OFEV
Nintedanib

COMPOSITION

Ofev 100 mg soft capsules
1 capsule contains 100 mg of nintedanib (= free base)
corresponding to 120.4 mg 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) (= nintedanib esilate).

Ofev 150 mg soft capsules
1 capsule contains 150 mg of nintedanib (= free base)
corresponding to 180.6 mg 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) (= nintedanib esilate).

Excipients ***

Capsule fill:	Medium chain triglycerides, hard fat, soya lecithin (E322)
Capsule shell:	Gelatine, glycerol 85 %, titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172), black ink (Opacode®)
Black ink:	Shellac glaze, iron oxide black (E172), propylene glycol (E1520)

INDICATIONS/ USAGE

Ofev is indicated for the treatment of Idiopathic Pulmonary Fibrosis (IPF).
Ofev is indicated for slowing the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD).
Ofev is indicated in adults for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype (also known as progressive fibrosing ILD).

DOSAGE AND ADMINISTRATION/ RECOMMENDED INTAKE

Treatment with Ofev should be initiated by physicians experienced in the diagnosis and treatment for which OFEV is indicated.

Posology and method of administration

The recommended dose is 150 mg nintedanib twice daily administered approximately 12 hours apart. The 100 mg twice daily dose is only recommended to be used in patients who do not tolerate the 150 mg twice daily dose.
If a dose is missed, administration should resume at the next scheduled time at the recommended dose. If a dose is missed, the patient should not be given an additional dose.
The recommended maximum daily dose of 300 mg should not be exceeded.
For long-term use in IPF patients, please see section Clinical Trials.

Dose adjustments

In addition to symptomatic treatment if applicable, the management of adverse reactions to Ofev could include dose reduction and temporary interruption until the specific adverse reaction has resolved to levels that allow continuation of therapy. Ofev treatment may be resumed at the full dose (150 mg twice daily) or a reduced dose (100 mg twice daily). If a patient does not tolerate 100 mg twice daily, treatment with Ofev should be discontinued.

In case of interruptions due to aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations > 3x upper limit of normal (ULN), once transaminases have returned to baseline values, treatment with Ofev may be reintroduced at a reduced dose (100 mg twice daily) which subsequently may be increased to the full dose (150 mg twice daily).

Special populations

Elderly patients (> 65 years)

No overall differences in safety and efficacy were observed for elderly patients. No a-priori dose adjustment is required on the basis of a patient's age. Patients >75 years may be more likely to require dose reduction to manage adverse effects.

Renal impairment

Less than 1% of a single dose of nintedanib is excreted via the kidney. 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 (<30 ml/min creatinine clearance).

Hepatic Impairment

Nintedanib is predominantly eliminated via biliary/faecal excretion (> 90 %). Exposure increased in patients with hepatic impairment (Child Pugh A, Child Pugh B). In patients with mild hepatic impairment (Child Pugh A), the recommended dose of Ofev is 100 mg twice daily

approximately 12 hours apart. In patients with mild hepatic impairment (Child Pugh A), treatment interruption or discontinuation for management of adverse reactions should be considered.
The safety and efficacy of nintedanib have not been investigated with hepatic impairment classified as Child Pugh B and C. Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic imapairment with Ofev is not recommended.

PAEDIATRIC POPULATION
The safety and efficacy of Ofev in children aged 0-18 years have not been established.
No data are available.

Race
Based on population pharmacokinetic (PK) analyses, no a priori dose adjustments of Ofev are necessary. Safety data for Black patients are limited.

Body weight
Based on population PK analyses, no a priori dose adjustments of Ofev are necessary.

Method of administration
Ofev capsule should be taken orally, preferably with food, swallowed whole with water, and should not be chewed.

The capsule should not be opened or crushed. If contact with the content of the capsule occurs, hands should be washed immediately and thoroughly.

INSTRUCTIONS FOR USE / HANDLING
The capsule should not be opened or crushed. If contact with the content of the capsule occurs, hands should be washed immediately and thoroughly.

CONTRAINDICATIONS
Ofev is contraindicated in patients with known hypersensitivity to nintedanib, peanut or soya, or to any of the excipients (see section ***Composition***).
Ofev is contraindicated during pregnancy (see sections ***Pregnancy, Lactation*** and ***Fertility, Toxicology***).

SPECIAL WARNINGS AND PRECAUTIONS
Gastrointestinal –Disorders

- *Diarrhoea*

  In the clinical trials (see section ***Clinical trials***), diarrhoea was the most frequent gastro-intestinal event reported. In most patients, the event was of mild to moderate intensity and occurred within the first 3 months of treatment. In the INPULSIS trials in patients with IPF, diarrhoea was reported in 62.4 % versus 18.4 % of patients treated with **Ofev** and placebo, respectively. Diarrhoea led to dose reduction of Ofev in 10.7% of the patients and to discontinuation of Ofev in 4.4% of the patients. In the INBUILD trial in patients with other chronic fibrosing ILDs with a progressive phenotype, diarrhoea was reported in 66.9% versus 23.9% of patients treated with Ofev and placebo, respectively. Diarrhoea led to dose reduction of Ofev in 16.0% of the patients and to discontinuation of Ofev in 5.7% of the patients. In the SENSCIS trial in patients with SSc-ILD, diarrhoea was reported in 75.7% versus 31.6% of patients treated with Ofev and placebo, respectively. Diarrhoea led to dose reduction of Ofev in 22.2% of the patients and discontinuation of Ofev in 6.9% of the patients.

Diarrhoea should be treated at first signs with adequate hydration and anti-diarrhoeal medicinal products, e.g. loperamide, and may require dose reduction or treatment interruption. **Ofev** treatment may be resumed at a reduced dose (100 mg twice daily) or at the full dose (150 mg twice daily). In case of persisting severe diarrhoea despite symptomatic treatment, therapy with **Ofev** should be discontinued.

- *Nausea and vomiting*
  Nausea and vomiting were frequently reported adverse events (see section **Adverse Reactions**). In most patients with nausea and vomiting, the event was of mild to moderate intensity. In the INPULSIS trials, nausea led to discontinuation of Ofev in 2.0% of patients and vomiting led to discontinuation in 0.8% of the patients. In the INBUILD trial, the frequency of nausea and vomiting leading to Ofev discontinuation were 0.3% and 0.9%, respectively.
  In the SENSCIS trial, the frequency of nausea and vomiting leading to Ofev discontinuation 2.1% and 1.4% respectively.

  If symptoms persist despite appropriate supportive care (including anti-emetic therapy), dose reduction or treatment interruption may be required. The treatment may be resumed at a reduced dose (100 mg twice daily) or at the full dose (150 mg twice daily). In case of persisting severe symptoms therapy with **Ofev** should be discontinued.

Diarrhoea and vomiting may lead to dehydration with or without electrolyte disturbances which may progress to renal function impairment.

Hepatic Function
The safety and efficacy of **Ofev** has not been studied in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Therefore treatment with **Ofev** is not recommended in such patients *(*see sections ***Pharmacokinetics****)*.

Based on increased exposure, the risk for adverse events may be increased in patients with mild hepatic impairment (Child Pugh A). Patients with mild hepatic impairment (Child Pugh A) should be treated with a reduced dose of Ofev (see Dosage and Administration, Pharmacokinetics).

Cases of drug-induced liver injury have been observed with nintedanib treatment. In the post-marketing 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. Therefore, hepatic transaminase and bilirubin levels should be investigated upon initiation of treatment with **Ofev**, at regular intervals during the first three months of treatment and periodically thereafter (e.g. at each patient visit) or as clinically indicated.

Elevations of liver enzymes (ALT, AST, ALKP, gamma-glutamyl transferase (GGT) and bilirubin were reversible upon dose reduction or interruption in the majority of cases.
If transaminase (AST or ALT) elevations > 3x upper limit of normal (ULN) are measured, dose reduction or interruption of the therapy with **Ofev** is recommended and the patient should be monitored closely. Once transaminases have returned to baseline values, treatment with **Ofev** may be re-increased to the full dose (150 mg twice daily) or reintroduced at a reduced dose (100 mg twice daily) which subsequently may be increased to the full dose. (see section ***Dosage and administration/Recommended intake***). If any liver test elevations are associated with clinical signs or symptoms of liver injury, e.g. jaundice, treatment with **Ofev** should be

permanently discontinued. Alternative causes of the liver enzyme elevations should be investigated.

Patients with low body weight (< 65 kg), Asian and female patients have a higher risk of elevations in liver enzymes.

Nintedanib exposure increased linearly with patient age, which may also result in a higher risk of developing liver enzyme elevations (see section Pharmacokinetics).

Close monitoring is recommended in patients with these risk factors.

Haemorrhage

VEGFR inhibition might be associated with an increased risk of bleeding.

In the clinical trials with **Ofev**, the frequency of patients who experienced bleeding adverse events was slightly higher in patients treated with Ofev or comparable between the treatment arms (Ofev 10.3% versus placebo 7.8% for INPULSIS; Ofev 11.1% versus placebo 12.7 for INBUILD; Ofev 11.1% versus placebo for 8.3% for SENSCIS). Non-serious epistaxis was the most frequent bleeding event reported. Serious bleeding events occurred with low and similar frequencies in the 2 treatment groups (Ofev: 1.3% versus placebo: 1.4% for INPULSIS; Ofev 1.4% versus placebo 0.7% for SENSCIS).

Patients at known risk for bleeding including patients with inherited predisposition to bleeding or patients receiving a full dose of anticoagulative treatment were not included in the clinical trials. Therefore these patients should only be treated with **Ofev** if the anticipated benefit outweighs the potential risk.

In the post-marketing period non-serious and serious bleeding events, some of which were fatal, have been observed.

Arterial thromboembolic events

Patients with a recent history of myocardial infarction or stroke were excluded from the clinical trials. In the clinical trials, arterial thromboembolic events were infrequently reported: Ofev 2.5% versus placebo 0.7% for INPULSIS; Ofev 0.9% versus placebo 0.9% for INBUILD; Ofev 0.7% versus placebo 0.7% for SENSCIS). In the INPULSIS trials, a higher percentage of patients experienced myocardial infarctions in the Ofev group (1.6%) compared to the placebo group (0.5%), while adverse events reflecting ischaemic heart disease were balanced between the Ofev and placebo group. In INBUILD and the SENSCIS trial, myocardial infarction was observed with low frequency: Ofev 0.9% versus placebo 0.9% for INBUILD; Ofev 0% versus placebo 0.7% for SENSCIS.

Use caution when treating patients with a higher cardiovascular risk including known coronary artery disease. Treatment interruption should be considered in patients who develop signs or symptoms of acute myocardial ischaemia.

Venous thromboembolism

In the clinical trials no increased risk of venous thromboembolism was observed in Ofev treated patients. Due to the mechanism of action of nintedanib patients might have an increased risk of thromboembolic events.

Gastrointestinal perforations

In the clinical trials no increased risk of gastrointestinal perforation was observed in Ofev treated patients. Due to the mechanism of action nintedanib patients might have an increased risk of gastrointestinal perforations. Cases of gastrointestinal perforations, some of which were fatal, have been reported in the post-marketing period. Particular caution should be exercised when treating patients with previous abdominal surgery, a recent history of a hollow organ

perforation, previous history of peptic ulceration, diverticular disease or receiving concomitant corticosteroids or NSAIDs. Ofev should therefore only be initiated at least 4 weeks after major, incl. abdominal, surgery. Therapy with Ofev should be permanently discontinued in patients who develop gastrointestinal perforation.

