

1. NAME OF THE MEDICINAL PRODUCT

OFEV Soft Capsules 100 mg
OFEV Soft Capsules 150 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One capsule contains 100 mg nintedanib (as esilate)
One capsule contains 150 mg nintedanib (as esilate)

Excipient of animal origin: Gelatin (porcine)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsule.

100 mg capsules: Peach-colored, opaque, oblong, soft gelatin capsules, marked with dark grey on one side with Boehringer Ingelheim company symbol and with "100", and containing a bright yellow viscous suspension.

150 mg capsules: Brown-colored, opaque, oblong, soft gelatin capsules, marked with dark grey on one side with Boehringer Ingelheim company symbol and with "150", and containing a bright yellow viscous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

OFEV is indicated in adults for the treatment of Idiopathic Pulmonary Fibrosis (IPF).

OFEV is also indicated in adults for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype (see section 5.1 "Clinical Efficacy and Safety").

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

4.2 Posology and Method of Administration

Adults

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

Posology

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 take an additional dose. The recommended maximum daily dose of 300 mg should not be exceeded.

Dose adjustments

In addition to symptomatic treatment if applicable, the management of adverse effects to OFEV (see section 4.4 and 4.8) 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) (see sections 4.4 and 4.8).

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 (see section 5.2).

Renal impairment

Less than 1 % of a single dose of nintedanib is excreted via the kidney (see section 5.2). 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 CrCL).

Hepatic Impairment

Nintedanib is predominantly eliminated via biliary/faecal excretion (> 90 %). Exposure increased in patients with hepatic impairment (Child Pugh A, Child Pugh B; see section 5.2). 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 in patients with hepatic impairment classified as Child Pugh B and C. Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with OFEV is not recommended (see section 5.2).

Paediatric population

Treatment of paediatric patients with nintedanib for fibrosing Interstitial Lung Diseases (ILDs) is not registered.

Method of administration

OFEV is for oral use. The capsules should be taken with food, swallowed whole with water, and should not be chewed.

OFEV capsules may be taken with a small amount (teaspoonful) of cold or room temperature soft food, such as apple sauce or chocolate pudding, and must be swallowed unchewed immediately, to ensure the capsule stays intact.

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

4.3 Contraindications

- Pregnancy (see section 4.6)

- Hypersensitivity to nintedanib, to peanut or soya, or to any of the excipients listed in section 6.1.

4.4 Special Warnings and Precautions for Use

Gastrointestinal disorders

Diarrhoea

In the clinical trials (see section 5.1), 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 SENSICIS 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 to discontinuation of OFEV in 6.9% of the patients (see section 4.8).

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 gastrointestinal adverse reactions (see section 4.8). 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 SENSICIS trial, the frequency of nausea and vomiting leading to OFEV discontinuation were 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 section 4.2). 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 sections 4.2 and 5.2).

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, alkaline phosphatase (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 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 resumed at 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 4.2). 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 (< 65kg), 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 5.2).

Close monitoring is recommended in patients with these risk factors.

Haemorrhage

Vascular endothelial growth factor receptor (VEGFR) inhibition might be associated with an increased risk of bleeding.

In the clinical trials in adult patients 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 8.3% for SENSICIS). Non-serious epistaxis was the most frequent bleeding event reported. Serious bleeding events occurred with low frequencies in the 2 treatment groups (OFEV 1.3% versus placebo 1.4% for INPULSIS; OFEV 0.9% versus placebo 1.5% for INBUILD; OFEV 1.4% versus placebo 0.7% for SENSICIS).

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.

Cases of haemorrhage have been reported in post-marketing period (including patients with or without anticoagulant therapy or other drugs that could cause bleeding). 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 in adult patients, 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 SENSICIS). 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 groups. In the INBUILD and the SENSICIS trial, myocardial infarction was observed with low frequency: OFEV 0.9% versus placebo 0.9% for INBUILD; OFEV 0% versus placebo 0.7% for SENSICIS.

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 ischemia.

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.

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 and ischaemic colitis

In the clinical trials, the frequency of patients with perforation was up to 0.3% in both treatment groups. Due to the mechanism of action nintedanib, patients might have an increased risk of gastrointestinal perforations. Cases of gastrointestinal perforations and cases of ischaemic colitis, 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, previous history of peptic ulceration, diverticular disease or receiving concomitant corticosteroids or NSAIDs. OFEV should only be initiated at least 4 weeks after abdominal surgery. Therapy with OFEV should be permanently discontinued in patients who develop gastrointestinal perforation or ischaemic colitis. Exceptionally, Ofev can be reintroduced after complete resolution of ischaemic colitis and careful assessment of patient's condition and other risk factors.

Hypertension

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

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 OFEV was discontinued. Treatment interruption should be considered in patients who develop signs or symptoms of nephrotic syndrome.

