ILD has met the statutory evidentiary requirements for efficacy on clinically meaningful endpoints.

Given the heterogeneity of the study population, it was necessary to address several issues during the review. First, a concern existed that a particular subset of patients may have been responsible for driving the efficacy. This was addressed based on subgroup analyses by demographics and ILD diagnosis (Figure 6), demonstrating similar treatment effects across subgroups. Second, the inadvertent inclusion of IPF patients in the study 247 population was a concern. This was addressed by noting that the demographics of the study 247 population (Table 7) was different than that of prior IPF studies, as well as efficacy analyses excluding ILD diagnoses that could potentially “hide” IPF patients (e.g. uIIP or Other ILDs) showing no difference in treatment response (Figure 7). Third, concern existed regarding the study not being powered to assess response in subgroups precluding real-world application of results for particular ILD diagnoses. Given the prevalence of the various ILDs enrolled, enrolling sufficient number of patients for all ILD subtypes to allow for adequate powering is likely unfeasible.

Based on this data and considering the previously established efficacy of nintedanib in IPF, nintedanib 150 mg oral twice daily with possible dose modification strategies is recommended for Approval for the treatment of chronic fibrosing ILDs with a progressive phenotype.

## **8.2. Review of Safety**

### **8.2.1. Safety Review Approach**

The focus in the safety portion of review is on the overall population from study 247 and includes all patients who received at least one dose of study drug [treated set (TS)]. When relevant, discussion of subgroups (e.g. UIP subpopulation, demographic based subgroups etc.) is added. AE analyses are based on number of patients with AEs rather than number of events.

Although some patients were followed beyond 52 weeks (continued in a randomized and blinded fashion [part B]), the primary focus of this safety evaluation is the 52 week treatment period (part A). Pertinent findings from the whole trial (parts A+B) to DBL1 are discussed when relevant.

### **8.2.2. Review of the Safety Database**

#### **Overall Exposure**

Study 247 was the only clinical trial relevant to this patient population (PF-ILD).

The exposure for the 52 week treatment period (part A) of the trial is shown in Table 17. The median duration of exposure for both treatment arms was similar at 12 months. However, there were more treatment reductions, treatment interruptions, and treatment discontinuations in the nintedanib arm.

**Table 17: Exposure, 52 week Treatment Period, Overall Population**

	<b>Placebo (N=331)</b>	<b>Nintedanib (N=332)</b>
<b>Duration of Exposure (months)</b>		
Mean duration	11	10
Median duration	12	12
<b>Duration of exposure (categorical)</b>		
≤ 3 months	13 (4)	38 (11)
>3 to ≤6 months	15 (5)	17 (5)
>6 to ≤12 months	25 (8)	29 (9)
>12 months	278 (84)	248 (75)
<b>Treatment reduction, interruption, or discontinuation</b>		
Patients with at least 1 dose reduction	18 (5)	112 (34)
Patients with at least 1 treatment interruption	34 (10)	110 (33)
Patients prematurely discontinuing treatment	57 (17)	84 (25)
Duration of 150mg bid exposure (wks), mean	48	37
Duration of 100mg bid exposure (wks), mean	21	21

Source: Study 247 CSR, Table 10.5:1, p. 170

The majority of treatment changes (dose reductions, interruptions, or discontinuations) occurred early in the course of treatment with more nintedanib than placebo patients having a duration of exposure ≤ 3 months. Not surprisingly, median exposure for the whole trial (at DBL1) was longer at 17 months, with similar findings regarding dose reductions, treatment interruptions, and treatment discontinuations.

#### **Adequacy of the safety database:**

Given the known safety profile of nintedanib in other ILDs (IPF and SSc-ILD), the nature of the indicated disease, PF-ILD, and its enrollment of a subset of patients from a variety of individual ILDs, this safety database is adequate.

#### **8.2.3. Adequacy of Applicant's Clinical Safety Assessments**

##### **Issues Regarding Data Integrity and Submission Quality**

No OSI audits were conducted. There were no data integrity issues suspected.

##### **Categorization of Adverse Events**

MedDRA version 22.0 was used to code adverse events (AEs). AE and Serious AEs (SAEs) were defined per CFR 312.32.

Treatment emergent AEs were defined as AEs that occurred within 28 days (considered to be the residual effect period [REP] for nintedanib) from the last dose of study drug. Unless otherwise specified, safety analyses were based on TEAE. Causes of death and suspected major adverse cardiovascular events (nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death) were adjudicated. In all patients, vital status was assessed after patients completed the 52-week treatment period and on April 23, 2019 after the last patient last visit primary endpoint [LPLVPE] visit was performed.

### Routine Clinical Tests

The measures used to assess the safety objectives were reasonable and included standard hematology, chemistry, and urinalysis variables as well as vital signs.

#### 8.2.4. Safety Results

### Overall summary of AEs

Overall, in the 52 week treatment period, the majority of patients in both treatment arms experienced at least one AE with more nintedanib patients experiencing at least one AE compared to placebo. Similarly, more nintedanib patients versus placebo discontinued treatment due to AEs. This was not the case, however, for SAEs or deaths which were generally balanced between treatment arms (SAEs: 32% nintedanib vs. 33% placebo; deaths: 3% nintedanib vs. 5% placebo). This is summarized in Table 18.

**Table 18: Overall Safety Summary, 52 week Treatment Period, Overall Population**

	Placebo (N=331)	Nintedanib (N=332)
Patients with any AE	296 (89)	317 (96)
Patients with AEs leading to treatment discontinuation	34 (10)	65 (20)
Patients with AEs leading to permanent dose reduction	14 (4)	110 (33)
Patients with SAEs	110 (33)	107 (32)
Deaths	17 (5)	11 (3)

Source: Study 247 CSR Table 12.1.1:1, p.252; reviewer verified

Similar outcomes were noted for the UIP and HRCT Other subpopulations and are discussed further in the respective sections.

### Deaths

In this section, deaths during the 52 week treatment period (part A) are discussed with supplemental discussion of the whole trial (part A+B) when appropriate. Importantly, this safety section primarily focuses on on-treatment deaths defined as death occurring due to an AE that began within 28 days of last study drug intake. Whether a death is considered within the 52

week treatment period is determined by the onset of the AE that led to death (e.g. an ILD exacerbation reported at week 52 and within 28-days of last dose of study drug and leading to death in week 54 would be included in week 52 deaths).

There were more on-treatment deaths in the placebo group. The majority of deaths were in the Respiratory, thoracic, and mediastinal system organ class (RTMSOC), with no clear treatment arm imbalances of concern. This information is summarized in Table 19.

**Table 19: On-treatment Deaths, 52 week Treatment Period, Overall population**

PT/SOC	Placebo (N=331)	Nintedanib (N=332)
<b>Patients with any AE leading to death</b>	<b>17 (5)</b>	<b>11 (3)</b>
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>11 (3)</b>	<b>6 (2)</b>
Acute respiratory failure	0	3 (1)
Interstitial lung disease	4 (1)	2 (1)
Respiratory failure	4 (1)	2 (1)
Dyspnea	1 (<1)	0
Pneumothorax	1 (<1)	0
Respiratory distress	1 (<1)	0
<b>Infections and infestations</b>	<b>2 (1)</b>	<b>3 (1)</b>
Pneumonia	1 (<1)	2 (1)
Septic shock	0	1 (<1)
Infectious pleural effusion	1 (<1)	0
<b>General disorders and administration site conditions</b>	<b>2 (1)</b>	<b>1 (&lt;1)</b>
Death	0	1 (<1)
Sudden cardiac death	1 (<1)	0
Sudden death	1 (<1)	0
<b>Neoplasms benign, malignant and unspecified</b>	<b>1 (&lt;1)</b>	<b>0</b>
Neoplasm malignant	1 (<1)	0
<b>Cardiac disorders</b>	<b>0</b>	<b>1 (&lt;1)</b>
Arteriosclerosis coronary artery	0	1 (<1)
<b>Vascular disorders</b>	<b>1 (&lt;1)</b>	<b>0</b>
Aortic aneurysm rupture	1 (<1)	0
Hemorrhagic shock	1 (<1)	0
<b>Musculoskeletal and connective tissue disorders</b>	<b>1 (&lt;1)</b>	<b>0</b>
Connective tissue disorder	1 (<1)	0

Source: Study 247 CSR Table 15.3.1.1.2.1:9, p.1707; reviewer verified

On-study deaths during the 52-week treatment period were also analyzed by the medical reviewer (deaths that occurred anytime within the 52-week treatment period [part A] even if outside the treatment emergent window). Vital status was assessed at the 52-week timepoint.

Overall, there were more on-study deaths, and the number of deaths were balanced between treatment groups, with a total of 16 on-study placebo deaths versus 17 on-study nintedanib deaths. Discrepancies between the number of on-study and on-treatment deaths are not surprising, given the differences in how on-study and on-treatment was defined. In the placebo group, there was one less on-study death as compared to on-treatment death (16 on-study vs. 17 on-treatment). Patient (b) (6) was a 67 year old male with an ILD exacerbation on study day 186 recorded as ending on study day 523 with death; this was not recorded as an on-study death (day 523 > 52 weeks/day 373) but was recorded as an on-treatment death due to the AE beginning within the 52 week treatment period. With regard to the nintedanib arm, there were 6 additional on-study nintedanib deaths as compared to on-treatment nintedanib deaths (17 on-study vs. 11 on-treatment). This was due to study treatment discontinuation occurring >28 days prior to the AE leading to death. With regard to the specific AEs that led to the on-study deaths, these were consistent with the on-treatment deaths. Overall, the on-study analysis of deaths did not raise safety concerns.

Turning to the HRCT subpopulations, review of AEs leading to on-treatment deaths in the UIP subpopulation did not raise concerns. The UIP subpopulation had generally similar causes of death as described for the overall population (with the majority being from the RTM SOC) and were higher in the placebo arm. In regard to the HRCT Other subpopulation, a much smaller number of deaths was noted (5 total) making it difficult to draw conclusions. However, a treatment arm imbalance in deaths was noted in the HRCT Other subpopulation, albeit in a small number of patients (4 nintedanib deaths vs. 1 placebo death). This imbalance was reversed in a whole trial (parts A+B to DBL1) analysis of on-treatment deaths within this HRCT Other subgroup (4 nintedanib deaths vs. 7 placebo deaths), suggesting the numerical difference for on-treatment deaths in the HRCT other subpopulation for the 52 week treatment period may have been stochastic and related to small sample sizes.

Pertinent details from death narratives regarding on-treatment deaths over the whole trial (parts A+B) were also reviewed. There were a total of 30 placebo and 15 nintedanib on-treatment deaths over the whole trial. The AEs leading to death were consistent with that observed during the 52-week treatment period. These are presented in Table 20.