Nephrotic range proteinuria

Very few cases of nephrotic range proteinuria have been reported post-marketing. Histological findings in individual cases were consistent with glomerular microangiopathy with or without renal thrombi. Reversal of symptoms has been observed after Tradename® was discontinued. Treatment interruption should be considered in patients who develop signs or symptoms of nephrotic syndrome.

Wound healing complication

Based on the mechanism of action nintedanib may impair wound healing. No increased frequency of impaired wound healing was observed in the clinical trials. No dedicated studies investigating the effect of nintedanib on wound healing were performed. Treatment with **Ofev** should therefore only be initiated or – in case of perioperative interruption – resumed based on clinical judgement of adequate wound healing.

Soya lecithin

Ofev soft capsules contain soya lecithin (see section ***Contraindications).***

Hypertension

Administration of Ofev may increase blood pressure. Systemic blood pressure should be measured periodically and as clinically indicated.

Co-administration with pirfenidone

Concomitant treatment of nintedanib with pirfenidone was investigated in a parallel group design study in Japanese patients with IPF. Twenty four patients were treated for 28 days with 150 mg nintedanib twice daily (13 patients received nintedanib on top of chronic treatment with standard doses of pirfenidone; 11 patients received nintedanib alone). Due to the short duration of concomitant exposure and low number of patients the benefit/risk of the co-administration with pirfenidone has not been established.

Effect on QT interval

No evidence of QT prolongation was observed for nintedanib in the clinical trial programme. As some other tyrosine kinase inhibitors are known to exert an effect on QT, caution should be exercised when administered nintedanib in patients who may develop QT prolongation.

Allergic reaction

Dietary soya products are known to cause allergic reactions including severe anaphylaxis in persons with soya allergy. Patients with known allergy to peanut protein carry an enhanced risk for severe reactions to soya preparations.

Renal Function

Cases of renal impairment/failure, in some cases with fatal outcome, have been reported with nintedanib use.

Patients should be monitored during nintedanib theraphy, with particular attention to those patients exhibiting risk factors for renal impairment/failure. In case of renal impairment/failure, therapy adjustment should be considered.

Aneurysms and Artery Dissections

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating Ofev, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Pulmonary Hypertension
Data on the use of Ofev in patients with pulmonary hypertension is limited.
Patients with significant pulmonary hypertension (cardiac index smaller is equal to 2 L/min/m2, or parenteral epoprostenol/treprostinil, or significant right heart failure) were excluded from the INBUILD and SENCIS trials.
Ofev should not be used in patients with severe pulmonary hypertension. Close monitoring is recommended in patients with mild to moderate pulmonary hypertension.

INTERACTIONS
P-glycoprotein (P-gp)
Nintedanib is a substrate of P-gp (see section ***Pharmacokinetics***). Co-administration with the potent P-gp 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 potent P-gp inducer rifampicin, exposure to nintedanib decreased to 50.3 % based on AUC and to 60.3 % based on C_{max} upon co-administration with rifampicin compared to administration of nintedanib alone.
If co-administered with **Ofev**, potent P-gp inhibitors (e.g. ketoconazole or erythromycin) may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of nintedanib. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with **Ofev** (see section ***Dosage and administration***).
Potent P-gp inducers (e.g. rifampicin, carbamazepine, phenytoin, and St. John's Wort) may decrease exposure to nintedanib. Selection of an alternate concomitant medication with no or minimal P-gp induction potential should be considered.

Food
Ofev is recommended to be taken with food (see section ***Pharmacokinetics***).

Cytochrome (CYP)-enzymes
Only a minor extent of the biotransformation of nintedanib consisted of CYP pathways. Nintedanib and its metabolites, the free acid moiety BIBF 1202 and its glucuronide BIBF 1202 glucuronide, did not inhibit or induce CYP enzymes in preclinical studies (see section ***Pharmacokinetics***). The likelihood of drug-drug interactions with nintedanib based on CYP metabolism is therefore considered to be low.

Co-administration with other drugs
Co-administration of nintedanib with bosentan did not alter the pharmacokinetics of nintedanib (see section Pharmacokinetics).

Co-administration of nintedanib with oral hormonal contraceptives did not alter the pharmacokinetics of oral hormonal contraceptives to a relevant extent (see section Pharmacokinetics).

FERTILITY, PREGNANCY AND LACTATION
Fertility
Based on preclinical investigations, there is no evidence for impairment of male fertility (see section ***Toxicology***). From subchronic and chronic toxicity studies, there is no evidence that

female fertility in rats is impaired at a systemic exposure level comparable with that at the maximum recommended human dose (MRHD) of 150 mg twice daily (see section ***Toxicology***).

Contraception

Nintedanib may cause foetal harm (see section Toxicology). Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Ofev and to use highly effective contraceptive methods at initiation of, during and at least 3 months after the last dose of **Ofev.** Nintedanib does not relevantly affect the plasma exposure of ethinylestradiol and levonorgestrel (see section Pharmacokinetics). The efficacy of oral hormonal contraceptives may be compromised by vomiting and/or diarrhoea or other conditions where the absorption may be affected. Women taking oral hormonal contraceptives experiencing these conditions should be advised to use an alternative highly effective contraceptive measure.

Pregnancy

There is no information on the use of **Ofev** in pregnant women, but pre-clinical studies in animals have shown reproductive toxicity of this drug (see section ***Toxicology***). As nintedanib may cause foetal harm also in humans, it must not be applied during pregnancy (see section Contraindications) and pregnancy testing must be conducted at least prior to treatment with **Ofev** and during treatment as appropriate.

Female patients should be advised to notify their doctor or pharmacist if becoming pregnant during therapy with **Ofev**.

If the patient becomes pregnant while receiving **Ofev** treatment must be discontinued the patient should be apprised of the potential hazard to the foetus.

Breastfeeding / lactation

There is no information on the excretion of nintedanib and its metabolites in human milk. Pre-clinical studies showed that small amounts of nintedanib and its metabolites (≤ 0.5 % of the administered dose) were secreted into milk of lactating rats.

A risk to the newborns/infants cannot be excluded. Breastfeeding should be discontinued during treatment with **Ofev**.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies of the effects on the ability to drive and use machines have been performed.

Patients should be advised to be cautious when driving or using machines during treatment with **Ofev**.

ADVERSE REACTIONS

Summary of the safety profile

Ofev has been studied in clinical trials including 1529 patients suffering from Idiopathic Pulmonary Fibrosis (IPF), 663 patients with other chronic fibrosing Interstitial Lung Diseases (ILDs) with a progressive phenotype and 576 patients with Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD).

The safety data provided in the following are based on:

- Two Phase III, randomised, double-blind, placebo-controlled trials comparing treatment with Ofev 150 mg twice daily to placebo for 52 weeks (INPULSIS-1 and INPULSIS-2) in 1061 patients with IPF.
- One phase III randomised, double-blind, placebo-controlled trial comparing treatment with Ofev 150 mg twice daily to placebo for at least 52 weeks in 663 patients with other chronic fibrosing ILDs with a progressive phenotype (INBUILD).

- One phase III randomised, double-blind, placebo-controlled trial comparing treatment with Ofev 150 mg twice daily to placebo for at least 52 weeks in 576 patients with SSc-ILD (SENSCIS).
- Data observed during the post-marketing experience.

In clinical trials, the most frequently reported adverse reactions associated with the use of Ofev included diarrhoea, nausea and vomiting, abdominal pain, decreased appetite, weight decreased and hepatic enzyme increased.

The safety profile of Ofev in a long term extension trial in patients with IPF, treated from 1 up to more than 5 years, was consistent with that observed in the phase III trials (see section Clinical Trials).

For the management of selected adverse reactions see section ***Special Warnings and Precautions*.**

Tabulated list of adverse reactions
The below table provide a summary of the adverse reactions by MedDRA System Organ Class (SOC) and frequency category.

Table 1 summarizes the frequencies of adverse drug reactions (ADRs) that were reported in the nintedanib group (638 patients) pooled from the two placebo-contolled Phase III clinical trials of 52 weeks duration or from the postmarketing period.

Frequency categories are defined using the following convention:
very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping adverse reactions are presented in order of decreasing seriousness.

Table 1 Summary of Adverse Reactions per frequency category

System Organ Class	Adverse Reaction	Frequency		
		IPF	PF-ILD	SSc-ILD
Blood and lymphatic system	Thrombocytopenia	Uncommon	Uncommon	Uncommon
Metabolism and nutrition disorder	Decreased appetite	Common	Very common	Common
	Weight decreased	Common	Common	Common
	Dehydration	Uncommon	Uncommon	Not known
Cardiac Disorder	Myocardial infarction	Uncommon	Uncommon	Not known
Vascular disorders	Hypertension	Uncommon	Common	Common
	Bleeding[1,2]	Common	Common	Common
	Aneurysms and artery	Not known	Not known	Not known
Gastrointestinal disorders	Diarrhorea	Very common	Very common	Very common
	Nausea	Very common	Very common	Very common
	Abdominal pain	Very common	Very common	Very common
	Vomitting	Common	Very common	Very common
	Pancreatitis	Uncommon	Uncommon	Not known

	Colitis	Uncommon	Uncommon	Uncommon
Renal and Urinary Disorders	Renal failure	Not known	Uncommon	Uncommon
Nervous System	Headache	Common	Common	Common
Hepatobiliary disorders	Drug-induced liver injury	Uncommon	Common	Uncommon
	Hepatic enzyme increased	Very common	Very common	Very common
	Alanine aminotransferase increased	Common	Very common	Common
	Aspartate aminotransferase increased	Common	Common	Common
	Gamma-glutamyltransferase increased	Common	Common	Common
	Blood alkaline phosphatase increased	Uncommon	Common	Common
	Hyperbilirubinaemia	Uncommon	Uncommon	Not known
Skin and subcutaneous tissue Disorders	Rash	Common	Common	Uncommon
	Pruritus	Uncommon	Uncommon	Uncommon
	Alopecia	Uncommon	Uncommon	Not known
	Headache	Common	Common	Common
Renal and urinary disorders	Proteinuria	Uncommon	common	common

1) Term represents a group of events that describe a broader medical concept rather than a single condition or MedDRA preferred term.
2) Non-serious and serious bleeding events, some of which were fatal, have been observed in the post-marketing period in line with clinical trial experience.

OVERDOSE

There is no specific antidote or treatment for **Ofev**overdose. The highest single dose of nintedanib administered in phase I studies was 450 mg once daily. In addition, 2 patients in the oncology programme had an overdose of maximum 600 mg twice daily (b.i.d) up to eight days. Observed adverse events were consistent with the known safety profile of nintedanib, i.e. increased liver enzymes and gastrointestinal symptoms. Both patients recovered from these adverse reactions.

In the INPULSIS 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.

In case of overdose, treatment should be interrupted and general supportive measures initiated as appropriate.

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents - Protein-tyrosine kinase inhibitors.
ATC code: L01XE31

Mechanism of action

Nintedanib is a small molecule tyrosine kinase inhibitor including the receptors platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, and vascular endothelial growth factor receptor (VEGFR) 1-3. In addition, nintedanib inhibits Lck, Lyn, Src, and CSF1R kinases. Nintedanib binds competitively to the ATP binding pocket of these kinases and blocks the intracellular signalling cascades, which have been demonstrated to be involved in the pathogenedsis of fibrotic tissue remodelling in interstitial lung disease.