Posterior reversible encephalopathy syndrome (PRES)

Very few cases of posterior reversible encephalopathy syndrome (PRES) have been reported post-marketing.

PRES is a neurological disorder which can present with headache, visual disturbances, seizure, lethargy, confusion and other neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES.

If PRES is suspected, nintedanib treatment must be discontinued. The safety of reinitiating nintedanib therapy in patients previously experiencing PRES is not known.

Wound healing complication

No increased frequency of impaired wound healing was observed in the clinical trials. Based on the mechanism of action nintedanib may impair wound healing. 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.

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 (Section 5.1). 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 QTc 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.

4.5 Interaction with other medicinal products and other forms of interaction

P-glycoprotein (P-gp)

Nintedanib is a substrate of P-gp (see section 5.2). 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, erythromycin or cyclosporine) 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 4.2).

Potent P-gp inducers (e.g. rifampicin, carbamazepine, phenytoin, and St. John's Wort) may decrease exposure to nintedanib. Selection of an alternate concomitant medicinal product with no or minimal P-gp induction potential should be considered.

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 5.2). The likelihood of drug-drug interactions with nintedanib based on CYP metabolism is therefore considered to be low.

Co-administration with other medicinal products

Co-administration of nintedanib with bosentan did not alter the pharmacokinetics of nintedanib (see section 5.2).

Co-administration of nintedanib with oral hormonal contraceptives did not alter the pharmacokinetics of oral hormonal contraceptives to a relevant extent (see section 5.2).

4.6 Fertility, Pregnancy and Lactation

Women of childbearing potential / Contraception

Nintedanib may cause foetal harm in humans (see section 5.3). Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV and to use highly effective contraceptive methods at the 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 active substance (see section 5.3). As nintedanib may cause foetal harm also in humans, it must not be applied during pregnancy (see section 4.3) and pregnancy testing must be conducted prior to treatment with OFEV and during treatment as appropriate.

Female patients should be advised to notify their doctor or pharmacist if they become pregnant during therapy with OFEV.

If the patient becomes pregnant while receiving OFEV, treatment must be discontinued and the patient should be apprised of the potential hazard to the foetus.

Breast-feeding

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 ($\leq 0.5\%$ 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.

Fertility

Based on preclinical investigations, there is no evidence for impairment of male fertility (see section 5.3). 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 5.3).

4.7 Effects on Ability to Drive and Use Machines

OFEV has minor influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines during treatment with OFEV.

4.8 Undesirable Effects

Summary of the safety profile

Clinical trial in adult patients

OFEV has been studied in clinical trials including 1,529 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 5.1 "Clinical Efficacy and Safety").

For the management of selected adverse reactions see section 4.4.

Tabulated list of adverse reactions

The below table provides 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 pooled from the two placebo-controlled Phase III INPULSIS trials of 52 weeks duration (638 patients with IPF), from the placebo-controlled phase III INBUILD trial (332 patients with other

chronic fibrosing ILDs with a progressive phenotype), from the placebo-controlled Phase III SENSICIS trial (288 patients with SSc-ILD) or from the post-marketing period.

They are ranked under headings of System Organ Class and frequency using the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Table 1: Summary of ADRs per frequency category

MedDRA System Organ Class terminology	Nintedanib adverse reactions	Frequency category		
		IPF	Other chronic fibrosing ILDs with a progressive phenotype	SSc-ILD
Blood and lymphatic system disorders	Thrombocytopenia	Uncommon	Uncommon	Uncommon
Metabolism and nutrition disorders	Decreased appetite	Common	Very common	Common
	Weight decreased	Common	Common	Common
Vascular disorders	Hypertension	Uncommon	Common	Common
	Bleeding ^{1, 2}	Common	Common	Common
	Aneurysms and artery dissections	Not known	Not known	Not known
Gastrointestinal disorders	Diarrhoea	Very common	Very common	Very common
	Nausea	Very common	Very common	Very common
	Abdominal pain	Very common	Very common	Very common
	Vomiting	Common	Very common	Very common
	Pancreatitis	Uncommon	Uncommon	Not known
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

Nervous system disorders	Headache	Common	Common	Common
	Posterior reversible encephalopathy syndrome	Not known	Not known	Not known
Renal and urinary disorder	Proteinuria	Uncommon	Uncommon	Not known

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

Description of selected adverse reactions

Diarrhoea

Diarrhoea was reported in 62.4% of patients treated with nintedanib. The event was reported to be of severe intensity in 3.3% of nintedanib treated patients. More than two thirds of patients experiencing diarrhoea reported its first onset already during the first three months of treatment. Diarrhoea led to permanent treatment discontinuation in 4.4% of patients; otherwise the events were managed by anti-diarrhoeal therapy, dose reduction or treatment interruption (see section 4.4).