**Table 20: On-Treatment Death Details, Overall Population, Whole Trial (Parts A + B)**

Patient	Age	Sex	Treatment	AE leading to death	Last dose (study day)	Days after last dose, death*	HRCT cohort	Part A or B
(b) (4)	64	M	Nintedanib	Pneumonia	14	26	UIP	A
	60	F	Nintedanib	Arteriosclerosis coronary artery	16	1	UIP	A
	71	M	Nintedanib	Acute respiratory failure	163	34	UIP	A
	66	F	Nintedanib	ILD	164	417	UIP	A
	58	M	Nintedanib	Respiratory failure	167	11	Other	A
	67	M	Nintedanib	Pneumonia	177	17	UIP	A
	77	M	Nintedanib	Acute respiratory failure	208	1	UIP	A
	68	F	Nintedanib	Respiratory failure	245	5	Other	A
	73	M	Nintedanib	Acute respiratory failure	263	1	UIP	A
	38	M	Nintedanib	Death	305	1	Other	A
	63	F	Nintedanib	Septic shock	319	1	Other	A
	87	M	Nintedanib	Lung infection, pulmonary fibrosis	444	5	UIP	B
	69	M	Nintedanib	pulmonary sepsis	546	1	UIP	B
	67	M	Nintedanib	Bacterial sepsis, acute respiratory failure	576	2	UIP	B
	67	M	Nintedanib	Pulmonary fibrosis	616	44	UIP	B
	73	M	Placebo	ILD	45	15	UIP	A
	73	M	Placebo	Aortic aneurysm rupture, shock haemorrhagic	60	1	UIP	A
	68	F	Placebo	ILD	106	1	UIP	A
	62	M	Placebo	Infectious pleural effusion	114	78	UIP	A
	70	F	Placebo	Dyspnea	114	1	UIP	A
80	F	Placebo	Sudden cardiac death	169	26	UIP	A	
73	F	Placebo	Pneumothorax	198	74	UIP	A	
59	M	Placebo	Respiratory failure	247	12	UIP	A	

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(b) (4)	59	F	Placebo	Neoplasm malignant	274	13	UIP	A
	59	M	Placebo	Respiratory failure	274	1	UIP	A
	69	F	Placebo	Connective tissue disorder, ILD	283	6	UIP	A
	58	M	Placebo	Respiratory distress	345	5	Other	A
	77	M	Placebo	Pneumonia	350	2	UIP	A
	86	M	Placebo	Respiratory failure	361	14	UIP	A
	80	M	Placebo	Sudden death	366	1	UIP	A
	65	M	Placebo	Respiratory failure	361	9	UIP	A
	65	F	Placebo	Chronic respiratory failure	401	1	Other	B
	75	F	Placebo	ILD	404	6	UIP	B
	77	M	Placebo	Hypersensitivity pneumonitis	406	1	Other	B
	64	M	Placebo	Cerebral hemorrhage	428	1	UIP	B
	81	F	Placebo	Bronchitis	467	<13	UIP	B
	72	M	Placebo	Myocardial infarction	487	1	Other	B
	72	M	Placebo	Lung squamous cell lung carcinoma metastatic	491	1	UIP	B
	67	M	Placebo	ILD	505	18	UIP	A
	79	F	Placebo	Respiratory failure	511	1	UIP	B
	66	M	Placebo	Pneumonia	527	1	UIP	B
	75	M	Placebo	Cardiac death	528	1	Other	B
	76	M	Placebo	Pneumonia	535	1	Other	B
82	M	Placebo	Respiratory distress	553	1	Other	B	
76	M	Placebo	Hepatic cirrhosis	622	16	UIP	B	

\*AE leading to death may have occurred on or before day of death

Source: Study 247 CSR Death Narratives 15.4.3, p.3263, Tables 12.2.1:4 and 12.2.1:5

Based on information shown for the deaths in Table 20, this reviewer did not find concerning safety findings in regard to causes, demographics, dose, duration, or timing. There continued to be more deaths in the placebo arm with a larger difference between arms than that seen in the 52 week treatment period (whole trial overall population on-treatment deaths 9% placebo vs. 5% nintedanib). The causes of on-treatment deaths over the whole trial remained largely similar to that seen in the 52 week treatment period.

To determine if any death imbalances existed by specific ILD diagnosis, this reviewer performed an analysis of on-study deaths by ILD diagnosis for the 52 week treatment period (part A) as well as whole trial (Parts A+B) (Table 21). In all patients, vital status was assessed after completion of the 52-week treatment period (part A) and for the whole trial (parts A+B) on April 23, 2019 after LPLVPE. As the number of patients in the ILD subgroups were small, on-study deaths were chosen for this analysis as there were more on-study deaths (than on-treatment). A similar analysis with on-treatment deaths (instead of on-study deaths) [not shown] did not change overall conclusions. Small sample sizes notwithstanding, no new safety concerns were raised from these analyses.

**Table 21: On-study Deaths by ILD Diagnosis, 52 week Treatment Period (Part A) and Whole Trial (A+B)**

	52 week period		Whole trial	
	Placebo	Nintedanib	Placebo	Nintedanib
<b>Total Patients</b>	<b>N=331</b>	<b>N=332</b>	<b>N=331</b>	<b>N=332</b>
Patients with exposure related ILD	N=18	N=21	N=18	N=21
Exposure related ILD deaths, n(%)	1 (6)	2 (10)	2 (10)	2 (10)
Patients with CHP	N=89	N=84	N=89	N=84
CHP patient deaths, n(%)	2 (2)	4 (5)	8 (9)	7 (8)
Patients with iNSIP	N=61	N=64	N=61	N=64
iNSIP patient deaths, n(%)	6 (10)	4 (6)	8 (13)	4 (6)
Patients with other fibrosing ILD	N=30	N=23	N=30	N=23
Other fibrosing ILD patient deaths, n(%)	3 (10)	0	4 (13)	1 (4)
Patients with RA-ILD	N=47	N=42	N=47	N=42
RA-ILD patient deaths, n(%)	4 (9)	4 (10)	9 (19)	6 (14)
Patients with SSc-ILD	N=16	N=23	N=16	N=23
SSc-ILD patient deaths, n(%)	0	1 (4)	0	1 (4)
Patients with MCTD	N=12	N=7	N=12	N=7
MCTD patient deaths, n(%)	0	0	0	0
Sarcoidosis	N=8	N=4	N=8	N=4
Sarcoid patient deaths, n(%)	0	0	0	0
Patients with uIIP	N=50	N=64	N=50	N=64
uIIP patient deaths, n(%)	1 (2)	1 (2)	7 (14)	6 (9)
<b>Total Deaths</b>	<b>17</b>	<b>16</b>	<b>38</b>	<b>27</b>
Abbreviations: ILD – interstitial lung disease, CHP – hypersensitivity pneumonitis, iNSIP – idiopathic non-specific interstitial pneumonitis, RA-ILD – rheumatoid arthritis ILD, SSc-ILD – systemic sclerosis ILD, uIIP – unclassifiable idiopathic interstitial pneumonitis, MCTD – mixed connective tissue disease				

Source: Reviewer generated (ADSL, TRTFL=Y, VITSTAT="Dead", DTHTSY <373, DIAGUND, TRT01P)

Not surprisingly, the highest number of deaths by ILD diagnoses were in patients with CHP, iNSIP, and RA-ILD, consistent with these diagnoses having the largest contributions to the study population (see Table 8 for details). The only ILD diagnosis for which there were more than 2 deaths in any arm, and greater in nintedanib than placebo, was CHP. The numerical difference favoring placebo reversed when considering the whole trial. Overall, given the small numbers of deaths within each ILD subgroup, no definitive conclusions can be drawn, however, there does not appear to be a concerning safety finding.

Next, adjudicated cause of on-treatment deaths was reviewed for the 52 week treatment period. Adjudication was performed in a blinded manner by the independent adjudication committee (AC) comprised of board-certified cardiologists, pulmonologists, and

rheumatologists without any financial conflict of interest. The AC determined whether the cause of death was respiratory, cardiovascular (CV), non-CV/non-respiratory, or undetermined. The majority of adjudicated deaths were respiratory in origin. This information is summarized in Table 22.

**Table 22: Adjudicated Causes of On-Treatment Deaths, 52 week Treatment Period, Overall Population**

	<b>Placebo (N=331)</b>	<b>Nintedanib (N=332)</b>
Patients with any AE leading to death	17 (5)	11 (3)
Respiratory deaths	13 (4)	6 (2)
Cardiovascular (CV) deaths	3 (1)	3 (1)
Non CV/Non Respiratory deaths	0	1 (<1)
Undetermined deaths	1 (<1)	1 (<1)

*Source: Study 247 CSR Table 12.2.1: 3, p.281*

In summary, review of on-treatment deaths, death narratives, adjudicated deaths, and whole trial deaths, does not raise safety concerns.

### **Serious Adverse Events**

Overall, approximately 33% of study patients experienced SAEs with relatively similar frequencies for nintedanib and placebo treated patients. As expected given the population, SAEs from the respiratory, thoracic, and mediastinal disorders system organ class (RTM SOC) were the most common. SAE data are summarized in Table 23.

**Table 23: Serious Adverse Events, 52 week Treatment Period, >1% in any arm, Overall Population**

SOC/PT	Placebo (N=331)	Nintedanib (N=332)
Patients with any SAE	110 (33)	107 (32)
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>64 (19)</b>	<b>44 (13)</b>
Interstitial lung disease	31 (9)	11 (3)
Acute respiratory failure	2 (1)	10 (3)
Respiratory failure*	9 (3)	6 (2)
Pulmonary hypertension	4 (1)	5 (2)
Pulmonary fibrosis	2 (1)	5 (2)
Pneumothorax	4 (1)	2 (1)
Dyspnea	9 (3)	1 (<1)
<b>Infections and infestations</b>	<b>27 (8)</b>	<b>29 (9)</b>
Pneumonia	11 (3)	12 (4)
Bronchitis	3 (1)	4 (1)
Influenza	3 (1)	4 (1)
<b>Hepatobiliary disorders</b>	<b>3 (1)</b>	<b>11 (3)</b>
Drug-induced liver injury	0	6 (2)
<b>Cardiac disorders<sup>^</sup></b>	<b>15 (5)</b>	<b>12 (4)</b>
<b>Musculoskeletal and connective tissue disorders<sup>^</sup></b>	<b>9 (3)</b>	<b>6 (2)</b>
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)<sup>^</sup></b>	<b>7 (2)</b>	<b>8 (2)</b>
<b>Gastrointestinal disorders<sup>^</sup></b>	<b>4 (1)</b>	<b>10 (3)</b>
<b>Injury, poisoning and procedural complications<sup>^</sup></b>	<b>5 (2)</b>	<b>6 (2)</b>
<b>Vascular disorders<sup>^</sup></b>	<b>5 (2)</b>	<b>5 (2)</b>
*Respiratory failure as described in narratives encompassed acute respiratory failure and chronic respiratory failure. The overall impact of separating acute from chronic was minimal.		
<sup>^</sup> individual PTs not shown as all PTs in this SOC were <1% in each arm		

Source: Study 247 CSR Tables 12.2.2:1, p.285; reviewer verified (ADAE: TRTFL, TREMFL, ONT52FL, AESER)

Based on PTs, there were more RTM SOC SAEs in the placebo arm compared to nintedanib, mostly accounted for by the PT interstitial lung disease (i.e. ILD exacerbation); this is consistent with efficacy results on exacerbations in section 8.1.2. Of note, exacerbations for efficacy analyses had to meet pre-specified protocol defined criteria whereas ILD exacerbations for safety analyses were investigator-reported without the need to meet any specific criteria. Minor differences between arms are present for other PTs within the RTM SOC, with minimal impact on the overall conclusion. Unsurprisingly, there were more hepatobiliary disorders with nintedanib treatment, and specifically cases of drug induced liver injury, both of which are

already included on the nintedanib product label as Warnings and Precautions. This is explored further in section 8.2.5.