Pharmacodynamic effects

In *in vitro* studies using human cells nintedanib has been shown to inhibit processes assumed to be involved in the initiation of the fibrotic pathogenesis, the release of pro-fibrotic mediators from peripheral blood monocytic cells and macrophage polarisation to alternatively activated macrophages. Nintedanib has been demonstrated to inhibit fundamental processes in organ fibrosis, proliferation and migration of fibroblasts and transformation to the active myofibroblast phenotype and secretion of extracellular matrix. In animal studies in multiple models of IPF, SSc/SSc-ILD, RA-ILD and other organ fibrosis, nintedanib has shown anti-inflammatory effects and anti-fibrotic effects in the lung, skin, heart, kidney, and liver. Nintedanib also exerted vascular activity. It reduced dermal microvascular endothelial cell apoptosis and attenuated pulmonary vascular remodelling by reducing the proliferation of vascular smooth muscle cells, the thickness of pulmonary vessel walls and percentage of occluded pulmonary vessels.

CLINICAL TRIALS

Idiopathic Pulmonary Fibrosis (IPF)

The clinical efficacy of Ofev has been studied in patients with IPF in two phase 3, randomised, double-blind, placebo-controlled studies with identical design (INPULSIS-1 and INPULSIS-2). Patients were randomized in a 3:2 ratio to treatment with Ofev 150 mg or placebo twice daily for 52 weeks.

The primary endpoint was the annual rate of decline in Forced Vital Capacity (FVC). The key secondary endpoints were change from baseline in Saint George's Respiratory Questionnaire (SGRQ) total score at 52 weeks and time to first acute IPF exacerbation.

Annual rate of decline in FVC

The annual rate of decline of FVC (in mL) was significantly reduced in patients receiving Ofev compared to patients receiving placebo. The treatment effect was consistent in both trials. See Table 2 for individual and pooled study results.

Table 2 Annual rate of decline in FVC (mL) in trials INPULSIS-1, INPULSIS-2 and their pooled data - treated set

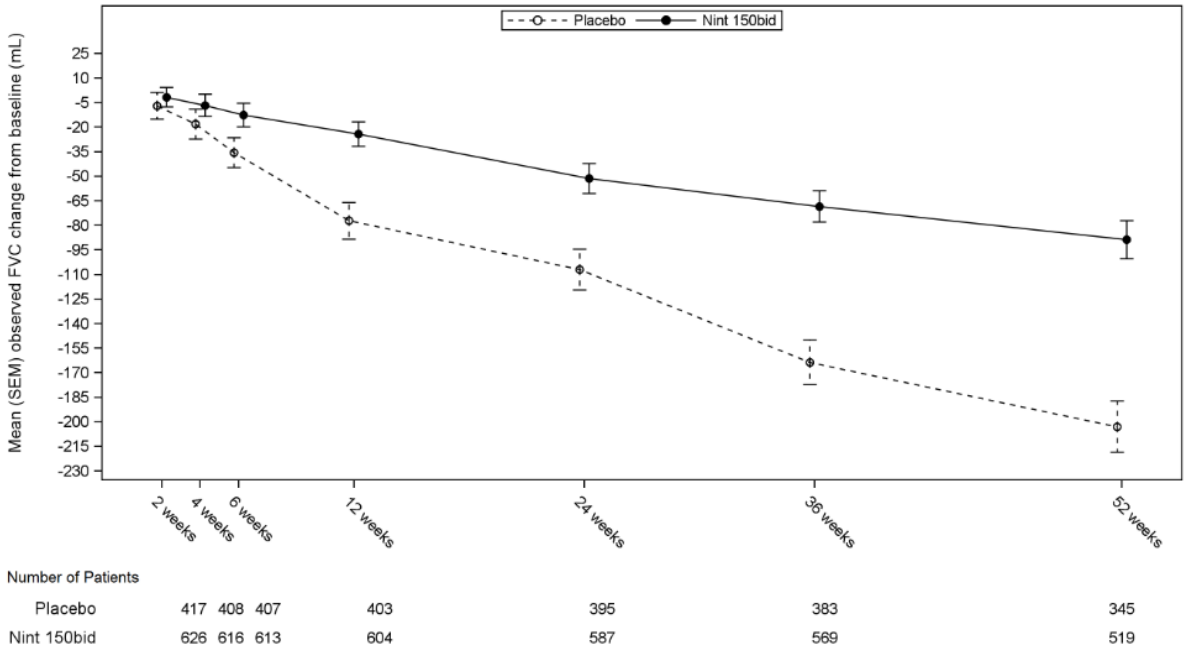
	INPULSIS-1		INPULSIS-2		INPULSIS-1 and INPULSIS-2 pooled	
	Placebo	**Ofev**150 mg twice daily	Placebo	**Ofev**150 mg twice daily	Placebo	**Ofev**150 mg twice daily
Number of analysed patients	204	309	219	329	423	638
Rate[1] (SE) of decline over 52 weeks	−239.9 (18.71)	−114.7 (15.33)	−207.3 (19.31)	−113.6 (15.73)	−223.5 (13.45)	−113.6 (10.98)
Comparison vs placebo						
Difference[1]		125.3		93.7		109.9
95% CI		(77.7, 172.8)		(44.8, 142.7)		(75.9, 144.0)
p-value		<0.0001		0.0002		<0.0001

[1] Estimated based on a random coefficient regression model.

The robustness of the effect of Ofev in reducing the annual rate of decline in FVC was confirmed in all pre-specified sensitivity analyses.

In addition, similar effects were observed on other lung function endpoints e.g. change from baseline in FVC at week 52 and FVC responder analyses providing further substantiation of the effects of Ofev on slowing disease progression. See Figure 2 for the evolution of change from baseline over time in both treatment groups, based on the pooled analysis of studies INPULSIS-1 and INPULSIS-2.

Figure 1 Mean (SEM) observed FVC change from baseline (mL) over time, studies INPULSIS-1 and INPULSIS-2 pooled



bid = twice daily

FVC responder analysis

In both INPULSIS trials, the proportion of FVC responders, defined as patients with an absolute decline in FVC % predicted no greater than 5% (a threshold indicative of the increasing risk of mortality in IPF), was significantly higher in the Ofev group as compared to placebo. Similar results were observed in analyses using a conservative threshold of 10%. See Table 3 for individual and pooled study results.

Table 3 Proportion of FVC responders at 52 weeks in trials INPULSIS-1, INPULSIS-2 and their pooled data - treated set

	INPULSIS-1		INPULSIS-2		INPULSIS-1 and INPULSIS-2 pooled	
	Placebo	**Ofev**150 mg twice daily	Placebo	**Ofev**150 mg twice daily	Placebo	**Ofev**150 mg twice daily
Number of analysed patients	204	309	219	329	423	638
5% threshold						
Number (%) of FVC responders[1]	78 (38.2)	163 (52.8)	86 (39.3)	175 (53.2)	164 (38.8)	338 (53.0)
Comparison vs placebo						
Odds ratio		1.85		1.79		1.84
95% CI		(1.28, 2.66)		(1.26, 2.55)		(1.43, 2.36)
p-value[2]		0.0010		0.0011		<0.0001
10% threshold						
Number (%) of FVC responders[1]	116 (56.9)	218 (70.6)	140 (63.9)	229 (69.6)	256 (60.5)	447 (70.1)
Comparison vs placebo						
Odds ratio		1.91		1.29		1.58
95% CI		(1.32, 2.79)		(0.89, 1.86)		(1.21, 2.05)
p-value[2]		0.0007		0.1833		0.0007

[1]Responder patients are those with no absolute decline greater than 5% or greater than 10% in FVC %predicted, depending on the threshold and with an FVC evaluation at 52 weeks.
[2]Based on a logistic regression

Time to progression (≥ 10% absolute decline of FVC % predicted or death)

In both INPULSIS trials, the risk of progression was statistically significantly reduced for patients treated with Ofev compared with placebo. In the pooled analysis, the HR was 0.60 indicating a 40% reduction in the risk of progression for patients treated with Ofev compared with placebo, see Table 4.

Table 4: Frequency of patients with ≥ 10% absolute decline of FVC % predicted or death over 52 weeks and time to progression in trials INPULSIS-1, INPULSIS-2, and their pooled data - treated set

	INPULSIS-1		INPULSIS-2		INPULSIS-1 and INPULSIS-2 pooled	
	Placebo	Ofev 150 mg twice daily	Placebo	Ofev 150 mg twice daily	Placebo	Ofev 150 mg twice daily
Number at risk	204	309	219	329	423	638
Patients with events, N (%)	83 (40.7)	75 (24.3)	92 (42.0)	98 (29.8)	175 (41.4)	173 (27.1)
Comparison vs placebo[1]						
p-value[2]		0.0001		0.0054		<0.0001
Hazard ratio[3]		0.53		0.67		0.60
95% CI		(0.39, 0.72)		(0.51, 0.89)		(0.49, 0.74)

[1] Based on data collected up to 372 days (52 weeks + 7 day margin).
[2] Based on a Log-rank test.
[3] Based on a Cox's regression model.

Change from baseline in SGRQ total score at week 52
St. George's Respiratory Questionnaire (SGRQ) total score measuring health related quality of life (HRQoL) was analysed at 52 weeks. In INPULSIS-2, patients receiving placebo had a larger increase from baseline SGRQ total score as compared to patients receiving Ofev 150 mg bid. The deterioration of HRQoL was smaller in the Ofev group; the difference between the treatment groups was statistically significant (-2.69; 95% CI: -4.95, -0.43; p=0.0197).

In INPULSIS-1, the increase from baseline in SGRQ total score at week 52 was comparable between Ofev and placebo (difference between treatment groups: -0.05; 95% CI: -2.50, 2.40; p=0.9657). In the pooled analysis of the INPULSIS trials, the estimated mean change from baseline to week 52 in SGRQ total score was smaller in the Ofev group (3.53) than in the placebo group (4.96), with a difference between the treatment groups of -1.43 (95% CI: -3.09, 0.23; p = 0.0923). Overall, the effect of Ofev on health-related quality of life as measured by the SGRQ total score is modest, indicating less worsening compared to placebo.

Time to first acute IPF exacerbation
In the INPULSIS-2 trial, the risk of first acute IPF exacerbation over 52 weeks was significantly reduced in patients receiving Ofev compared to placebo, in the INPULSIS-1 trial there was no difference in between the treatment groups. In the pooled analysis of the INPULSIS trials, a numerically lower risk of first acute exacerbation was observed in patients receiving Ofev compared to placebo. See Table 5 for individual and pooled study results.

Table 5 Time to first acute exacerbation over 52 weeks based on investigator-reported events in trials INPULSIS-1, INPULSIS-2, and their pooled data - treated set

	INPULSIS-1		INPULSIS-2		INPULSIS-1 and INPULSIS-2 pooled	
	Placebo	**Ofev**150 mg twice daily	Placebo	**Ofev**150 mg twice daily	Placebo	**Ofev**150 mg twice daily
Number at risk	204	309	219	329	423	638
Patients with events, N (%)	11 (5.4)	19 (6.1)	21 (9.6)	12 (3.6)	32 (7.6)	31 (4.9)
Comparison vs placebo[1]						
p-value[2]		0.6728		0.0050		0.0823
Hazard ratio[3]		1.15		0.38		0.64
95% CI		(0.54, 2.42)		(0.19, 0.77)		(0.39, 1.05)

[1] Based on data collected up to 372 days (52 weeks + 7 day margin).
[2] Based on a Log-rank test.
[3] Based on a Cox's regression model

All adverse events of acute IPF exacerbation reported by the investigator were adjudicated by a blinded adjudication committee. A pre-specified sensitivity analysis of the time to first 'suspected' adjudicated acute IPF exacerbation was performed on the pooled data. The frequency of patients with at least 1 adjudicated exacerbation occurring within 52 weeks was lower in the Ofev group (1.9% of patients) than in the placebo group (5.7% of patients). Time to event analysis of the adjudicated exacerbation events using pooled data yielded an HR of 0.32 (95% CI 0.16, 0.65; p = 0.0010).This indicates that the risk of having a first acute IPF exacerbation was statistically significantly lower in the Ofev group than in the placebo group at any time point.

Survival analysis
In the pre-specified pooled analysis of survival data of the INPULSIS trials, overall mortality over 52 weeks was lower in the Ofev group (5.5%) compared with the placebo group (7.8%). The analysis of time to death resulted in a HR of 0.70 (95% CI 0.43, 1.12; p = 0.1399). The results of all survival endpoints (such as on-treatment mortality and respiratory mortality) showed a consistent numerical difference in favour of Ofev (see Table 6).

Table 6: All-cause mortality over 52 weeks in trials INPULSIS-1, INPULSIS-2, and their pooled data - treated set

	INPULSIS-1		INPULSIS-2		INPULSIS-1 and INPULSIS-2 Pooled	
	Placebo	Ofev 150 mg twice daily	Placebo	Ofev 150 mg twice daily	Placebo	Ofev 150 mg twice daily
Number at risk	204	309	219	329	423	638
Patients with events, N (%)	13 (6.4)	13 (4.2)	20 (9.1)	22 (6.7)	33 (7.8)	35 (5.5)
Comparison vs placebo[1]						
p-value[2]		0.2880		0.2995		0.1399
Hazard ratio[3]		0.63		0.74		0.70

95% CI		(0.29, 1.36)		(0.40, 1.35)		(0.43, 1.12)

[1] Based on data collected up to 372 days (52 weeks + 7 day margin).
[2] Based on a Log-rank test.
[3] Based on a Cox's regression model.

Supportive evidence from the phase II trial (1199.30) **Ofev** 150 mg twice daily results:
Additional evidence of efficacy is provided by the randomised, double-blind, placebo-controlled, dose finding phase II trial including an Ofev 150 mg bid dose group.
The primary endpoint, rate of decline in FVC over 52 weeks was lower in the Ofev arm (-0.060 L/year, N=84) than the placebo arm (-0.190 L/year, N=83). The estimated difference between the treatment groups was 0.131 L/year (95% CI 0.027, 0.235). The difference between the treatment groups reached nominal statistical significance (p = 0.0136).
The estimated mean change from baseline in SGRQ total score at 52 weeks was 5.46 for placebo, indicating worsening of the health-related quality of life and -0.66 for Ofev, indicating stable health-related quality of life. The estimated mean difference for Ofev compared with placebo was -6.12 (95% CI: -10.57, -1.67; p = 0.0071).
The number of patients with acute IPF exacerbations over 52 weeks was lower in the Ofev group (2.3%, N=86) compared to placebo (13.8%, N=87). The estimated hazard ratio of Ofev versus placebo was 0.16 (95% CI 0.04, 0.71; p = 0.0054).

Long-term treatment with Ofev in patients with IPF (INPULSIS-ON)
An open-label extension trial of Ofev included 734 patients with IPF. Some patients were treated with Ofev for more than 5 years. Patients who completed the 52-week treatment period in an INPULSIS trial received open-label Ofev treatment in the extension trial INPULSIS-ON. Median exposure time for patients treated with Ofev in both the INPULSIS and INPULSIS-ON trials was 44.7 months (range 11.9–68.3). The adjusted annual rate of decline in FVC over 192 weeks was −135.1 (5.8) mL/year in all patients treated and were consistent with the annual rate of FVC decline in patients treated with Ofev in the INPULSIS phase III trials (−113.6 mL per year). The adverse event profile of Ofev in INPULSIS-ON was similar to that in the INPULSIS phase III trials.

Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD)
The clinical efficacy of Ofev has been studied in in patients with SSc-ILD in a double-blind, randomised, placebo-controlled phase III trial (SENSCIS). Patients were diagnosed with SSc-ILD based upon the 2013 American College of Rheumatology / European League Against Rheumatism classification criteria for SSc and a chest high resolution computed tomography (HRCT) scan conducted within the previous 12 months. A total of 580 patients were randomised in a 1:1 ratio to receive either Ofev 150 mg bid or matching placebo for at least 52 weeks, of which 576 patients were treated. Randomisation was stratified by Antitopoisomerase Antibody status (ATA). Individual patients stayed on blinded trial treatment for up to 100 weeks (median Ofev exposure 15.4 months; mean Ofev exposure 14.5 months).

The primary endpoint was the annual rate of decline in Forced Vital Capacity (FVC) over 52 weeks. Key secondary endpoints were absolute change from baseline in the modified Rodnan Skin Score (mRSS) at week 52 and absolute change from baseline in the Saint George's Respiratory Questionnaire (SGRQ) total score at week 52.
In the overall population, 75.2% of the patients were female. The mean (standard deviation [SD, Min-Max]) age was 54.0 (12.2, 20-79) years. Overall, 51.9% of patients had diffuse cutaneous Systemic Sclerosis (SSc) and 48.1% had limited cutaneous SSc. The mean (SD) time since first onset of a non-Raynaud symptom was 3.49 (1.7) years. 49.0% of patients were on stable therapy with

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

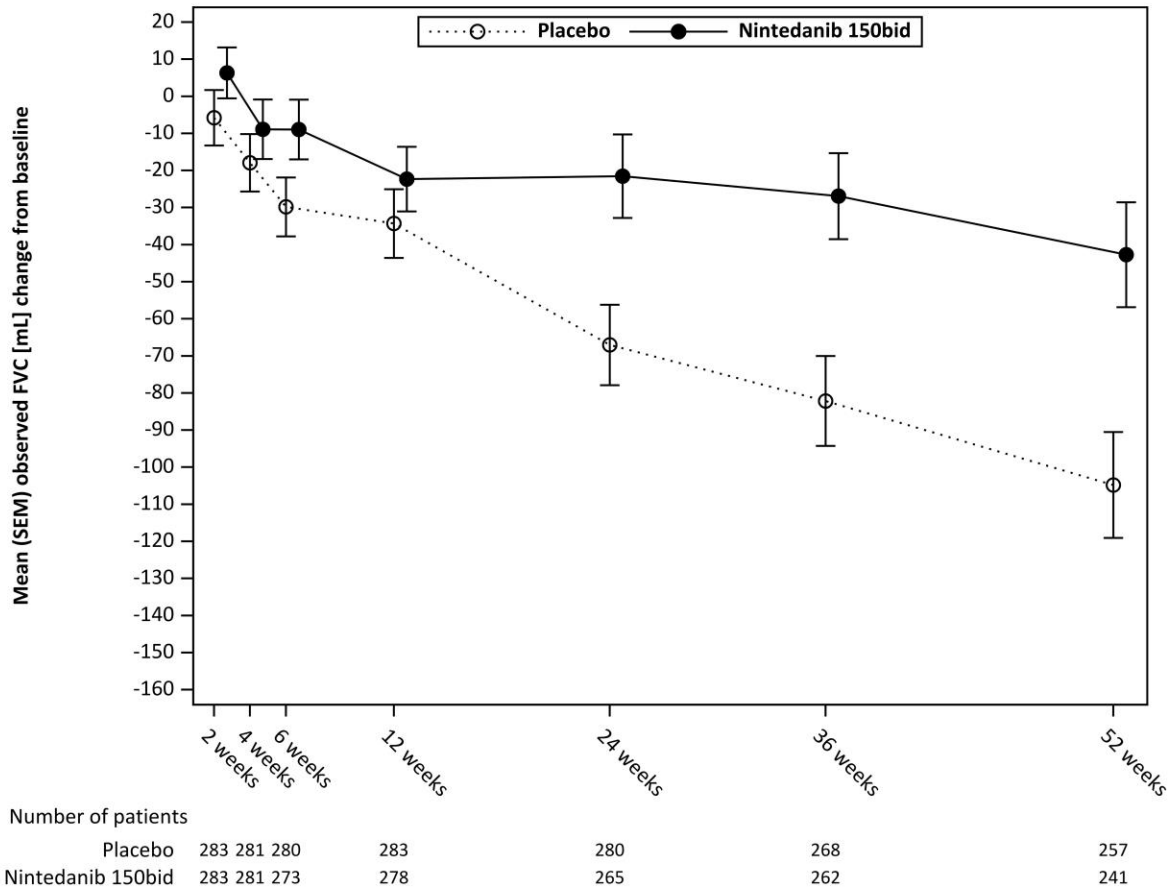
Annual rate of decline in FVC
The annual rate of decline of FVC (in mL) over 52 weeks was significantly reduced by 41.0 mL in patients receiving Ofev compared to patients receiving placebo (Table 7) corresponding to a relative treatment effect of 43.8%.

Table 7 Annual rate of decline in FVC (mL) over 52 weeks

	Placebo	Ofev 150 mg twice daily
Number of analysis patients	288	287
Rate[1] (SE) of decline over 52 weeks	-93.3 (13.5)	-52.4 (13.8)
Comparison vs placebo		
Difference[1]		
95% CI		41.0
p-value		<0.05
[1]Based on a random coefficient regression with fixed categorical effects of treatment, ATA status, gender, fixed continuous effects of time, baseline FVC [mL], age, height, and including treatment-by-time and baseline-by-time interactions. Random effect was included for patient specific intercept and time. Within-patient errors were modelled by an unstructured variance-covariance matrix. Inter-individual variability was modelled by a variance-components variance-covariance matrix.		

The effect of Ofev in reducing the annual rate of decline in FVC was similar across pre-specified sensitivity analyses and no heterogeneity was detected in pre-specified subgroups (e.g. by age, gender, and mycophenolate use).
In addition, similar effects were observed on other lung function endpoints, e.g absolute change from baseline in FVC in mL at week 52 (Figure 2 and Table 8) and rate of decline in FVC in % predicted over 52 weeks (Table 9) providing further substantiation of the effects of Ofev on slowing progression of SSc-ILD. Furthermore, fewer patients in the Ofev group had an absolute FVC decline >5% predicted (20.6% in the Ofev group vs. 28.5% in the placebo group, OR=0.65, p=0.0287). The relative FVC decline in mL >10% was comparable between both groups (16.7% in the Ofev group vs. 18.1% in the placebo group, OR=0.91, p=0.6842). In these analyses, missing FVC values at week 52 were imputed with the patient's worst value on treatment.
An exploratory analysis of data up to 100 weeks (maximum treatment duration in SENSCIS) suggested that the on treatment effect of Ofev on slowing progression of SSc-ILD persisted beyond 52 weeks.