In considering the UIP and HRCT Other subpopulations, minor differences as compared to the overall population were noted which did not raise additional safety concerns. One minor difference was that differences between arms favoring nintedanib were accentuated in the UIP subpopulation for total SAEs as well as certain common respiratory SAEs (such as ILD exacerbation). Another minor difference was related to the HRCT Other subpopulation. There were more total SAEs in nintedanib treated patients vs placebo (35% vs. 26%), however, this was not due to a discernible pattern based on SOC or PT.

Given concerns that SAEs could be disproportionately driven by a certain ILD subgroup, the clinical reviewer analyzed SAEs by ILD diagnoses (such as UIP, cHP, RA-ILD, iNSIP). Due to the small sample sizes within subgroups, results are difficult to interpret, and no definite conclusions can be drawn. Results from this diagnosis-based analysis are shown by SOC in Table 24.

**Table 24: Serious Adverse Events, 52 week Treatment Period, >1% in any arm, Overall population, Grouped by ILD diagnosis**

SOC*	Underlying Diagnosis^															
	CHP		RA-ILD		uIIP		iNSIP		Other		Exposure ILD		SScILD		Sarcoid	
Treatment	Pbo (N=89)	Nint (N=84)	Pbo (N=47)	Nint (N=42)	Pbo (N=50)	Nint (N=64)	Pbo (N=61)	Nint (N=64)	Pbo (N=30)	Nint (N=23)	Pbo (N=18)	Nint (N=21)	Pbo (N=16)	Nint (N=23)	Pbo (N=8)	Nint (N=4)
Any SAE	34 (38)	29 (35)	18 (38)	20 (48)	17 (34)	25 (39)	17 (28)	14 (22)	12 (40)	10 (43)	5 (28)	5 (24)	3 (19)	3 (13)	3 (38)	0
Respiratory	17 (19)	13 (15)	11 (23)	3 (7)	11 (22)	14 (22)	11 (18)	7 (11)	9 (30)	5 (22)	2 (11)	2 (10)	2 (13)	0	1 (13)	0
Infections	9 (10)	8 (10)	6 (13)	7 (17)	1 (2)	5 (8)	7 (11)	4 (6)	4 (13)	2 (9)	0	1 (5)	0	2 (9)	0	0
Hepatobiliary	2 (2)	1 (1)	0	1 (2)	0	5 (8)	1 (2)	3 (5)	0	1 (4)	0	0	0	0	0	0
Cardiac	8 (9)	2 (2)	2 (4)	4 (10)	2 (4)	2 (3)	0	3 (5)	2 (7)	0	1 (6)	0	0	1	0	0
GI	2 (2)	2 (2)	0	2 (5)	1 (2)	4 (6)	0	1 (2)	0	1 (4)	1 (6)	0	0	0	0	0
Injury	1 (1)	3 (4)	0	2 (5)	2 (4)	0	0	0	1 (3)	0	1 (6)	0	0	0	0	0

Abbreviations: *ILD – interstitial lung disease; RA – rheumatoid arthritis; uIIP – unclassifiable idiopathic interstitial pneumonitis; iNSIP – idiopathic non-specific interstitial pneumonitis; CHP – chronic hypersensitivity pneumonitis; SScILD – systemic sclerosis ILD*

\*SOCs where subgroup by ILD diagnosis did not have at least >2 patients in any arm are not shown. Respiratory refers to the Respiratory, thoracic, and mediastinal disorders SOC; Infections refers to the Infections and Infestations SOC; Hepatobiliary refers to the Hepatobiliary disorders SOC; Cardiac refers to the Cardiac disorders SOC; GI refers to the Gastrointestinal disorders SOC; Injury refers to the Injury, poisoning and procedural complications SOC

^results of mixed connective tissue disease as an underlying diagnosis not shown; one nintedanib patient in the Injury, poisoning and procedural complications SOC and one placebo patient in the Musculoskeletal and connective tissue disorders SOC were noted.

Source: Study 247 CSR Table 12.1.2.7:5; reviewer verified

Overall, only limited conclusions can be drawn due to the small sample sizes within the subgroups. With that said, SAEs did not appear grossly imbalanced when separated by underlying diagnoses. In the majority of diagnoses, there were equal or more placebo patients than nintedanib with SAEs. Exceptions to this were RA-ILD (20 nintedanib patients [48%] vs. 18 placebo [38%]) and uIIP (25 nintedanib patients [39%] vs. 17 placebo [34%]). There was no clear pattern; however, hepatobiliary and GI AEs account for a sizeable portion of the differences. This is understandable as the uIIP subpopulation had a disproportionately larger percent of Asians known to be at risk for elevated liver enzymes and drug-induced liver injury (product label section 5.2). Moreover, hepatobiliary and GI events are known safety concerns with nintedanib and are included in labeling. Within the RTM SOC, nintedanib use across almost all ILD diagnoses was generally associated with slightly lower SAEs. This SAE analysis done by underlying diagnosis does not reveal a clear ILD diagnosis-related safety concern.

In regard to the whole trial (parts A + B), patterns of SAEs were generally similar as compared to the 52 week treatment period. As expected with the longer treatment and study duration, there were more patients with SAEs during the whole trial than in just the 52 week period. Similar to the 52 week period, respiratory SAEs were the most common during the whole trial period among which ILD and respiratory failure were the most common PTs.

In summary for the SAEs, treatment arms were fairly balanced with slightly higher respiratory SAEs in placebo-treated patients. The SAEs noted are consistent with the known safety profile of nintedanib, and no new safety concerns are raised.

### **Dropouts and/or Discontinuations Due to Adverse Effects**

Because nintedanib treatment allows dose interruptions and dose reductions (to 100mg twice daily from 150mg twice daily) and because these strategies are commonly employed in clinical practice for treating IPF patients (Hughes et al. 2016), this section focuses on AE leading to permanent treatment discontinuation only as AEs of greater import. AEs leading to temporary dose interruptions are not discussed.

Overall, there were more nintedanib patients discontinuing treatment permanently than placebo patients, and this was primarily related to gastrointestinal [GI] AEs (especially diarrhea). These data are summarized in Table 25.

**Table 25: Adverse Events leading to Treatment Discontinuation, 52 week Treatment Period, >1% in any arm, Overall Population**

PT/SOC	Placebo (N=331)	Nintedanib (N=332)
Patients with any AE leading to premature treatment discontinuation	34 (10)	65 (20)
<b>Gastrointestinal disorders</b>	<b>2 (1)</b>	<b>23 (7)</b>
Diarrhea	1 (<1)	19 (6)
<b>Hepatobiliary disorders</b>	<b>1 (&lt;1)</b>	<b>10 (3)</b>
Drug-induced liver injury	0	4 (1)
<b>Investigations</b>	<b>3 (1)</b>	<b>9 (3)</b>
Liver enzymes increased*	2 (1)	10 (3)
<b>Respiratory, thoracic, and mediastinal disorders</b>	<b>18 (5)</b>	<b>9 (3)</b>
Interstitial lung disease	10 (3)	2 (1)
*combines "AST increased" and "ALT increased"		

Source: Study 247 CSR Tables 12.1.2.4:1, p.263; reviewer verified

AEs occurring in the GI, hepatobiliary, and Investigations SOC accounted for approximately 65% of AEs leading to permanent drug discontinuation in the nintedanib arm (42 of 65 patients), with more nintedanib patients in each PT within those SOCs. The reverse was noted in the RTM SOC AEs such as interstitial lung disease (exacerbation) [3% placebo vs. 1% nintedanib] as well as dyspnea and respiratory distress (each with 1% placebo vs. 0.3% nintedanib). The ILD exacerbation treatment arm differences are consistent with efficacy results showing less exacerbations in nintedanib treated patients.

Similar patterns of AEs leading to discontinuations were seen in the UIP and HRCT Other subpopulations.

Analysis of AEs leading to permanent dose reductions were generally consistent with the analysis of AEs leading to permanent treatment discontinuation, though more pronounced in regard to treatment arm differences (33% of nintedanib patients had an AE leading to permanent dose reduction vs. 4% of placebo, of which diarrhea accounted for nearly half of all nintedanib patient permanent dose reductions).

In summary, AEs leading to permanent treatment discontinuation or dose reduction were generally more common in nintedanib patients compared to placebo. The AEs were primarily GI and hepatobiliary in nature. These AEs leading to permanent treatment discontinuations are consistent with the known safety profile of nintedanib, and no new safety concerns are raised.

### Treatment Emergent Adverse Events

Almost all patients experienced treatment emergent AEs, with more nintedanib patients experiencing AEs than placebo patients. As expected based on the known safety profile of nintedanib, the most common AEs were gastrointestinal and liver enzyme related. TEAE results are summarized in Table 26. Given the patient population, respiratory system based complaints were common, however, were more frequent in placebo patients (not shown in Table below).

**Table 26: All Treatment Emergent Adverse Events, 52 week Treatment Period, Nintedanib > Placebo for PT and incidence >5% in any arm, Overall population**

PT/SOC	Placebo (N=331)	Nintedanib (N=332)
<b>Patients with any AE</b>	<b>296 (89)</b>	<b>317 (96)</b>
<b>Gastrointestinal disorders</b>	<b>149 (45)</b>	<b>268 (81)</b>
Diarrhea	79 (24)	222 (67)
Nausea	31 (9)	96 (29)
Vomiting	17 (5)	61 (18)
Abdominal pain*	21 (6)	72 (22)
<b>Infections and Infestations</b>	<b>185 (56)</b>	<b>177 (53)</b>
Nasopharyngitis	40 (12)	44 (13)
Upper respiratory tract infection	19 (6)	24 (7)
Urinary tract infection	13 (4)	20 (6)
<b>Investigations</b>	<b>56 (17)</b>	<b>114 (34)</b>
ALT increased	12 (4)	43 (13)
Weight decreased	11 (3)	41 (12)
AST increased	12 (4)	38 (11)
GGT increased	7 (2)	19 (6)
<b>General disorders and administration site conditions</b>	<b>85 (26)</b>	<b>86 (26)</b>
Fatigue	20 (6)	33 (10)
<b>Musculoskeletal and connective tissue disorders</b>	<b>87 (26)</b>	<b>77 (23)</b>
Back pain	16 (5)	19 (6)
<b>Metabolism and nutrition disorders</b>	<b>38 (12)</b>	<b>69 (21)</b>
Decreased appetite	17 (5)	48 (15)
<b>Nervous system disorders</b>	<b>54 (16)</b>	<b>69 (21)</b>
Headache	23 (7)	35 (11)
<b>Hepatobiliary disorders</b>	<b>10 (3)</b>	<b>38 (11)</b>
Hepatic function abnormal	3 (1)	19 (6)
* "Abdominal pain" combines "abdominal pain", "abdominal pain lower", "abdominal discomfort", and "abdominal pain upper"		

*Source: Study 247 CSR Table 12.1.2.1:1, p.255; reviewer verified (ADAE, TRTFL, ONT52FL)*

Consistent with the known safety profile of nintedanib, gastrointestinal and hepatobiliary AEs included under the Gastrointestinal, Investigations, Metabolism and nutrition, and Hepatobiliary SOCs combined account for the vast majority of AEs and were much more frequent in nintedanib treated patients. Of these AEs, diarrhea and nausea were the most common (67% and 29%, respectively). A separate analysis of hepatobiliary and GI AEs is discussed in section 8.2.5.