Figure 2 Mean (SEM) observed FVC change from baseline (mL) over 52 weeks



Bid = twice daily

Table 8 Absolute change from baseline in FVC (mL) at week 52

	Placebo	Ofev 150 mg twice daily
Number of analysed patients	288	288
Mean (SD) at Baseline	2541.0 (815.5)	2458.5 (735.9)
Mean[1] (SE) change from baseline at week 52	-101.0 (13.6)	-54.6 (13.9)
Comparison vs placebo Mean[1] 95% CI p-value		 46.4 (8.1, 84.7) <0.05
[1]Based on MMRM, with fixed categorical effects of ATA status, visit, treatment-by-visit interaction baseline-by-visit interaction, age, gender and height. Visit was the repeated measure. Within-patient errors were modelled by unstructured variance-covariance structure. Adjusted mean was based on all analysed patients in the model (not only patients with a baseline and measurement at Week 52)		

Table 9 Annual rate of decline in FVC (% predicted) over 52 weeks

	Placebo	Ofev 150 mg twice daily
Number of analysed patients	288	287

Rate[1] (SE) of decline over 52 weeks	-2.6 (0.4)	-1.4 (0.4)
Comparison vs placebo Difference[1] 95% CI p-value		 1.15 (0.09, 2.21) <0.05
[1]Based on a random coefficient regression with fixed categorical effects of treatment, ATA status, fixed continuous effects of time, baseline FVC [% pred], and including treatment-by-time and baseline-by-time interactions. Random effect was included for patient specific intercept and time. Within-patient errors were modelled by an unstructured variance-covariance matrix. Inter-individual variability was modelled by a variance-components variance-covariance matrix		

Change from baseline in Modified Rodnan Skin Score (mRSS) at week 52
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; p = 0.5785).

Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at week 52
The adjusted mean absolute change from baseline in SGRQ total score at week 52 was comparable between the Ofev group (0.81 (95% CI -0.92, 2.55)) and the placebo group (-0.88 (95% CI -2.58, 0.82)). The adjusted mean difference between the treatment groups was 1.69 (95% CI -0.73, 4.12; p = 0.1711).

Survival analysis
Mortality over the whole trial was comparable between the Ofev group (N = 10; 3.5%) and the placebo group (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; p = 0.7535).

Other chronic fibrosing Interstitial Lung Diseases (ILDs) with a progressive phenotype
The clinical efficacy of Ofev has been studied in patients with chronic fibrosing Interstitial Lung Diseases (ILDs) with a progressive phenotype in a double-blind, randomised, placebo-controlled phase III trial (INBUILD). Patients with IPF were excluded. Patients with a clinical diagnosis of chronic fibrosing ILD were selected if they had relevant fibrosis (> 10% fibrotic features) on high resolution computed tomography (HRCT) and presented with clinical signs of progression. A total of 663 patients were randomised in a 1:1 ratio to receive either Ofev 150 mg bid or matching placebo for at least 52-weeks. (The median Ofev exposure over the whole trial: 7.4 months; and the mean Ofev exposure over the whole trial: 6 months). Randomisation was stratified based on HRCT fibrotic pattern as assessed by central readers. 412 patients with HRCT with usual interstitial pneumonia (UIP)-like fibrotic pattern and 251 patients with other HRCT fibrotic patterns were randomised. 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 fibrotic pattern. Patients with other HRCT fibrotic patterns represented the 'complementary' population.
The primary endpoint was the annual rate of decline in Forced Vital Capacity (FVC) (in mL) over 52 weeks. Main secondary endpoints were absolute change from baseline in King's Brief Interstitial Lung Disease Questionnaire (K-BILD) total score at week 52, time to first acute ILD exacerbation or death over 52 weeks, and time to death over 52 weeks.
Patients had a mean (standard deviation [SD, Min-Max]) age of 65.8 (9.8, 27-87) years and a mean FVC percent predicted of 69.0% (15.6, 42-137). The underlying clinical ILD diagnoses in groups represented in the trial were hypersensitivity pneumonitis (26.1%), autoimmune ILDs (25.6%), idiopathic nonspecific interstitial pneumonia (18.9%), unclassifiable idiopathic interstitial pneumonia (17.2%), and other ILDs (12.2%).

Annual rate of decline in FVC
The annual rate of decline in FVC (in mL) over 52 weeks was significantly reduced by 107.0 mL in patients receiving Ofev compared to patients receiving placebo (Table 10) corresponding to a relative treatment effect of 57.0%.

Table 10 Annual rate of decline in FVC (mL) over 52 weeks

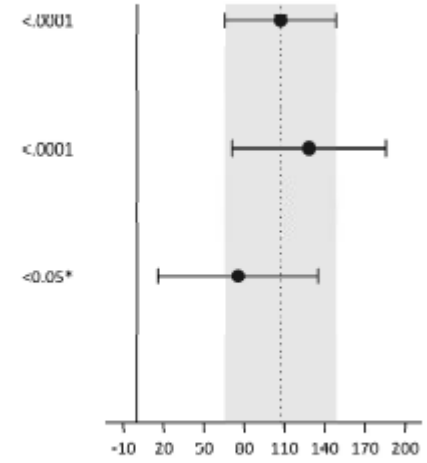
	Placebo	Ofev 150 mg twice daly
Number of analysed patients	331	332
Rate[1] (SE) of decline over 52 weeks	-187.8 (14.8)	-80.8 (15.1)
Comparison vs placebo		
Difference[1]		107.0
95% CI		(65.4, 148.5)
p-value		< 0.0001

[1]Based on a random coefficient regression 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

Similar results were observed in the co-primary population of patients with HRCT with UIP-like fibrotic pattern: the annual rate of decline in FVC was -211.1 mL/year in the placebo group (n=206) and -82.9 mL/year in the Ofev group (n=206). The difference between the treatment groups was 128.2 mL/year (95% CI: 70.8, 185.6; p<0.0001). Further, the treatment effect was consistent in the complementary population of patients with other HRCT fibrotic patterns. The annual rate of decline in FVC was -154.2 mL/year in the placebo group (n=125) and -79.0 mL/year in the Ofev group (n=126). The difference between the treatment groups was 75.2 mL/year (95% CI: 15.5, 135.0) with a nominal p-value <0.05 (p=0.014).

Figure 3 Forest plot of the annual rate of decline in FVC (mL) over 52 weeks in the patient populations

	N analysed		Estimate [95% CI]	p-value
	Placebo	Nintedanib 150bid		
Overall population	331	332	107.0 [65.4; 148.5]	<.0001
Co-primary population (Patients with HRCT with UIP-like fibrotic pattern)	206	206	128.2 [70.8; 185.6]	<.0001
Complementary population (Patients with other HRCT fibrotic patterns)	125	126	75.2 [15.5; 135.0]	<0.05*



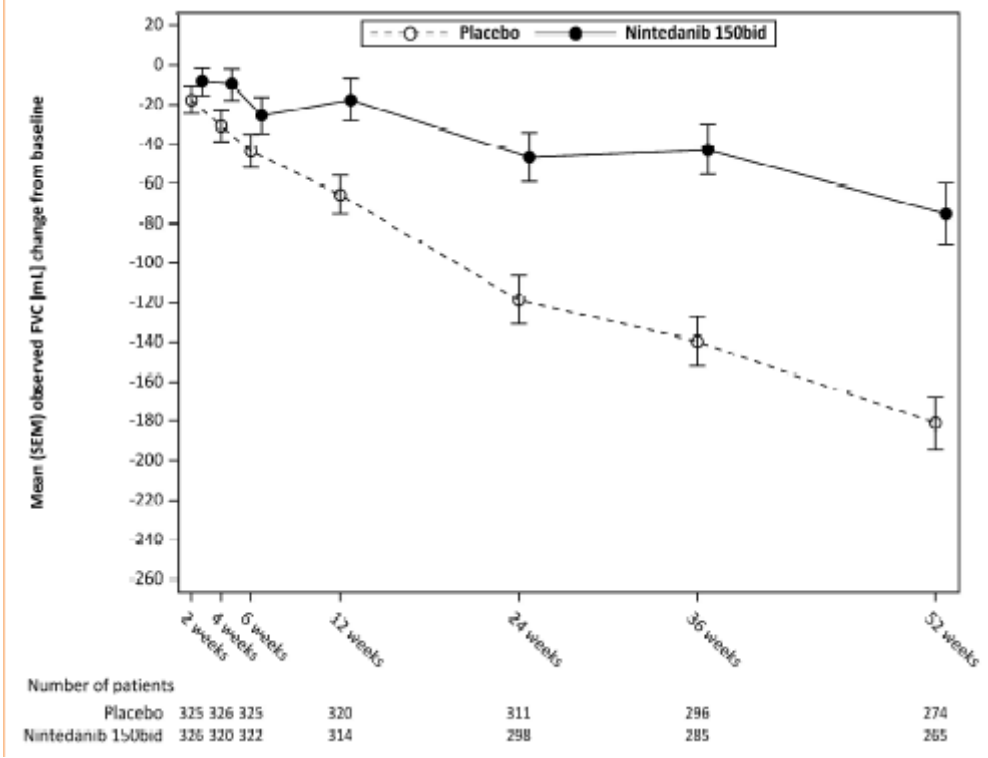
* nominal p-value (p=0.014)

bid=twice daily

The robustness of the effect of Ofev in reducing the annual rate of decline in FVC was confirmed in all pre-specified sensitivity analyses and consistent results were observed in all pre-specified subgroups (e.g. gender, age group, race, baseline FVC % predicted, and original underlying clinical ILD diagnosis in groups).

Figure 4 shows the evolution of change in FVC from baseline over time in the treatment groups.

Figure 4 Mean (SEM) observed FVC change from baseline (mL) over 52 weeks



bid=twice daily

In addition, favourable effects of Ofev were observed on the adjusted mean absolute change from baseline in FVC % predicted at week 52.The adjusted mean absolute change from baseline to week 52 in FVC % predicted was lower in the nintedanib group (-2.62%) than in the placebo group (-5.86%).

The adjusted mean difference between the treatment groups was 3.24 (95% CI: 2.09, 4.40, nominal p<0.0001).

FVC responder analysis

The proportion of FVC responders, defined as patients with a relative decline in FVC % predicted no greater than 5%, was higher in the Ofev group as compared to placebo. Similar results were observed in analyses using a threshold of 10% (Table 11).

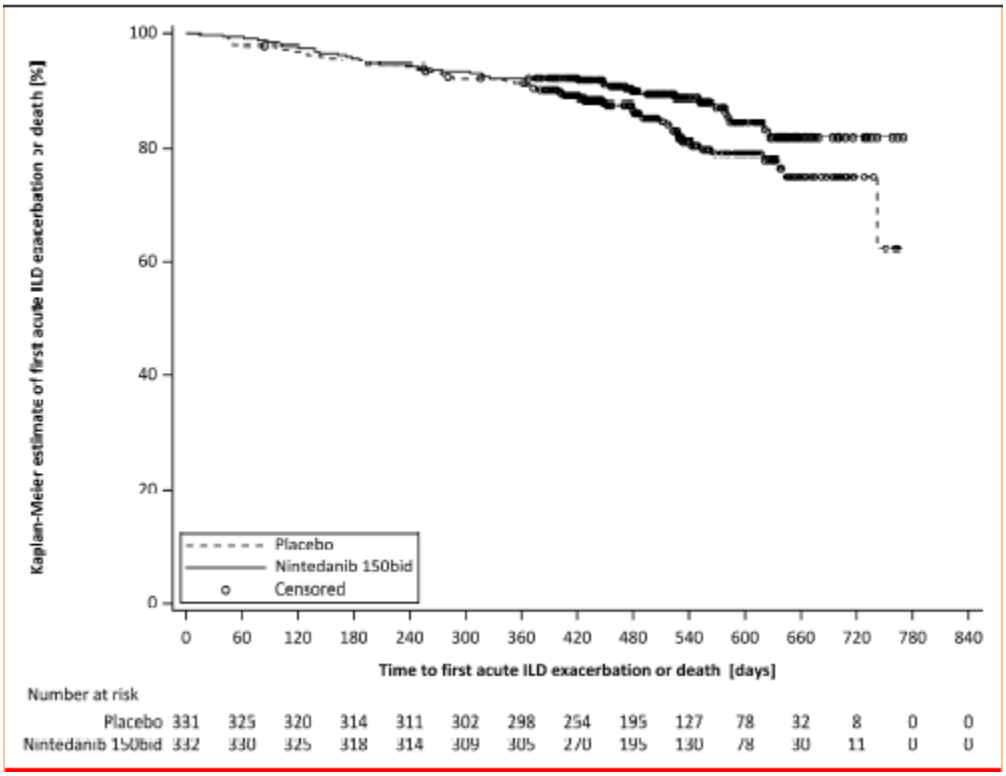
Table 11 Proportion of FVC responders at 52 weeks in INBUILD

	Placebo	Ofev 150 mg twice daily
Number of analysed patients	331	332
5% threshold		
Number (%) of FVC responders[1]	104 (31.4)	158 (47.6)
Comparison vs placebo		
Odds ratio[2]		2.01
95% CI		(1.46, 2.76)
Nominal p-value		< 0.0001
10% threshold		
Number of FVC responders1	169 (51.1)	197 (59.3)
Comparison vs placebo		
Odds ratio2		1.42
95% CI		(1.04, 1.94)

Nominal p-value		0.0268

[1]Responder patients are those with no relative decline greater than 5% or greater than 10% in FVC % predicted, depending on the threshold and with an FVC evaluation at 52 weeks (patients with missing data at Week 52 were considered as nonresponders).
[2]Based on a logistic regression model with continuous covariate baseline FVC % predicted and binary covariate HRCT pattern

Time to first acute ILD exacerbation or death
The proportion of patients with at least one event of first acute ILD exacerbation or death over 52 weeks was 7.8% in the Ofev group and 9.7% in the placebo group. The risk of having an event of first acute ILD exacerbation or death was numerically lower in the Ofev group compared to placebo: HR 0.80 (95% CI: 0.48, 1.34; nominal p=0.3948).
When analysing data over the whole trial, the risk of first acute ILD exacerbation or death further decreased in the Ofev group compared with the placebo group: the HR was 0.67 (95% CI: 0.46, 0.98; nominal p=0.0387), indicating a 33% reduction in the risk of first acute ILD exacerbation or death in patients receiving Ofev compared to placebo (Figure 5).
Figure 5 Kaplan–Meier plot of time to first acute ILD exacerbation or death over the whole trial.



bid = twice daily

Survival analysis
The proportion of patients who died over 52 weeks was 4.8% in the Ofev group compared to 5.1% in the placebo group. The HR was 0.94 (95% CI: 0.47, 1.86; nominal p=0.8544).
In the analysis of data over the whole trial, the risk of death was lower in the Ofev group compared to the placebo group. The HR was 0.78 (95% CI: 0.50, 1.21; nominal p=0.2594), indicating a 22% reduction in the risk of death in patients receiving Ofev compared to placebo.

Time to progression (≥ 10% absolute decline of FVC % predicted) or death
In the INBUILD trial, the risk of progression (≥ 10% absolute decline of FVC % predicted) or death was reduced for patients treated with Ofev. The proportion of patients with an event over 52 weeks was 25.6% in the Ofev group and 37.5% in the placebo group. The HR was 0.65 (95% CI: 0.49, 0.85; nominal p=0.0017).
In the analysis of data over the whole trial, the proportion of patients with an event of progression (≥ 10% absolute decline of FVC % predicted) or death was 40.4% in the Ofev group and 54.7% in the placebo group. The HR was 0.66 (95% CI: 0.53, 0.83; p= 0.0003), indicating a 34% reduction of the risk of progression (≥ 10% absolute decline of FVC % predicted) or death in patients receiving Ofev compared to placebo.

Quality of life
In the INBUILD trial health related quality of life at 52 weeks was measured using the:

- Absolute change from baseline in King's Brief Interstitial Lung Disease Questionnaire (KBILD) total score (range from 0-100, higher scores indicate a better health status)
- Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms dyspnoea domain score (range from 0-100, the higher the score the greater the impairment)
- Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms cough domain score (range from 0-100, the higher the score the greater the impairment)

The adjusted mean change from baseline in K-BILD total score at week 52 was -0.79 units in the placebo group and 0.55 in the Ofev group. The difference between the treatment groups was 1.34 (95% CI: -0.31, 2.98; nominal p=0.1115).

The adjusted mean absolute change from baseline in L-PF Symptoms dyspnoea domain score at week 52 was 4.28 in the Ofev group compared with 7.81 in the placebo group. The adjusted mean difference between the groups in favour of Ofev was -3.53 (95% CI: -6.14, -0.92; nominal p=0.0081).

The adjusted mean absolute change from baseline in L-PF Symptoms cough domain score at week 52 was -1.84 in the Ofev group compared with 4.25 in the placebo group. The adjusted mean difference between the groups in favour of Ofev was -6.09 (95% CI: -9.65, -2.53; nominal p=0.0008).

QT interval
In a dedicated study in renal cell cancer pateints, 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.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with **Ofev** in all studies of the paedriatic population in IPF.

PHARMACOKINETICS
The pharmacokinetics (PK) of nintedanib can be considered linear with respect to time (i.e. single-dose data can be extrapolated to multiple-dose data). Accumulation upon multiple administrations was 1.04-fold for C_{max} and 1.38-fold for AUC_{τ}. Nintedanib trough concentrations remained stable for more than one year.

Absorption
Nintedanib reached maximum plasma concentrations approximately 2 - 4 hours after oral administration as soft gelatin capsule under fed conditions (range 0.5 - 8 hours;). The absolute

bioavailability of a 100 mg dose was 4.69 % (90 % CI: 3.615 - 6.078) in healthy volunteers. Absorption and bioavailability are decreased by transporter effects and substantial first-pass metabolism.
Dose proportionality was shown by increase of nintedanib exposure (dose range 50 - 450 mg once daily and 150 - 300 mg twice daily). Steady state plasma concentrations were achieved within one week of dosing at the latest.
After food intake, nintedanib exposure increased by approximately 20 % compared to administration under fasted conditions (CI: 95.3 - 152.5 %) and absorption was delayed (median t_{max} fasted: 2.00 hours; fed: 3.98 h).

Distribution
Nintedanib follows at least bi-phasic disposition kinetics. After intravenous infusion, a high volume of distribution (V_{ss} : 1050 L, 45.0 % gCV) 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 0.869

Biotransformation
The prevalent metabolic reaction for nintedanib is hydrolytic cleavage by esterases resulting in the free acid moiety BIBF 1202. BIBF 1202 is subsequently glucuronidated by UGT enzymes, namely UGT 1A1, UGT 1A7, UGT 1A8, and UGT 1A10 to BIBF 1202 glucuronide. Only a minor extent of the biotransformation of nintedanib consisted of CYP pathways, with CYP 3A4 being the predominant enzyme involved. The major CYP-dependent metabolite could not be detected in plasma in the human ADME study. *In vitro*, CYP-dependent metabolism accounted for about 5 % compared to about 25 % ester cleavage.

Elimination
Total plasma clearance after intravenous infusion was high (CL: 1390 mL/min, 28.8 % gCV). Urinary excretion of the unchanged active substance within 48 hours was about 0.05 % of dose (31.5 % gCV) after oral and about 1.4 % of the dose (24.2 % gCV) after intravenous administration; the renal clearance was 20 mL/min (32.6 % gCV). The major route of elimination of drug related radioactivity after oral administration of [^{14}C] nintedanib was via faecal/biliary excretion (93.4 % of dose, 2.61 % gCV). The contribution of renal excretion to the total clearance was low (0.649 % of dose, 26.3 % gCV). The overall recovery was considered complete (above 90 %) within 4 days after dosing. The terminal half-life of nintedanib was between 10 and 15 h (gCV % approximately 50 %).

Exposure-response relationship
Exposure–response analyses of patients with IPF, other chronic fibrosing ILDs with a progressive phenotype, and SSc-ILD indicated an E_{max}-like relationship between exposure and the annual rate of decline in FVC with an EC_{50} of around 3-5 ng/mL (relative standard errors: around 55%). For comparison, median observed nintedanib trough concentrations for 150 mg bid Ofev were about 10 ng/ml.
With respect to safety, there seemed to be a weak relationship between nintedanib plasma exposure and ALT and/or AST elevations. Actual administered dose might be the better predictor for the risk of developing diarrhea of any intensity, even if plasma exposure as risk determining factor could not be ruled out.(see section ***Special Warnings and Precautions***).

Intrinsic and Extrinsic Factors; Special Populations
The PK properties of nintedanib were similar in healthy volunteers, patients with IPF, patients with other chronic fibrosing ILDs with a progressive phenotype, patients with SSc-ILD, and

cancer patients. Based on results of Population PK (PopPK) analyses and descriptive investigations, exposure to nintedanib was not influenced by sex (body weight corrected), mild and moderate renal impairment (estimated by creatinine clearance), liver metastases, ECOG performance score, alcohol consumption, or P-gp genotype. Population PK analyses indicated moderate effects on exposure to nintedanib depending on following intrinsic and extrinsic factors. Based on the high inter-individual variability of exposure observed in the clinical trials these effects are not considered clinically relevant (see section ***Special Warnings and Precautions***).

Age

Exposure to nintedanib increased linearly with age. $AUC_{\tau,ss}$ decreased by 16 % for a 45-year old patient (5^{th} percentile) and increased by 13 % for a 76-year old patient (95^{th} percentile) relative to a patient with the median age of 62 years. The age range covered by the analysis was 29 to 85 years; approximately 5 % of the population was older than 75 years.
Studies in paediatric populations have not been performed.

Body weight

An inverse correlation between body weight and exposure to nintedanib was observed. $AUC_{\tau,ss}$ increased by 25 % for a 50 kg patient (5^{th} percentile) and decreased by 19 % for a 100 kg patient (95^{th} percentile) relative to a patient with the median weight of 71.5 kg.

Race

The population mean exposure to nintedanib was 33 - 50 % higher in Chinese, Taiwanese, and Indian patients and 16 % higher in Japanese patients while it was 16 - 22 % lower in Koreans compared to Caucasians (body weight corrected).

Data from Black individuals was very limited but in the same range as for Caucasians.

Hepatic impairment

In a dedicated single dose phase I study and compared to healthy subjects, exposure to nintedanib based on Cmax and AUC was 2.2-fold higher in volunteers with mild hepatic impairment (Child Pugh A; 90% CI 1.3 – 3.7 for Cmax and 1.2 – 3.8 for AUC, respectively). In volunteers with moderate hepatic impairment (Child Pugh B), exposure was 7.6-fold higher based on Cmax (90% CI 4.4 – 13.2) and 8.7-fold higher (90% CI 5.7-13.1) based on AUC, respectively, compared to healthy volunteers.
Subjects with severe hepatic impairment (Child Pugh C) have not been studied.

Concomitant treatment with pirfenidone

Concomitant treatment of nintedanib with pirfenidone was investigated in a parallel group design study in Japanese patients with IPF. Twenty four patients were treated for 28 days with 150 mg nintedanib bid. In 13 patients, nintedanib was added to chronic treatment with standard doses of pirfenidone. Eleven patients received nintedanib monotherapy. The exposure to nintedanib tended to be lower when nintedanib was administered on top of pirfenidone compared to administration of nintedanib alone. Nintedanib had no effect on the PK of pirfenidone. Due to the short duration of concomitant exposure and low number of patients no conclusion on the safety and efficacy of the combination can be drawn.