Generally, the AEs noted in the PF-ILD development program were consistent with the known safety profile as determined by the pivotal studies in the IPF and SScILD development programs (current label section 6.1). Diarrhea and nausea were the two most common AEs in IPF and SScILD patients (62% and 24% of nintedanib patients in the IPF pivotal studies; 76% and 32% of nintedanib patients in the SScILD pivotal study). The IPF and SScILD patients taking nintedanib also experienced liver enzyme elevations, weight and appetite decreases, and headaches at frequencies similar to those seen in the PF-ILD population.

The most common TEAEs in the UIP and HRCT Other subpopulations were generally consistent with the overall population. The most common TEAEs in the UIP and HRCT Other subpopulations in patients taking nintedanib, consistent with the overall population, in order of frequency were diarrhea, nausea, and vomiting.

To summarize, the observed common TEAEs were generally consistent with the known safety profile of nintedanib as seen in the IPF and SScILD clinical trials.

### **Laboratory Findings**

Clinical laboratory tests included complete blood counts, basic metabolic panels, electrolytes, coagulation measurements, and urinalyses. All analyses reflect results from a central laboratory rather than any local laboratories.

The Applicant's determination of possible clinically significant abnormalities (PCSA) was reviewed (Listing 1.1, Appendix 16.2.8) and felt to be reasonable. While certain values may differ from "standard" definitions (e.g. Applicant's determination of clinically significant eosinophilia defined as >1000/microliter vs. conventional definition of eosinophilia of 500/microliter [without determination of clinical significance]), generally the criterion were reasonable.

There were minor differences between treatment arms in regard to PCSAs for hematology parameters (hemoglobin, hematocrit, MCV, platelets, RBC, WBC, eosinophils, neutrophils). There were slightly more nintedanib patients than placebo with an elevated MCV (4% vs. 1%). Given the lack of differences in hemoglobin or hematocrit (and no differences in frequencies of the AE "anemia"), the significance of this finding in isolation is unclear. There were slightly

more nintedanib patients than placebo with elevated eosinophils [absolute and %]. This is likely due to the majority of nintedanib (and placebo) patients with eosinophilia having underlying conditions associated with potentially increased levels of eosinophils (such as seasonal allergies, allergic rhinitis, eczema, asthma, rheumatoid arthritis, Sjogren's syndrome, hypersensitivity pneumonitis). Also, eosinophilia was a criteria for hepatic injury when accompanied by elevated liver enzymes. Reassuringly, the majority of nintedanib patients with eosinophilia did not have concomitant liver enzyme elevations, suggesting that hepatic injury was not the main cause of eosinophilia seen in nintedanib treated patients. Hepatic injury is further explored in section 8.2.5.

For coagulation parameters, there were no noticeable treatment arm differences.

Cardiac biomarkers, serum electrolytes, renal function, and urinalyses were reviewed and no striking differences between treatment arms was noted. Although there were slightly more nintedanib than placebo patients having PCSAs for potassium, phosphate, and creatinine, the frequencies and differences were low, and likely related to nintedanib's known risk of causing diarrhea (hypophosphatemia: 10% nintedanib vs. 8% placebo; hypokalemia: 1% nintedanib vs. <1% placebo; elevated creatinine: 3% nintedanib vs. 1% placebo).

Shift table analyses from the Applicant in regard to hematology, coagulation, cardiac biomarkers, metabolic panels, and urinalyses were reviewed. These did not reveal any new safety concerns.

Overall, there were no new safety concerns raised in reviewing clinical laboratory findings.

### **Vital Signs**

The Applicant performed analyses for vital signs of SBP, DBP, and pulse using thresholds for "marked changes" defined as SBP>150 and increase >25 mmHg above baseline, DBP >90 and increase >10 mmHg above baseline, or pulse > 100 and increased >10 bpm above baseline.

While there were more nintedanib patients with increases in systolic and diastolic blood pressure using these thresholds (SBP: 12% vs. 8%, DBP: 21% vs.14%), the clinical significance of this is unclear. This clinical reviewer performed a focused AE analysis (Vascular disorders SOC, PT "hypertension" and "white coat hypertension") which showed slightly more nintedanib patients than placebo with "hypertension" (nintedanib 14 patients (4%) vs. placebo 11 patients (3%)). Another analysis looking for more severe repercussions from persistently elevated blood pressure (PTs "hypertensive crisis", "hypertensive heart disease", or "congestive heart failure") did not reveal any safety concerns. Hypertension was noted in the IPF development studies to be slightly more common in nintedanib patients (5% nintedanib vs. 4% placebo, product label section 6). Overall, these findings do not change the known safety profile.

In regard to pulse, there were no meaningful differences by the thresholds described above for

“marked changes”.

Body weight decreases were more common in nintedanib treated patients than placebo using a threshold of 10% decrease (15% nintedanib vs. 9% placebo). This was similar to the differences in proportions of patients with the AE “weight decreased” in study 247 (12% nintedanib vs. 3% placebo, Table 26), and similar to findings in the IPF and SSc-ILD development programs (IPF: 10% nintedanib vs. 3% placebo; SSc-ILD: 12% nintedanib vs. 4% placebo; product label, section 6). These findings do not change the known safety profile .

Overall, while there are a higher proportion of nintedanib treated patients with elevated blood pressures and decrease in body weight, these observations do not raise new concerns as they are labeled AEs.

### **Electrocardiograms (ECGs)**

There are no ECG or QT studies as part of this supplement.

ECG sub studies and QT/QTc studies performed as part of nintedanib’s IPF development program were reviewed by Dr. Miya Paterniti in her clinical review dated September 3, 2014.

### **Immunogenicity**

Not applicable as nintedanib is a small molecule.

#### **8.2.5. Analysis of Submission-Specific Safety Issues**

Based on nintedanib’s known safety profile (the current label), the following adverse event categories are discussed in this section:

1. Hepatobiliary Events (including elevated liver enzymes and drug-induced liver injury (DILI))
2. Gastrointestinal and Metabolic AEs (including diarrhea, nausea, vomiting, perforations, weight and appetite decreases)
3. Pneumonia

Additionally, major adverse cardiovascular events were also explored as a focused safety topic and presented in this section.

### *Hepatobiliary Events*

Liver enzyme elevations as assessed in this section, are based on fold increase as compared to the upper limit of normal (ULN) (e.g. > 3x ULN or > 5x ULN), and based on central laboratory measurements.

There were more nintedanib than placebo patients with maximum ALT and/or AST >3xULN, >5xULN, and >8xULN (13% vs. 2%, 3% vs. <1%, 1% vs. <1%, respectively). Similarly, there were more nintedanib than placebo patients with maximum alkaline phosphatase (ALKP) >1.5xULN and >2x ULN (5% vs. 2%, 2% vs. 1%, respectively), however, this was not true for bilirubin or INR. These elevations occurred in the first 30 days of treatment for most nintedanib patients (25 of 43 patients).

Hepatic injury was defined by combining liver enzyme elevations with other laboratory tests or clinical findings as any of the following:

- ALT and/or AST  $\geq$  8x ULN
- ALT and/or AST  $\geq$  3x ULN and total bilirubin  $\geq$  2x ULN
- ALT and/or AST  $\geq$  3x ULN and unexplained INR > 1.5
- ALT and/or AST  $\geq$  3x ULN and unexplained eosinophilia (>5%)
- ALT and/or AST  $\geq$  3x ULN and symptoms (fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever and/or rash)

There were more nintedanib patients than placebo with on-treatment hepatic injury (liver elevations with eosinophilia: 4% vs. 0; liver elevations with symptoms: 7% vs. 0; ALT and/or AST  $\geq$  8x ULN: 1% vs. <1%, other categories had no nintedanib patients). Reassuringly, in all nintedanib patients, hepatic injury was reversible following dose reduction, treatment interruption, or treatment discontinuation. In regard to hepatic injury with accompanying eosinophilia, of the 12 nintedanib patients (4%), all were female age 60 years or older, and 6 patients were Asian with a low body weight (<65kg). These factors are labeled risks for hepatic injury with nintedanib use (section 5.2 product label). In regard to hepatic injury with accompanying symptoms, of the 23 nintedanib patients (7%), many had symptoms that had been ongoing and predated the liver enzyme elevation. Also, symptoms used to define hepatic injury in the protocol overlap with common GI symptoms known to occur with nintedanib use (nausea, vomiting).

Potential Hy's law cases occurred in two patients, one in each treatment arm. The placebo patient (patient (b) (6)) is not discussed further. The nintedanib patient (patient (b) (6)) identified as a potential Hy's law case had had diarrhea requiring dose reduction to 100mg. Liver enzymes rose to >3x ULN (local laboratory, not central laboratory) and bilirubin to >2xULN on day 57 of treatment. Study treatment was terminated, and all values recovered to normal within 28 days. This event was considered serious (but was not considered life-threatening or requiring hospitalization), and considered by investigator as related to study

drug. No other reasons for these liver enzyme elevations were noted in the narrative provided.

Demographic subgroup analyses (of gender, race, age, body weight) were performed in patients having liver enzyme elevations  $\geq 3x$  ULN. Patients who had a higher frequency of elevations were female, Asian, and with low body weight, with no difference noted by age. These findings are generally in line with labeled warnings and precautions. In regard to subgroup analysis of patients with liver enzyme elevations by ILD diagnosis, the frequencies of liver enzyme elevations were highest in uIIP (20%), followed by autoimmune ILDs (15%), iNSIP (14%), other ILDs (8%), and CHP (7%). This is likely due to the uIIP category having disproportionately more Asians (40%) and low body weight patients (36%), and CHP having disproportionately less Asians (11%) and low body weight patients (13%). Overall, these subgroup analyses should be interpreted with caution due to the small sample sizes.

Turning towards reported AEs, there were more nintedanib patients than placebo with hepatobiliary AEs. This reviewer used a JMP analysis where MedDRA high level group terms “hepatic and hepatobiliary disorders” and “hepatobiliary investigations” were combined to capture relevant AEs (using SOC level data was either incomplete or too broad). These results are summarized in Table 27.