Concomitant treatment with bosentan

In a dedicated pharmacokinetic study, concomitant treatment of Ofev with bosentan was investigated in healthy volunteers. Subjects received a single dose of 150 mg Ofev before and after multiple dosing of 125 mg bosentan twice daily at steady state. The adjusted geometric

mean ratios (90% confidence interval (CI)) were 103% (86% - 124%) and 99% (91% - 107%) for Cmax and AUC0-tz of nintedanib, respectively (n=13), indicating that co-administration of nintedanib with bosentan did not alter the pharmacokinetics of nintedanib.

Concomitant treatment with oral hormonal contraceptives

In a dedicated pharmacokinetic study, female patients with SSc-ILD received a single dose of a combination of 30 µg ethinylestradiol and 150 µg levonorgestrel before and after twice daily dosing of 150 mg nintedanib for at least 10 days. The adjusted geometric mean ratios (90% confidence interval (CI)) were 117% (108% - 127%; C_{max}) and 101% (93% - 111%; AUC_{0-tz}) for ethinylestradiol and 101% (90% - 113%; C_{max}) and 96% (91% - 102%; AUC_{0-tz}) for levonorgestrel, respectively (n=15), indicating that co-administration of nintedanib has no relevant effect on the plasma exposure of ethinylestradiol and levonorgestrel.

Drug-Drug Interaction Potential

Metabolism

Drug-drug interactions between nintedanib and CYP substrates, CYP inhibitors, or CYP inducers are not expected, since nintedanib, BIBF 1202, and BIBF 1202 glucuronide did not inhibit or induce CYP enzymes preclinically nor was nintedanib metabolized by CYP enzymes to a relevant extent.

Transport

Nintedanib is a substrate of P-gp. For the interaction potential of nintedanib with this transporter, see section ***Interactions***. Nintedanib was shown to be not a substrate or inhibitor of OATP-1B1, OATP-1B3, OATP-2B1, OCT-2 or MRP-2 *in vitro*. Nintedanib was also not a substrate of BCRP. Only a weak inhibitory potential on OCT-1, BCRP, and P-gp was observed *in vitro* which is considered to be of low clinical relevance. The same applies for nintedanib being a substrate of OCT-1.

TOXICOLOGY

General toxicology

Single dose toxicity studies in rats and mice indicated a low acute toxic potential of nintedanib.
In repeat dose toxicology studies in rats, adverse effects (e.g. thickening of epiphyseal plates, lesions of the incisors) were mostly related to the mechanism of action (i.e. VEGFR-2 inhibition) of nintedanib. These changes are known from other VEGFR-2 inhibitors and can be considered class effects.
Diarrhoea and vomiting accompanied by reduced food consumption and loss of body weight were observed in toxicity studies in non-rodents.
There was no evidence of liver enzyme increases in rats, dogs, and Cynomolgus monkeys. Mild liver enzyme increases which were not due to serious adverse effects such as diarrhoea were only observed in Rhesus monkeys.

Reproduction toxicity

A study of male fertility and early embryonic development up to implantation in rats did not reveal effects on the male reproductive tract and male fertility.

In rats, embryo-foetal lethality and teratogenic effects were observed at exposure levels below human exposure at the maximum recommended human dose (MRHD) of 150 mg twice daily. Effects on the development of the axial skeleton and on the development of the great arteries were also noted at subtherapeutic exposure levels.

In rabbits, embryo-foetal lethality and teratogenic effects comparable to those in rats were observed at an exposure slightly higher than in rats.

In rats, small amounts of radiolabelled nintedanib and/or its metabolites were excreted into the milk (≤ 0.5 % of the administered dose).
From the 2-year carcinogenicity studies in mice and rats, there was no evidence for a carcinogenic potential of nintedanib.

Genotoxicity studies indicated no mutagenic potential for nintedanib.

SPECIAL PRECAUTIONS FOR DISPOSAL
Any unused medicinal product or waste material should be disposed of in accordance with local requirement.

Availability :
Soft Capsules 100 g
Box, 6 Alu Blisters @ 10 Soft Capsules Reg. No: DKI1752503502A1

Soft Capsules 150 mg
Box, 6 Alu Blisters @ 10 Soft Capsules Reg. No: DKI1752503502B1

Storage conditions :
Store below 25°C, in a safe place, out of the reach of children
Store in the original package in order to protect from moisture and light.

Only on doctor's prescription
Harus dengan resep dokter

Bulk Manufactured by :
Catalent Germany Eberbach GmbH, Eberbach, Germany

Packed and Released by :
Boehringer Ingelheim Pharma GmbH & Co. KG
Ingelheim am Rhein
Germany

For :
Boehringer Ingelheim International GmbH
Ingelheim am Rhein, Germany

Imported by :
PT Boehringer Ingelheim Indonesia
Bogor, Indonesia

MENGANDUNG BABI

B. LEMBAR INFORMASI OBAT

Lembar informasi obat: Informasi untuk pasien

Ofev kapsul 100 mg dan 150 mg
Nintedanib

▼ Obat ini merupakan obat dalam pengawasan khusus. Hal ini memungkinkan didapatkannya informasi baru keamanan obat secara cepat. Anda dapat membantu dengan melaporkan semua efek samping yang terjadi. Lihat bagian akhir bab 4 untuk cara pelaporan efek samping obat.

Bacalah lembar informasi ini sebelum mulai mengkonsumsi obat ini. Informasi dalam lembar ini penting bagi Anda.
- Simpanlah lembar informasi ini. Anda mungkin akan perlu membacanya lagi.
- Jika Anda membutuhkan informasi lebih lanjut, tanyakanlah pada dokter ataupun apoteker Anda.
- Obat ini diresepkan hanya untuk Anda. Jangan berikan pada orang lain karena dapat membahayakan mereka walaupun tanda dan gejala yang dialami serupa dengan Anda.
- Jika Anda mengalami efek samping, konsultasikan dengan dokter Anda atau apoteker Anda, termasuk jika efek samping yang dialami belum ada dalam daftar pada leaflet ini. Lihat bab 4.

Apa saja yang ada pada leaflet ini

1. Apa itu Ofev dan indikasi pemberiannya

Kapsul Ofev mengandung bahan aktif yang disebut dengan nintedanib.
Nintedanib digunakan untuk mengobati Fibrosis Paru Idiopatik / *Idiopathic Pulmonary Fibrosis* (FPI / *IPF*), untuk mengurangi laju penurunan fungsi paru pada pasien dewasa penderita *systemic sclerosis-associated interstitial lung disease (SSc-ILD),* dan untuk mengobati fibrosis kronis dari penyakit paru interstitial lainnya dengan jenis fenotipe yang terus berkembang (*progressive phenotype*).

IPF adalah suatu kondisi bila jaringan paru anda menjadi tebal, kaku dan berubah menjadi jaringan parut seiring waktu. Jaringan parut mengurangi kemampuan mentransfer oksigen dari paru kedalam aliran darah dan akibatnya anda menjadi sulit bernapas dalam. Ofev membantu mengurangi terbentuknya jaringan parut dan kekakuan paru Anda.

Systemic sclerosis (SSc), juga dikenal sebagai skleroderma, adalah penyakit autoimun langka yang bersifat kronis yang bisa terjadi pada banyak jaringan tubuh. *SSc* menyebabkan fibrosis (terbentuknya jaringan parut dan kaku) pada kulit dan organ dalam seperti paru-paru. Ketika paru-paru terkena fibrosis, disebut dengan istilah *Insterstitial Lung Disease (ILD),* maka kondisi seperti ini dinamakan *SSc-ILD*. Fibrosis pada paru-paru mengurangi kemampuan untuk mentransfer oksigen ke dalam aliran darah dan juga kemampuan bernapas. OFEV membantu mengurangi terjadinya jaringan parut dan kekakuan pada paru-paru.

Selain IPF, terdapat juga kondisi dimana jaringan paru menjadi lebih tebal, kaku, dan berkembang menjadi jaringan parut (fibrosis paru) dan terus memburuk (*progressive*

phenotype). Contohnya adalah pada kondisi dimana terjadi radang akibat hipersensitifitas paru, ILD karena autoimun (rheumatoid arthtritis karena ILD), pneumonia idiopatik yang tidak spesifik atau tidak terklasifikasi, dan ILD lainnya. Ofev membantu mengurangi perkembangan tebantuknya jaringan parut dan kaku pada paru.

2. Apa yang perlu Anda ketahui sebelum mengonsumsi Ofev

Jangan konsumsi Ofev jika Anda:

- Memiliki alergi terhadap nintedanib atau komponen lain yang terkandung dalam obat ini (diuraikan dalam bab 6), dan jika anda hamil.

Kapsul tidak boleh dibuka atau dihancurkan. Jika terjadi kontak dengan isi kapsul, tangan harus segera dicuci dan dibersihkan.

Peringatan dan hal yang perlu diperhatikan

Konsultasikan dengan dokter ataupun apoteker Anda sebelum mulai mengonsumsi obat ini, Sampaikan kepada dokter atau apoteker anda sebelum anda menggunakan Ofev,

- Bila anda sedang mengalami atau memiliki riwayat masalah hati.
- Bila anda sedang mengalami atau memiliki riwayat masalah perdarahan.
- Bila anda sedang menggunakan obat pengencer darah (seperti warfarin, phenprocoumon atau heparin) untuk mencegah pembekuan darah.
- Bila anda sedang mengalami atau memiliki riwayat penyakit jantung (contohnya serangan jantung).
- Bila anda baru saja menjalani pembedahan. Nintedanib dapat mempengaruhi penyembuhan luka anda, oleh karena itu pengobatan anda dengan nintedanib biasanya dihentikan sementara ketika anda menjalani pembedahan. Dokter yang akan memutuskan kapan anda bisa melanjutkan kembali pengobatan anda.
- Bila anda sedang atau pernah mengalami masalah dengan ginjal anda.
- Bila anda mempunyai tekanan darah tinggi.
- Bila anda mempunyai tekanan darah tinggi yang tidak normal dalam pembuluh darah paru (pulomary hypertension).
- Bila anda mempunyai aneurisme (perbesaran atau perlemahan dinding pembuluh darah atau robeknya dinding pembuluh darah).

Berdasarkan informasi ini dokter anda akan melakukan beberapa tes darah, seperti memeriksa fungsi hati. Dokter akan mendiskusikan hasil tes ini dengan anda dan memutuskan apakah anda dapat menerima Ofev.

Segera hubungi dokter Anda jika terjadi hal-hal berikut ini saat Anda masih mengonsumsi obat ini,

- Bila anda mengalami diare. Mengobati diare secara dini adalah penting (lihat bagian 4);
- Bila anda mengalami muntah atau merasa mual (nausea).
- Bila anda mengalami nyeri hebat di area lambung, demam, menggigil, mual, muntah atau kram perut atau kembung, karena ini dapat merupakan gejala perforasi (lubang) pada dinding usus anda (perforasi gastrointestinal).
- Bila anggota tubuh anda mengalami nyeri, bengkak, kemerahan, teraba lebih panas dibandingkan anggota tubuh lainnya karena ini dapat merupakan gejala terdapatnya bekuan darah pada salah satu vena anda (salah satu jenis pembuluh darah).
- Bila anda mengalami rasa tertekan pada dada, nyeri, khususnya pada sisi kiri tubuh, nyeri pada leher, rahang, bahu atau lengan, berdebar (detak jantung cepat), sesak napas, mual, muntah karena ini dapat merupakan gejala dari serangan jantung.
- Bila anda mengalami perdarahan hebat.