**Table 27: Hepatobiliary AEs and SAEs, Overall Population, 52 week Treatment Period, >1 patient any arm**

Preferred Term	Placebo (N=331)	Nintedanib (N=332)
<b>Patients with any Hepatobiliary AE*</b>	<b>24 (8)</b>	<b>91 (27)</b>
ALT increased	12 (4)	43 (13)
AST increased	12 (4)	38 (11)
GGT increased	7 (2)	19 (6)
Hepatic function abnormal	3 (1)	19 (6)
Liver function test increased	1 (<1)	6 (2)
Drug-induced liver injury	0	6 (2)
Liver injury	2 (1)	4 (1)
Transaminases increased	0	4 (1)
Hepatic enzyme increased	1 (<1)	2 (1)
Liver disorder	0	3 (1)
<b>Patients with any Hepatobiliary SAE**</b>	<b>5 (2)</b>	<b>14 (4)</b>
Drug-induced liver injury	0	6 (2)
Liver injury	2 (1)	3 (1)
ALT increased	1 (<1)	2 (1)
AST increased	1 (<1)	2 (1)
*High level group terms combined (“hepatobiliary investigations”, “hepatic and hepatobiliary disorders”) **<2 patients in any treatment arm not shown (hepatic steatosis, hepatocellular injury, blood bilirubin increased, cholestasis, gallbladder adenocarcinoma, hepatic cancer, hepatic cirrhosis, hepatic cyst, hepatobiliary disease, hyperbilirubinemia, hypertransaminasemia, nonalcoholic fatty liver disease) ***not shown one patient each (nintedanib: transaminases increased, hepatic enzyme increased, hepatic cancer, hepatic cirrhosis; placebo: GGT increased, hepatic enzyme increased, gallbladder adenocarcinoma)		

Source: medical reviewer generated

The vast majority of these hepatobiliary AEs were related to liver function test abnormalities, discussed at the beginning of this section. The most frequent SAE was drug-induced liver injury. Both of these are labeled warnings and precautions.

There was one fatal SAE in a placebo patient (patient (b) (6), hepatic cirrhosis). There were no hepatobiliary SAEs leading to death in the nintedanib arm. Most SAEs recovered with the following exceptions: one placebo death (noted above) and one nintedanib patient described next. Patient (b) (6) had a non-fatal SAE hepatic cirrhosis noted as “not recovered”. However, this was felt by the investigator to be related to his chronic hepatitis B at baseline. Additionally, he also developed hepatic cancer which was not felt related to nintedanib use by the investigator.

The frequencies of these hepatobiliary AEs were generally similar to the labeled frequencies noted for IPF and SSc-ILD.

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Overall, more nintedanib treated patients than placebo had hepatobiliary AEs of which liver enzyme elevations account for the vast majority. The findings discussed in this section are in line with the known safety profile of nintedanib.

#### *Gastrointestinal and Metabolic AEs*

As noted previously, more nintedanib patients than placebo had gastrointestinal (GI) AEs. The majority of GI AEs were related to diarrhea, nausea, vomiting, and abdominal pain. This is summarized along with other GI and metabolic AEs in Table 28.

**Table 28: Gastrointestinal AEs and SAEs, Overall Population, 52 week Treatment Period, >1% in any arm**

Preferred Term	Placebo (N=331)	Nintedanib (N=332)
<b>Patients with any Gastrointestinal AE</b>	<b>149 (45)</b>	<b>268 (81)</b>
Diarrhea	79 (24)	222 (67)
Nausea	31 (9)	96 (29)
Vomiting	17 (5)	61 (18)
Abdominal pain*	16 (5)	60 (18)
Abdominal distension	6 (2)	10
Constipation	25	23
Dyspepsia	12	13
GERD	6 (2)	13
Dry mouth	2	8
Hemorrhoids	3	6 (2)
Flatulence	2	6 (2)
Stomatitis	2	5 (2)
<b>Patients with any Metabolic AEs**</b>	<b>25 (8)</b>	<b>69 (21)</b>
Weight decreased^	11 (3)	43 (13)
Decreased appetite	17 (5)	48 (15)
<b>Patients with any Gastrointestinal SAEs^^</b>	<b>4 (1)</b>	<b>10 (3)</b>
<b>Patients with any Metabolic SAEs^^^</b>	<b>1</b>	<b>0</b>
*combines the following PTs: abdominal pain, abdominal pain lower, abdominal pain upper, abdominal rebound tenderness, abdominal rigidity, abdominal tenderness, gastrointestinal pain, infantile colic, esophageal pain **Patients with any Metabolic AEs determined using only PTs “weight decreased” and “decreased appetite” ^includes PTs “weight decreased” and “abnormal loss of weight” ^^only PTs “gastrointestinal hemorrhage” and “ileus” had >1 patient (3 nintedanib vs. 0 placebo and 0 nintedanib vs. 3 placebo, respectively). ^^one placebo SAE PT “Malnutrition”		

Source: reviewer generated (ADAE, AESER, TRTFL, ONTFL52, AEDECOD, AEBODSYS, TRT01P)

While GI AEs were common, SAEs were much less frequent. No clear pattern of GI SAEs was present to account for the slightly higher frequency in nintedanib patients. In regard to metabolic AEs, there were more nintedanib patients with weight and appetite decreases as expected based on the known safety profile, however, this too did not result in frequent nintedanib patient metabolic SAEs.

Comparing GI and metabolic AEs from study 247 to the labeled frequencies from the IPF and SSc-ILD programs does not reveal any noticeable differences. The frequencies of GI AEs were fairly similar to the labeled frequencies in IPF and SScILD (e.g. diarrhea occurred in 62% and

76% of nintedanib treated patients in IPF and SSc-ILD, respectively). And, the frequency of “weight decreased” as noted in the table above was generally similar to that seen in the IPF and SSc-ILD development programs (weight decreased in 10% and 12% of nintedanib treated patients in IPF and SSc-ILD, respectively).

In regard to gastrointestinal perforation, the Applicant’s SMQ Narrow PTs were reviewed and felt to be reasonably comprehensive (Applicant’s submission, Appendix 16.2.7 Listing 3.1), and included but were not limited to gastrointestinal ulcers, perforations, fistulas, and abscesses. Using this SMQ, one patient in each arm was identified and thus, no significant safety concerns for GI perforation were raised. This is currently a labeled warning (product label, section 5.7).

In summarizing this focused section on GI and metabolic AEs, findings from study 247 do not reveal any new safety concerns.

### *Pneumonia*

“Pneumonia” is discussed as some concerns were raised in review of the most recent development program, SSc-ILD.

Pneumonia had been a concern in the SScILD development program (study 214 SAE pneumonia: 2.8% nintedanib vs. 0.3% placebo), however, this was not clearly seen in the overall population of study 247 (4% nintedanib vs. 3% placebo) albeit recognizing different study populations. Also, this concern was not present in the IPF development program.

A reviewer analysis using JMP with a broader group of PTs (pneumonia, pneumonia bacterial, pneumonia viral, lower respiratory tract infection, and atypical pneumonia) was performed to further explore whether concerns for an increased frequency of pneumonia was present in study 247 (Table 29). This group of PTs will be referred to as “pneumonia AEs” in this section.

**Table 29: Pneumonia AEs and SAEs, 52 week Treatment Period, Overall Population**

Preferred Term	Placebo (N=331)	Nintedanib (N=332)
<b>Patients with any pneumonia AEs*</b>	<b>29 (9)</b>	<b>26 (8)</b>
Pneumonia	20 (6)	19 (6)
Lower respiratory tract infection	7 (2)	5 (2)
Pneumonia bacterial	3 (1)	2 (1)
Atypical pneumonia	0	2 (1)
Pneumonia viral	1 (<1)	0
<b>Patients with any pneumonia SAEs*</b>	<b>15 (5)</b>	<b>14 (4)</b>
Pneumonia	11 (3)	12 (4)
Lower respiratory tract infection	2 (1)	1 (<1)
Pneumonia bacterial	2 (1)	1 (<1)
Atypical pneumonia	0	1 (<1)
Pneumonia viral	1 (<1)	0
*includes PTs of pneumonia, pneumonia bacterial, pneumonia viral, lower respiratory tract infection, and atypical pneumonia. PTs felt to be ambiguous and not included: atypical mycobacterial infection, fungal infection, haemophilus infection, infectious pleural effusion, influenza, metapneumovirus infection, respiratory tract infection, respiratory tract infection viral, sputum purulent, staphylococcal infection, lung infection		

Source: reviewer generated (ADAE, TRTFL, ONT52FL, TRT01P, AEDECOD)

There was no noticeable imbalance between arms for pneumonia AEs. Using the same grouping of PTs, no imbalance between treatment arms was noted for pneumonia SAEs. The frequencies noted in the table above were relatively similar to those seen in the SSc-ILD program (in nintedanib treated patients: 3% study 214 vs. 4% study 247).

In considering pneumonia SAEs in subpopulations, there were more placebo than nintedanib patients with serious pneumonias in the UIP subpopulation (4% placebo vs. 2% nintedanib) with the reverse present in the HRCT Other subpopulation (1% placebo vs. 2% nintedanib). It is difficult to draw conclusions as these are relatively infrequent events.

Overall, there does not appear to be a clear safety concern in regard to a pneumonia imbalance between treatment arms in study 247.

*Major adverse cardiovascular events (MACE)*

The Applicant conducted a MACE analysis. An event was considered by the Applicant to be a MACE based on the following:

1. AEs related to myocardial infarction (MI),
2. AEs related to stroke, or
3. AEs leading to death due to cardiac or vascular cause

In addition, an adjudicated analysis of MACE was also performed by an adjudication committee (AC). MACE adjudication by the AC classified events as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke.

The frequency of MACE overall was relatively low and similar between treatment arms for both adjudicated (2% each arm) and non-adjudicated (3% placebo vs. 4% nintedanib) events. Specifically, non-fatal myocardial infarction (MI) and strokes were similar between arms for both adjudicated (MI: placebo <1% vs. nintedanib 1%; stroke: placebo 1% vs. nintedanib <1%) and non-adjudicated (MI: placebo 2% vs. nintedanib 3%; stroke: placebo 1% vs. nintedanib <1%). As noted in Table 22, deaths were adjudicated by the AC as either respiratory, cardiovascular, other, or undetermined. In regard to the cardiovascular deaths, the treatment arms were balanced (adjudicated fatal MACE 1% each arm).

Overall, review of MACE results does not raise new safety concerns.

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

None

#### **8.2.7. Safety Analyses by Demographic Subgroups**

Subgroup safety analyses by gender, age, and race are discussed in this section.

In regard to gender related safety differences, nausea and vomiting were slightly more frequent in females (nausea: nintedanib 38% vs. placebo 12%; vomiting: nintedanib 10% vs. placebo 5%) than males (nausea: nintedanib 21% vs. placebo 7%; vomiting: nintedanib 10% vs. placebo 5%) with no noticeable differences in diarrhea. Hepatobiliary AEs (including liver enzyme elevations) were more common in females taking nintedanib than in males taking nintedanib, consistent with current labeling.

In regard to age-related safety differences, older patients ( $\geq 65$  years) had more non-fatal SAEs than younger patients ( $<65$  years), but no noticeable differences between treatment arms ( $\geq 65$  years: nintedanib 38% vs. placebo 38%;  $<65$  years: nintedanib 25% vs. placebo 26%), and no concerning differences in SAEs resulting in death. Older patients taking nintedanib also had more AEs leading to study drug discontinuation ( $\geq 65$  years: nintedanib 24% vs. placebo 11%;  $<65$  years: nintedanib 13% vs. placebo 9%), mostly related to diarrhea.