- Bila anda mengalamai gejala yang tidak jelas seperti terjadinya warna kuning pada kulit atau pada bagian putih mata (jaundice), warna urin yang gelap atau coklat (seperti warna teh), nyeri pada bagian kanan atas perut anda (abdomen), perdarahan atau luka yang lebih mudah terjadi dibandingkan biasanya, atau merasa kelelahan. Hal ini bisa jadi merupakan gejala penyakit hati yang serius.

Anak dan dewasa
Ofev tidak boleh digunakan oleh anak dan dewasa usia dibawah 18 tahun.

Penggunaan obat lain beserta Ofev
Beritahukan kepada dokter atau apoteker bila anda sedang menggunakan, akhir-akhir ini menggunakan atau mungkin menggunakan obat apapun, termasuk obat herbal dan obat yang diperoleh tanpa resep dokter.

Ofev dapat berinteraksi dengan obat lainnya. Obat berikut ini adalah contoh yang dapat meningkatkan kadar Nintedanid (zat aktif Ofev) dalam darah, sehingga dapat meningkatkan risiko efek tidak diinginkan (lihat Bagian 4):
- Obat yang digunakan untuk mengobati infeksi jamur (ketokonazol)
- Obat yang digunakan untuk mengobati infeksi bakterial (eritromisin)
- Obat yang mempengaruhi sistem imun (siklosporin)

Obat berikut ini adalah contoh yang dapat menurunkan kadar Nintedanib dalam darah, sehingga dapat menyebabkan berkurangnya efektivitas Ofev:
- Antibiotika yang digunakan untuk mengobati tuberkulosis (rifampisin)
- Obat untuk mengobati kejang (karbamazepin, fenitoin)
- Obat herbal untuk mengobati depresi (St. John's Wort)

Kehamilan, menyusui dan fertilitas
Kehamilan
Jika Anda sedang hamil atau menyusui, atau menduga hamil, atau berencana hamil, konsultasikan pada dokter atau apoteker Anda sebelum mulai mengonsumsi obat ini.

Jangan mengonsumsi obat ini selama hamil karena dapat menyebabkan gangguan janin.

Metode kontrasepsi yang efektif harus digunakan pasien yang mengonsumsi Ofev sampai dengan 3 bulan setelah mengonsumsi dosis terakhir. Konsultasikan segera dengan dokter Anda jika kehamilan terjadi saat sedang mengonsumsi Ofev.

Menyusui
Pemberian ASI dari ibu yang mengonsumsi Ofev tidak dianjurkan karena terdapat risiko yang mungkin berbahaya pada bayi.

Fertilitas / kesuburan
Pengaruh obat ini pada tingkat fertilitas/kesuburan belum diketahui.

Mengemudikan kendaraan bermotor dan mengoperasikan mesin
Ofev mungkin memiliki pengaruh minimal terhadap kemampuan mengemudikan kendaraan bermotor dan mengoperasikan mesin. Anda tidak dianjurkan mengemudikan kendaraan bermotor dan mengoperasikan mesin jika merasa sakit/mual.

Ofev mengandung soya lecithin

Obat ini mengandung soya lecithin. Bila anda alergi terhadap kedelai atau kacang, jangan gunakan obat ini (lihat bagian 2).

3. Bagaimana cara mengonsumsi Ofev

Selalu menggunakan obat ini dengan tepat sesuai dengan instruksi dokter atau apoteker anda. Tanyakan kepada dokter atau apoteker anda bila anda tidak yakin.

Dosis yang direkomendasikan adalah dua kapsul 100 mg per hari atau dua kapsul 150 mg per hari. Gunakan satu kapsul dua kali sehari dengan jarak 12 jam pada waktu yang sama setiap harinya, contohnya satu kapsul pada pagi hari dan satu kapsul pada malam hari. Hal ini memastikan bahwa kadar nintedanib dalam aliran darah tetap terjaga. Telanlah seluruh kapsul dengan air putih dan jangan dikunyah atau digerus. Direkomendasikan untuk menelan kapsul bersama dengan makanan, contohnya ketika atau segera sebelum atau setelah makan.

Jangan gunakan Ofev lebih dari dosis maksimum yang direkomendasikan yaitu dua kapsul 100 mg per hari atau dua kapsul 150 mg per hari.

Bila anda tidak dapat menoleransi dosis yang direkomendasikan yaitu dua kapsul 100 mg per hari atau dua kapsul 150 mg per hari (lihat kemungkinan efek tidak diinginkan dalam bagian 4) maka dokter mungkin akan menghentikan pengobatan. Jangan mengurangi dosis atau menghentikan pengobatan sendiri tanpa berkonsultasi dengan dokter anda.

Bila anda menelan Ofev lebih banyak dari yang seharusnya
Hubungi dokter atau apoteker anda segera.

Bila anda lupa menelan Ofev
Jangan minum dosis ganda untuk menggantikan dosis yang terlupa. Telanlah dosis Ofev selanjutnya sesuai jadwal yang telah direncanakan dan dosis yang telah direkomendasikan oleh dokter atau apoteker anda.

Bila anda ingin berhenti menggunakan Ofev
Jangan berhenti menelan Ofev tanpa berkonsultasi dengan dokter anda terlebih dahulu. Penting bahwa anda menelan Ofev setiap hari selama dokter anda meresepkannya untuk anda.

Bila anda memiliki pertanyaan lebih lanjut mengenai cara menggunakan obat ini, tanyakan kepada dokter atau apoteker anda.

4. Efek samping yang mungkin terjadi

Seperti obat-obatan lainnya, obat ini memiliki efek samping, walaupun tidak semuanya terjadi pada setiap orang.
Anda perlu memperhatikan apakah efek samping berikut ini terjadi pada Anda selama terapi Ofev diberikan:

Diare (*sangat sering, dapat dialami lebih dari 1 orang dari 10 orang*):
Diare dapat menyebabkan hilangnya cairan dan garam penting (elektrolit, seperti natrium atau kalium) dalam tubuh anda. Pada saat anda mengalami tanda-tanda diare pertama segeralah minum banyak cairan dan hubungi dokter anda. Mulailah pengobatan antidiare yang tepat, contohnya loperamide, sesegera mungkin.

Efek tidak diinginkan berikut ini terjadi ketika dalam pengobatan dengan obat ini:
Efek tidak diinginkan yang sangat sering terjadi (dapat dialami lebih dari 1 orang dari 10 orang)
- Diare
- Merasa mual (nausea)
- Nyeri pada bagian bawah perut (abdomen)
- Berubahnya nilai enzim hati pada tes darah dari nilai normal
- Muntah
- Alanine aminotransferase meningkat

Efek tidak diinginkan yang sering terjadi (dapat dialami 1 dari 10 orang)
- Menurunnya nafsu makan
- Menurunnya berat badan
- Tekanan darah tinggi (hipertensi)
- Perdarahan
- Muntah
- Sakit kepala
- Cedera hati akibat obat
- Alanine aminotransferase meningkat
- Aspartat aminotransferase meningkat
- Gamma-glutamyltransferase meningkat
- Alkali fosfatase darah meningkat
- Ruam

Efek tidak diinginkan yang tidak sering terjadi (dapat dialami hingga 1 dari 100 orang)
- Angka platelet rendah (trombositopenia)
- Dehidrasi
- Infark miokard
- Tekanan darah tinggi (hipertensi)
- Pankreatitis
- Radang usus besar
- Gagal ginjal
- Cedera hati akibat obat
- Penyakit kuning (hiperbilirubinemia), yaitu perubahan kulit berwarna kekuningan dan warna kekuningan pada bagian putih mata yang disebabkan oleh tingginya kadar bilirubin darah
- Ruam
- Gatal
- Alopecia
- Proteinuria

Melaporkan efek tidak diinginkan
Bila anda mengalami efek tidak diinginkan, sampaikan kepada dokter atau apoteker Anda, termasuk efek apapun yang anda alami meskipun tidak tertulis dalam leaflet ini. Anda juga dapat melaporkan langsung efek tidak diinginkan. Dengan melaporkan efek tidak diinginkan anda dapat membantu menyediakan lebih banyak informasi mengenai keamanan obat ini.

5. Bagaimana cara penyimpanan Ofev yang baik
Jauhkan obat ini dari jangkauan anak-anak.

Jangan menggunakan obat ini setelah tanggal kadaluarsa yang tertulis pada karton/blister. Tanggal kadaluarsa merujuk pada hari terakhir dari bulan tersebut.

Jangan simpan Ofev diatas suhu 25°C. Simpanlah dalam kemasan aslinya untuk melindungi dari kelembaban.

Jangan gunakan obat ini jika Anda melihat bahwa ada blister/kemasan yang mengandung kapsul yang terbuka atau rusak.

Jangan buang sisa obat ke pembuangan air/limbah rumah tangga. Tanyakan pada apoteker Anda bagaimana cara pembuangan obat yang sudah tidak digunakan lagi secara aman. Hal ini akan membantu melindungi lingkungan dari polusi zat kimia.

6. Isi kemasan dan informasi lainnya

Kandungan Ofev kapsul 100 mg

Bahan aktif Ofev adalah nintedanib. Setiap kapsul 100 mg Ofev mengandung 100 mg nintedanib (dalam bentuk esilate).

Bahan nonaktif :

Isi kapsul	:	Trigliserida, lemak padat rantai sedang, lesitin soya (E322)
Cangkang kapsul	:	Gelatin, gliserol (85 %), titanium dioxida (E171), besi oksida merah (E172), besi oksida kuning (E172), tinta hitam (Opacode)
Tinta cetak	:	*Shellac glaze*, besi oksida hitam (E172), propilen glikol (E1520)

Kandungan Ofev kapsul 150 mg

Bahan aktif Ofev adalah nintedanib. Setiap kapsul 150 mg Ofev mengandung 150 mg nintedanib (dalam bentuk esilate).

Bahan nonaktif :

Isi kapsul	:	Trigliserida, lemak padat rantai sedang, lesitin soya (E322)
Cangkang kapsul	:	Gelatin, gliserol (85 %), titanium dioxida (E171), besi oksida merah (E172), besi oksida kuning (E172), tinta hitam (Opacode)
Tinta hitam	:	*Shellac glaze*, besi oksida hitam (E172), propilen glikol (E1520)

Tampilan kapsul 100 mg Ofev dan isi kemasan

Ofev kapsul 100 mg berwarna *peach*, opak, kapsul oblong, dengan logo Boehringer Ingelheim tercetak hitam di salah satu sisinya dengan simbol perusahaan dan angka “100”.

Satu kotak berisi 6 blister alumunium Ofev kapsul 100 mg. Setiap blister mengandung 10 kapsul.

Tampilan kapsul 150 mg Ofev dan isi kemasan

Ofev kapsul 150 mg berwarna kecoklatan, opak, kapsul oblong, dengan logo Boehringer Ingelheim tercetak hitam di salah satu sisinya dengan simbol perusahaan dan angka “150”.

Satu kotak berisi 6 blister alumunium Ofev kapsul 150 mg. Setiap blister mengandung 10 kapsul.

Kemasan yang tersedia:

Kapsul lunak 100 g
Dus, 6 Alublister @ 10 kapsul lunak Reg. No: DKI1752503502A1

Kapsul lunak 150 mg
Dus, 6 Alu Blister @ 10 kapsul lunak Reg. No: DKI1752503502B1

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Harus dengan resep dokter.

MENGANDUNG BABI