In regard to race-related safety differences, this discussion only includes results on Asians and Whites as other races were low in number precluding accurate comments being made. Unsurprisingly, hepatobiliary AEs (including liver enzyme elevations) were more common in Asians taking nintedanib than in Whites taking nintedanib (labeled warning). There were no

concerning differences by race in deaths, SAEs, or AEs leading to drug discontinuation. While there were less SAEs leading to death among Asians taking nintedanib than placebo (nintedanib 0 vs. placebo 5), the small number of events makes this of unclear significance.

Subgroup safety analyses by ILD diagnoses were conducted for deaths and SAEs, and are discussed in section 8.2.4.

#### 8.2.8. **Specific Safety Studies/Clinical Trials**

None

#### 8.2.9. **Additional Safety Explorations**

##### **Human Carcinogenicity or Tumor Development**

No human carcinogenicity studies were conducted as part of this submission. See Dr. Miya Paterniti's clinical review dated September 3, 2014 for details (section 7.6.1).

##### **Human Reproduction and Pregnancy**

No human reproduction and pregnancy studies were conducted as part of this submission. See Dr. Miya Paterniti's clinical review dated September 3, 2014 for details (section 7.6.2).

##### **Pediatrics and Assessment of Effects on Growth**

No pediatric data or assessments of effects on growth were obtained as part of this submission. A PREA PMR will be required.

##### **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

No overdose, drug abuse potential, withdrawal, or rebound data is noted in study 247. In nintedanib's IPF development program, in study 1199.34 one patient was exposed to a dose of 600mg daily for 21 days, with no SAEs. See Dr. Miya Paterniti's clinical review dated September 3, 2014 for details (section 7.6.4).

#### 8.2.10. **Safety in the Postmarket Setting**

##### **Safety Concerns Identified Through Postmarket Experience**

The current nintedanib label notes the following adverse reactions identified in the postapproval (postmarketing) period: drug-induced liver injury, non-serious and serious bleeding events, some of which were fatal, pancreatitis, thrombocytopenia, rash, pruritus.

Of these, drug-induced liver injury is present in section 5.2 of the current label and discussed in section 8.2.5 of this review. The other listed adverse reactions were not serious and present at

frequencies < 5% in study 247 (thrombocytopenia: 2 placebo patients vs. 1 nintedanib patient; pancreatitis: 0 placebo vs. 2 nintedanib patients).

### **Expectations on Safety in the Postmarket Setting**

Post approval nintedanib is likely to be used in a broader population than study 247, one that includes patients with less rapidly progressive disease or in patients that may not have failed immunosuppressive therapy. This may result in observations not seen in clinical trials. However, this can be monitored for with standard postmarketing safety monitoring.

#### **8.2.11. Integrated Assessment of Safety**

The safety data submitted by the Applicant for analysis with this sNDA was sufficient for review. The data is derived from study 247 which was a placebo-controlled 2-part trial (part A fixed 52 weeks treatment period, part B variable duration) The total safety database from this study in addition to the known safety profile from nintedanib's prior development programs in IPF and SScILD, is adequate.

Overall, the safety assessment, which included an evaluation of deaths, SAEs, TEAEs, AEs leading to drug discontinuation, laboratory findings, and vital signs, was consistent with the known safety profile of nintedanib. No new safety signals were revealed. Deaths did not raise new safety concerns. SAEs were generally balanced between control and nintedanib arms. For TEAEs, reported events were consistent with nintedanib's known tolerability issues and AE profile in IPF and SScILD. Unsurprisingly, the most common TEAEs were GI and hepatobiliary in origin, and more common in nintedanib patients. Analysis of AE related treatment discontinuations were also in line with prior nintedanib development programs. Laboratory testing and vital sign analyses did not raise new concerns for nintedanib. And, focused AE analyses (hepatobiliary, GI, pneumonia, MACE) did not raise new safety concerns.

Given the heterogeneity of the study population, analyses of subgroups by ILD diagnoses for deaths and SAEs were also performed to ensure no safety concern was present in a particular ILD subset. Additionally, HRCT based subgroup safety results were reviewed. Neither of these revealed any higher risk subpopulations, nor did they reveal new safety concerns.

In conclusion, the safety profile of nintedanib 150 mg oral twice daily in study 247 is consistent with the known safety profile in IPF and SSc-ILD, and is consistent with the safety labeling in the approved package insert.

### **8.3. Statistical Issues**

Study 1199.247 is a study similar in design and analysis with previous nintedanib trials in IPF and SSc-ILD. The robustness of the primary efficacy results is demonstrated through tipping point sensitivity analysis. Supportive analyses with secondary endpoints and exploratory

endpoints were discussed in detail in the main text. There is no statistical issue.

#### **8.4. Conclusions and Recommendations**

Based on the clinical safety and efficacy data submitted, the clinical reviewer recommends a regulatory action of Approval for nintedanib 150mg oral twice daily for the treatment of chronic fibrosing ILDs with a progressive phenotype.

To support this application, the Applicant completed one phase 3 randomized, placebo controlled, 2-part trial (part A fixed 52 weeks treatment period, part B variable duration) efficacy/safety study in patients with chronic progressive fibrosing ILDs with a progressive phenotype. The primary endpoint was rate of decline over 52 weeks in FVC, which has been used as a primary endpoint for other ILD approvals (IPF and SSc-ILD). Secondary endpoints included time-to-first exacerbation and mortality. The study population was a grouping of patients from a variety of ILDs with rapidly progressive disease who had failed conventional treatment.

This study demonstrated a statistically significant improvement in the primary endpoint with support from secondary endpoints (time to first exacerbation and time to death). Specifically, the treatment effect (107 mL, 95% CI: 65 to 149mL; p-value<0.0001) on the primary endpoint (FVC) was similar to or better than that seen in nintedanib's IPF or SSc-ILD programs. Although secondary time-to-event endpoints (exacerbations, death) were not statistically significant, trends were favorable (HR 0.72 [95%CI: 0.38 to 1.37] and HR 0.94 [95%CI: 0.47 to 1.86], respectively). Sensitivity analyses on the primary endpoint, including a tipping point analysis, demonstrated robustness of the study results.

Given the heterogeneity of the study population (grouping of multiple ILDs), demographic and disease-based (by ILD) subgroup analyses were performed which did not reveal noteworthy differences between subgroup treatment responses. Additional analyses excluding select subgroups (SSc-ILD and ILD groups based on likelihood of containing inadvertent IPF patients) also did not reveal noticeable changes in the treatment response. This served to address concerns that a particular ILD subgroup (SSc-ILD or IPF) could have been responsible for the results.

In evaluating the evidence of effectiveness of nintedanib in chronic fibrosing ILDs with a progressive phenotype, the review team considered the totality of the data in the context of nintedanib experience in a distinct but related fibrosing lung disease, IPF, for which nintedanib is approved. The results from study 247 in conjunction with support from nintedanib's previously characterized benefit in IPF patients provided substantial evidence of effectiveness

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With regard to safety, the submitted study was adequate for evaluation and the overall safety results in study 247 were consistent with its known labeled profile. There were no concerning imbalances between treatment arms in regard to deaths or SAEs. Tolerability of nintedanib (mainly due to gastrointestinal and hepatobiliary AEs) in study 247 was similar to nintedanib's known safety profile based on common AEs and AEs leading to treatment discontinuation. ILD diagnosis-based subgroup analyses for deaths or SAEs did not reveal concerning findings. Focused analyses of hepatobiliary, gastrointestinal, and pneumonia-related AEs also did not raise new concerns.

In conclusion, the benefit risk balance for nintedanib in PF-ILD patients from the submitted study supports the recommended action of Approval.

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## **9 Advisory Committee Meeting and Other External Consultations**

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No Advisory committee meeting is planned for this NME. No other external consultations are planned for this NME.

## 10 **Pediatrics**

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Study 247 studied adults only. A pediatric PMR study is being required as part of PREA. See section 13 for details.

## 11 Labeling Recommendations

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### 11.1 Prescription Drug Labeling

Clinical study information in sections 5, 6, and 14 was edited to include results from study 247 and for consistency with the IPF and SSc-ILD portions of the label as applicable.

There were no major changes made by the review team to the Applicant's proposed label safety results in sections 5 and 6. Minor changes included removal of discussion of hypertension as this was not felt to add substantially to the safety information beyond that already present. The Applicant proposed to describe common adverse reactions in text format rather than table format given the similarity to that observed in the IPF program, and this was felt reasonable and consistent with Agency guidance documents.

Edits made to what was proposed by BI in section 14 were as follows:

- Changes to the presentation or discussion of subgroup efficacy results for both HRCT subgroups as well as ILD based subgroups
- Removal of (b) (4) figure
- Changes in the discussion of time-to-event endpoints as components (not composite)
- Removal of (b) (4) discussion

The Applicant proposed in their submitted label to show FVC results in several figures, many of which were consolidated or removed by the review team. Specifically, changes made in presentation of FVC results were as follows: (b) (4)  
(b) (4) a separate HRCT subgroup forest plot was consolidated into an existing table for the primary endpoint; and, a new figure showing FVC results by underlying ILD (e.g., autoimmune, hypersensitivity pneumonitis) was added.

Time-to-first-ILD-exacerbation or death (the Applicant's secondary endpoint) was separated by the review team into its components: time-to-first-ILD-exacerbation and time-to-death (survival).

The review team removed (b) (4)  
(b) (4)  
(b) (4)

## **12 Risk Evaluation and Mitigation Strategies (REMS)**

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No REMS are needed for this application.

## **13 Postmarketing Requirements and Commitment**

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This application triggers PREA.

The proposed pediatric PMR study recommendation to the Applicant as of the time of writing of this review is as follows:

“Conduct a randomized double-blind placebo-controlled trial of  $\geq 24$  weeks in pediatric patients ages 6 to less than 18 years with fibrosing interstitial lung disease with a progressive phenotype. The objective of this trial will be to characterize the pharmacokinetics and safety in this population, as well as collect efficacy data.”

Final protocol submission: 6/2020

Study completion: 6/2023

Final report submission: 3/2024

Studies in the <6 year old population have been waived for reasons of safety and concerns regarding identifying patients in this age group for whom there would be a favorable risk-benefit profile.

## **14 Division Director (Clinical) Comments**

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Boehringer Ingelheim (BI), submitted supplement 13 to NDA 205832 seeking approval for nintedanib for the treatment of chronic fibrosing interstitial lung disease (ILD) with a progressive phenotype, also known as progressive fibrosing interstitial lung disease (PF-ILD). Nintedanib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs). Nintedanib was approved for the treatment of IPF (2014) and for slowing the rate of decline in pulmonary function in patients with SSc-ILD (2019). The approved dosing regimen is 150 mg twice daily approximately 12 hours apart taken with food. The proposed dosage form and dosing regimen are the same as for the previously approved indications. The current efficacy supplement includes a single phase 3 clinical study in subjects with PF-ILD (Study 1199.247, Study 247).

Study 247 is a phase 3 trial, two-part study (A and B), assessing rate of decline in forced vital capacity (FVC) over 52 weeks. Part A included a 52-week placebo-controlled treatment period. In Part B (variable duration), the study continued to follow all patients in a blinded controlled fashion until the last patient enrolled completed the last visit. Study 247 randomized 663 patients with chronic fibrosing ILDs with a progressive phenotype to receive nintedanib 150 mg twice daily (n=332) or placebo (n=331) for at least 52 weeks. Randomization was stratified based on high resolution computed tomography (HRCT) fibrotic pattern, as assessed by central readers: 412 patients with UIP-like HRCT pattern and 251 patients with other HRCT fibrotic patterns. There were 2 co-primary populations defined for the analyses in this trial: all patients (the overall population) and patients with HRCT with UIP-like HRCT fibrotic pattern. While patients with other (non-UIP) fibrotic patterns on HRCT were not included in the multiple testing procedure, we also examined the efficacy of nintedanib in this subgroup for descriptive purposes. The primary endpoint was the annual rate of decline in FVC (in mL) over 52 weeks. Other important endpoints included time to first acute ILD exacerbation and time to death.

Patients with a clinical diagnosis of a chronic fibrosing ILD were selected if they had relevant fibrosis (greater than 10% fibrotic features) on HRCT and presented with clinical signs of progression (defined as FVC decline  $\geq 10\%$ , FVC decline  $\geq 5\%$  and  $<10\%$  with worsening symptoms or imaging, or worsening symptoms and worsening imaging all in the 24 months prior to screening). Patients were required to have an FVC greater than or equal to 45% of predicted and a DLCO 30% to less than 80% of predicted. Patients were required to have progressed despite management deemed appropriate in clinical practice by investigators for the patient's relevant ILD. Patients with IPF were specifically excluded and our review

confirmed that the study population was a distinct group (based on demographics and baseline characteristics).

The majority of patients were Caucasian (74%) or Asian (25%). Patients were mostly male (54%) and had a mean age of 66 years and a mean FVC percent predicted of 69%, and 49% were never-smokers. The underlying clinical ILD diagnoses in groups represented in the trial were hypersensitivity pneumonitis (26%), autoimmune ILDs (26%), idiopathic nonspecific interstitial pneumonia (19%), unclassifiable idiopathic interstitial pneumonia (17%), and other ILDs (12%) [the three most common “other” ILDs included exposure-related ILD, sarcoidosis, and pleuro-parenchymal fibrosis).

There was a statistically significant reduction in the annual rate of decline in FVC (in mL) over 52 weeks in patients receiving OFEV compared to patients receiving placebo. Results in the subpopulations of patients with HRCT with UIP-like fibrotic pattern and patients with other fibrotic patterns (Other HRCT) are shown in the table (from the package insert) below.

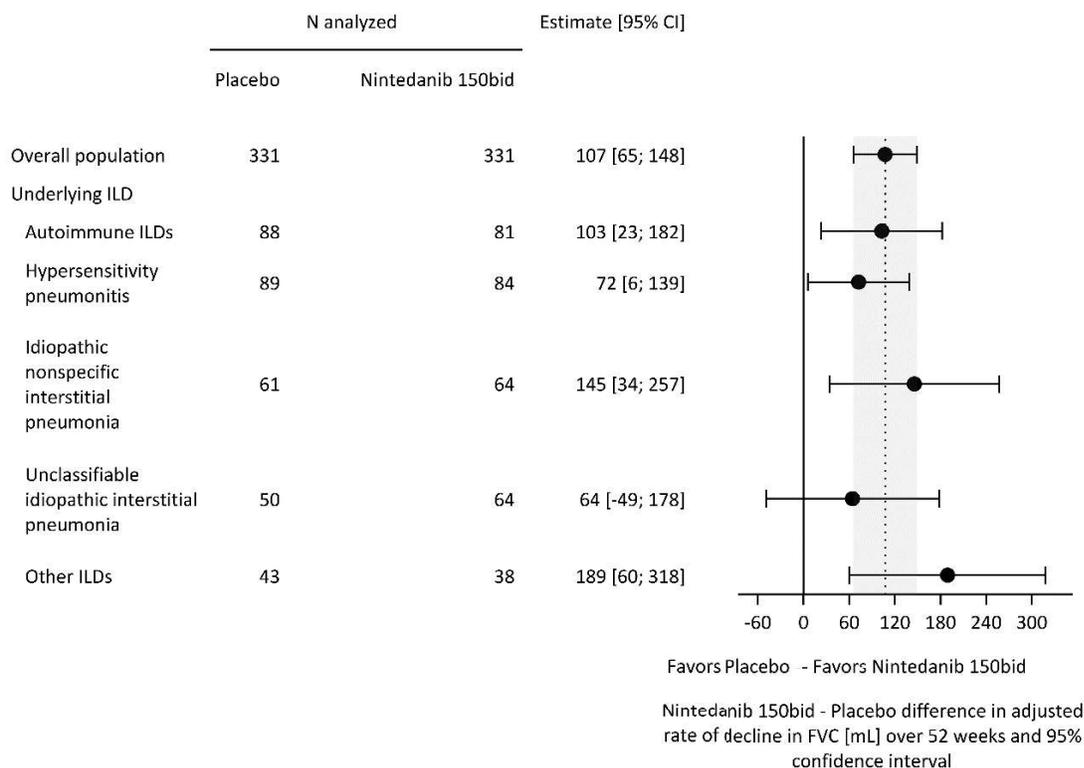
**Annual Rate of Decline in FVC (mL) in Study 247**

	Overall		UIP-like Subpopulation		Other HRCT Subpopulation	
	OFEV	Placebo	OFEV	Placebo	OFEV	Placebo
Number of analyzed patients	331	331	206	206	125	125
Adjusted annual rate of decline over 52 weeks	-81	-188	-83	-211	-79	-154
Comparison vs placebo difference <sup>a</sup>	107		128		75*	
95% CI	(65, 148)		(71, 186)		(16, 135)*	
*Comparison based on the Other HRCT subpopulation was not included in the multiple testing procedure. Values shown here are for descriptive purposes.						

<sup>a</sup>Based on a random coefficient regression model with fixed categorical effects of treatment, HRCT pattern, fixed continuous effects of time, baseline FVC (mL), and including treatment by time and baseline by time interactions

Study 247 enrolled patients who had a previously diagnosed fibrosing interstitial lung disease and who, despite disease management, had clinically significant disease progression. Therefore, it was important to examine the different subgroups by ILD diagnosis. While the number of patients in each subgroup of ILD was small, a post-hoc exploratory analysis by ILD diagnosis demonstrated a consistent FVC response across ILD diagnoses.

**Annual Rate of Decline in FVC (mL) over 52 Weeks based on Underlying ILD Diagnosis in Study 247\***



Source: Section 14, Package Insert, Ofev

ILD = interstitial lung disease; Autoimmune ILDs: includes rheumatoid arthritis-associated ILD, mixed connective tissue disease, systemic sclerosis-associated ILD, and other terms; Other ILDs: includes fibrosing ILDs not categorized under autoimmune ILDs, hypersensitivity pneumonitis, idiopathic nonspecific interstitial pneumonia, or unclassifiable idiopathic interstitial pneumonia. The three most common ILDs in this category are exposure-related ILD, sarcoidosis, and pleuro-parenchymal fibroelastosis. \*These results are from a post-hoc exploratory analysis. Values shown here are for descriptive purposes.

The results regarding exacerbations and survival were not statistically significant but numerically supportive of the primary endpoint.

PF-ILD represents a grouping of fibrotic lung diseases, based on rapid progression, and constitutes a novel indication. We acknowledge that the underlying ILDs that comprise PF-ILD have varying etiologies/triggers; however, for the subset of patients who are rapidly progressive, it is plausible that these heterogeneous diseases may be reduced to a common pathway. We also acknowledge that each of these ILDs is uncommon, and the progressive subset even less common. To study each separately, in individual sufficiently powered trials,

would likely be unfeasible. Therefore, studying them as a group was deemed reasonable. Review of individual subgroups demonstrated similar efficacy across subgroups.

In evaluating the evidence of effectiveness of nintedanib in chronic fibrosing ILDs with a progressive phenotype, we considered the totality of the data in the context of nintedanib experience in a distinct but related fibrosing lung disease, IPF, for which nintedanib is approved. The results from study 247 in conjunction with support from nintedanib's previously characterized benefit in IPF patients provided substantial evidence of effectiveness. No new safety concerns were identified. The regulatory action for this supplemental NDA is *Approval*.

## 15 Appendices

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### 15.1. References

1. Belloli EA et al. Idiopathic non-specific interstitial pneumonia. *Respirology* 2016, 21, pp.259–268
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9. Patel AS et al. The minimal important difference of the King's Brief Interstitial Lung Disease Questionnaire (K-BILD) and forced vital capacity in interstitial lung disease. *Resp Med* 2013, 107(9), pp. 1438-1443.
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11. Sinha A et al. The King's Brief Interstitial Lung Disease (KBILD) questionnaire: an updated minimal clinically important difference. *BMJ Open Res* 2019, 6(1), 000363.
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13. Vasakova M et al. Hypersensitivity Pneumonitis: Perspectives in Diagnosis and Management. *Am J Respir Crit Care Med* 2017, 196(6), pp.680-689
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### 15.2. Financial Disclosure

**Covered Clinical Study (Name and/or Number): Study 1199.247**

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Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>1,052</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>8</u> See below for discussion.		
<p>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)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>1</u></p> <p>Significant payments of other sorts: <u>7</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in S</p> <p>Sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>64</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

From study 1199.247 (the only submitted study), the Applicant certified the absence of financial arrangement for all primary and sub-investigators. There were 8 investigators (or sub-investigators) from 6 sites with significant payments requiring disclosure: (b) (4)

(b) (4) Of these 8 investigators, 7 investigators received compensation greater than \$25,000, related to lectures, education, or research funding. One investigator's spouse is employed by (b) (4) None of the sites for these 8 investigators enrolled more than 5 patients each.

From all investigators and sub-investigators, there were 64 principal investigators (PIs) or sub-investigators (subIs) that did not provide financial disclosure information. Of these 64, 44 were at sites that did not initiate and 8 were investigators or sub-investigators that did not participate in the trial. The remaining 12 were sub-investigators who had not provided a completed FDQ, however, in all twelve cases their PIs had provided completed FDQs. Furthermore, the number of patients randomized from these 12 sub-investigators (8 sites) was generally low ( $\leq 5$  patients each site). The exception was site 1199-247-JPN14 with 18 patients enrolled. A risk analysis based on weighted enrolled efficacy as well as safety (deaths) for this site did not suggest an issue with study conduct.

Given that the study was randomized, double-blinded, double-dummy, active controlled trial, with objective spirometry, exacerbation, and mortality endpoints; and since each investigator was only responsible for enrolling a small number of patients to this large, multi-center trial; it was determined that this financial disclosure information did not significantly affect trial conduct.

### 15.3. Pattern Mixture Modeling Approaches Sensitivity Analyses

To investigate the potential impact of missing data on the treatment effect, the applicant planned a series of pattern mixture modeling approach analyses: 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 30, missing data were imputed (resulting in (b) (4) 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.<sup>1</sup>

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<sup>1</sup> Rubin D. Multiple Imputation for Nonresponse in Surveys, John Wiley & Sons, 1987.

**Table 30. Primary and Sensitivity Analyses for Missing Data Handling (Pattern Mixture Model Approaches)**

Analysis	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	
	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 PF-ILD, 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.
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)		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 3	Based upon the slope (SE) estimates in Placebo patients 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	Rate of decline in all patients with missing week 52 data is similar to rate of decline in all Placebo patients (e.g. treatment effect does not persist after study drug discontinuation)	Multiple imputation of missing 52 week data due to death based on the same 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	Assuming that deaths observed in the study will likely be related to worsening of PF-ILD, 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 with most severe slopes.

Abbreviations: PF-ILD: progressive fibrosing interstitial lung disease; FVC: forced vital capacity; SE: standard error; MAR: missing at random

Source: SAP Table 7.4.2.1.2:1

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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.**

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/s/

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ROBERT H LIM  
03/09/2020 08:24:52 AM

BANU A KARIMI SHAH  
03/09/2020 08:26:37 AM



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Center for Drug Evaluation and Research  
Silver Spring, MD 20993

MEMORANDUM

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

**DATE:** February 21, 2020

**TO:** File for sNDA 205832

**FROM:** Robert Lim, MD

**SUBJECT:** Cross Disciplinary Team Leader (CDTL) review for sNDA 205832 supplement 13

**APPLICATION/DRUG:** sNDA 205832 OFEV (Nintedanib)

Boehringer Ingelheim submitted this supplemental NDA to add the treatment of chronic fibrosing interstitial lung diseases (ILDs) to the indications for nintedanib. Currently, nintedanib is approved for the treatment of idiopathic pulmonary fibrosis (IPF) and systemic sclerosis ILD (SSc-ILD).

In support of this added indication, the Applicant submitted one study (study 1199.247). This study was a randomized, double-blind, placebo-controlled, two part study (part A- 52-week treatment period, part B – variable length) assessing response to nintedanib compared to placebo in patients with chronic fibrosing ILDs with a progressive phenotype. There was a statistically significant reduction in decline of FVC at 52 weeks (primary endpoint) in nintedanib treated patients compared to placebo treated patients. Additional support was provided by favorable trends in secondary time-to-event endpoints (time to first exacerbation, time to death), though 95% confidence interval included null. No new safety concerns were raised beyond the known safety profile of nintedanib from IPF and SSc-ILD.

The CDTL, clinical team, statistical team, and clinical pharmacology team recommends Approval.

My CDTL review is complete and has been added to the Multi-Disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. My review is based on the information currently as noted above. An update will be provided to the review if additional information is added or reviewed.

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MEMORANDUM

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

**DATE:** February 14, 2020

**TO:** File for sNDA 205832

**FROM:** Khalid Puthawala

**SUBJECT:** Clinical review for sNDA 205832 supplement 13

**APPLICATION/DRUG:** sNDA 205832 OFEV (Nintedanib)

Boehringer Ingelheim submitted this supplemental NDA to add the treatment of chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype to the indications for nintedanib. Currently, nintedanib is approved for the treatment of idiopathic pulmonary fibrosis (IPF) and systemic sclerosis ILD (SSc-ILD).

In support of this proposed added indication, the Applicant submitted one study (study 1199.247). This study was a 52-week randomized, double-blind, placebo-controlled, multicenter study assessing response to nintedanib compared to placebo in patients with chronic fibrosing ILDs with a progressive phenotype. There was a statistically significant reduction in decline of FVC at 52 weeks (primary endpoint) in nintedanib treated patients. Additional support was provided by favorable trends in secondary time-to-event endpoints (time to first exacerbation, time to death) albeit without statistical significance. No new safety concerns were raised beyond the known safety profile of nintedanib from IPF and SSc-ILD.

The novel grouping of these patients in the study population (various respiratory diseases combined [e.g. autoimmune ILDs, hypersensitivity pneumonitis] based on disease behavior) had raised concerns for subgroups driving efficacy or disproportionate safety events. Subgroup analyses for efficacy on the primary endpoint did not reveal noticeable differences in the treatment response. Similarly, safety analyses by ILDs did not reveal concerning imbalances in any particular subgroup.

The primary clinical reviewer recommends approval.

My primary clinical review is complete and has been added to the Multi-Disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. My review is based on the information currently as noted above. An update will be provided to the review if additional information is added or reviewed.

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KHALID PUTHAWALA  
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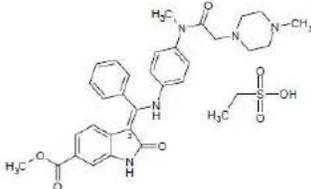
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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205832Orig1s013**

**PRODUCT QUALITY REVIEW(S)**

CHEMIST'S REVIEW <i>Review #1</i>		1. ORGANIZATION BRANCH 1/DPMA1/OLDP/OPQ	2. NDA NUMBER <b>205-832</b>
3. NAME AND ADDRESS OF APPLICANT ( <i>City and State</i> ) Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Road, P.O. Box 368 Ridgefield, CT 06877  <u>Name and Title of Applicant's Responsible Official</u> Lorraine W. Sachs, M.S., RAC, Senior Associate Director, Regulatory Affairs, BIPI Tel: (203) 791-5911, FAX: (203) 791-6262 <a href="mailto:ingeborg.arny-cornejo@boehringer-ingelheim.com">ingeborg.arny-cornejo@boehringer-ingelheim.com</a>		4. AF NUMBER	
6. NAME OF DRUG OFEV®		7. NONPROPRIETARY NAME Nintedanib	
8. SUPPLEMENT PROVIDES FOR: the addition of a new indication with clinical data..			
9. PROPOSED INDICATION FOR USE Treatment of Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD)		10. HOW DISPENSED RX <input checked="" type="checkbox"/> 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-carboxylate (1:1) 		15. RECORDS AND REPORTS CURRENT YES_NO REVIEWED YES_NO	
Molecular Formula: C <sub>31</sub> H <sub>33</sub> N <sub>5</sub> O <sub>4</sub> ·C <sub>2</sub> H <sub>6</sub> O <sub>3</sub> S; Molecular Weight: 649.76			
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 December 16, 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 chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype.”

Efficacy and safety information supporting the new indication is provided in the following trial report discussed in Module 2 and located in Module 5:

- Study No. 1199.247: “INBUILD®: A double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of nintedanib over 52 weeks in patients with Progressive Fibrosing Interstitial Lung Disease (PF-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 =  $10^9$   $\mu\text{g}/\text{kg}$  (conversion factor)

\* (b) (4) 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*

*BIFI'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.



Chong Ho  
Kim

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Comments: Labeling changes are acceptable from CMC standpoint.



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Raghavachari

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205832Orig1s013**

**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**

**PATIENT LABELING REVIEW**

Date: February 25, 2020

To: Jessica Lee, PharmD  
Senior Regulatory Project Manager  
**Division of Pulmonary, Allergy, and Rheumatology  
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: Lonice Carter, MS, RN, CNL  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Kyle Snyder, Pharm.D.  
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-013

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

## 1 INTRODUCTION

On September 9, 2019, Boehringer Ingelheim Pharmaceuticals, Inc. submitted for the Agency's review a Prior Approval Supplement-Efficacy for Supplemental New Drug Application (sNDA) 205832/ S-013 for OFEV (nintedanib) capsules, for oral use. The purpose of this sNDA is to propose the addition of a new indication for the "treatment of chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype" and provide updates to the Prescribing Information (PI) and Patient Package Insert (PPI) accordingly.

OFEV (nintedanib) was originally approved on October 15, 2014 and 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 a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on October 16, 2019 for DMPP and OPDP to review the Applicant's proposed PPI, for OFEV (nintedanib) capsules, for oral use.

## 2 MATERIAL REVIEWED

- Draft OFEV (nintedanib) PPI received on September 9, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 11, 2020.
- Draft OFEV (nintedanib) PI received on September 9, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 11, 2020.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> 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.

In our collaborative review of the PPI we:

- 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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LASHAWN M GRIFFITHS  
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**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** February 18, 2020

**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-013

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In response to DPARP's consult request dated October 16, 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 chronic fibrosing interstitial lung diseases with a progressive phenotype.

**PI:** OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DPARP on February 11, 2020, 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](mailto:kyle.snyder@fda.hhs.gov).

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LABEL AND LABELING REVIEW  
Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

\*\*\* This document contains proprietary information that cannot be released to the public\*\*\*

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Date of This Review:	February 4, 2020
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	NDA 205832
Product Name and Strength:	Ofev (nintedanib) Capsules, 100 mg, 150 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
FDA Received Date:	September 9, 2019
OSE RCM #:	2019-2230
DMEPA Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA Team Leader:	Ashleigh Lowery, PharmD, BCCCP

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## 1 REASON FOR REVIEW

Boehringer Ingelheim Pharmaceuticals, Inc. submitted a supplement for Ofev (nintedanib) Capsules to add a new indication: "Treatment of chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype." Subsequently, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the proposed Ofev prescribing information (PI) for areas of vulnerability that may lead to medication errors.

## 2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D -N/A
Other	E-N/A
Labels and Labeling	F

N/A=not applicable for this review

\*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 CONCLUSION

Our evaluation of the proposed Ofev prescribing information (PI) did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED  
 APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ofev that Boehringer Ingelheim Pharmaceuticals, Inc. submitted on September 9, 2019.

Table 2. Relevant Product Information for Ofev	
Initial Approval Date	October 15, 2014
Active Ingredient	nintedanib
Indication	Current: Treatment of idiopathic pulmonary fibrosis (IPF)  Proposed: Treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype.
Route of Administration	Oral
Dosage Form	Capsules
Strength	100 mg, 150 mg
Dose and Frequency	150 mg twice daily; with an option to reduce the dose to 100 mg twice daily due to adverse reactions or liver enzyme elevation Max dose: 300 mg/day
How Supplied	HDPE 60 count bottles, brown colored (150 mg) opaque, oblong soft gelatin capsules and peach-colored (100 mg) opaque, oblong soft gelatin capsules
Storage	25°C (77°F); excursions permitted 15°C – 30°C (59°F – 86°F)
Container Closure	N/A

## APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 30, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Ofev. Our search identified two previous reviews<sup>a,b</sup>. The referenced reviews did not provide any recommendations.

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<sup>a</sup> McMillan Teresa. Label and Labeling Review for Ofev (NDA 205832/S-004). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 DEC 16. RCM No.: 2016-2046.

<sup>b</sup> Abraham S. DAAA Section 915 New Molecular Entity NME Postmarket Safety Summary Analysis for Nintedanib (NDA 205832). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 16.

## APPENDIX F. LABELS AND LABELING

### F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>c</sup> along with postmarket medication error data, we reviewed the following Ofev labels and labeling submitted by Boehringer Ingelheim Pharmaceuticals, Inc..

- Prescribing Information (Image not shown) received on September 9, 2019

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<sup>c</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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