Hepatic enzyme increased

Liver enzyme elevations (see section 4.4) were reported in 13.6% of nintedanib treated patients. Elevations of liver enzymes were reversible and not associated with clinically manifest liver disease. For further information about special populations, recommended measures and dosing adjustments in case of diarrhoea and hepatic enzyme increased, refer additionally to sections 4.4 and 4.2, respectively.

4.9 Overdose

There is no specific antidote or treatment for OFEV overdose. Two patients in the oncology programme had an overdose of maximum 600 mg twice daily up to eight days. Observed adverse reactions 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitor, ATC code: L01EX09

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 adenosine triphosphate (ATP) binding pocket of these kinases and blocks the intracellular signaling cascades, which have been demonstrated to be involved in the pathogenesis of fibrotic tissue remodeling in interstitial lung diseases.

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 Efficacy and Safety

Idiopathic Pulmonary Fibrosis (IPF)

The clinical efficacy of OFEV has been studied in patients with IPF in two phase III, randomised, double-blind, placebo-controlled studies with identical design (INPULSIS-1 (1199.32) and INPULSIS-2 (1199.34)). Patients with FVC baseline < 50% predicted or carbon monoxide diffusing capacity (DLCO, corrected for haemoglobin) < 30% predicted at baseline were excluded from the trials. Patients were randomised 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.

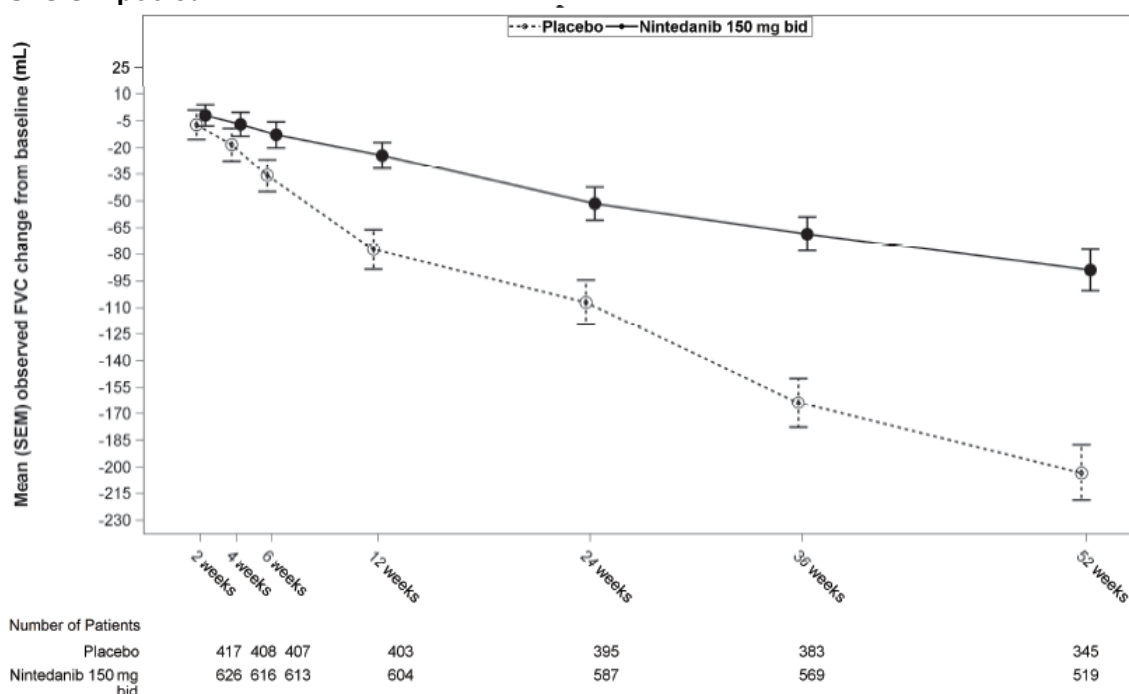
CI: confidence interval

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 patients with missing data, the primary analysis assumes that the decline in FVC after the last observed value would be similar to the decline in other patients in the same treatment group. In a sensitivity analysis which assumed that in patients with missing data at week 52 the FVC decline after the last observed value would be the same as in all placebo patients, the adjusted

difference in the annual rate of decline between OFEV and placebo was 113.9 mL/year (95% CI 69.2, 158.5) in INPULSIS-1 and 83.3 mL/year (95% CI 37.6, 129.0) in INPULSIS-2.

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 1 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.

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 twice daily. 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 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: Frequency of patients with acute IPF exacerbations over 52 weeks and time to first exacerbation analysis 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 'confirmed' or '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 a hazard ratio (HR) of 0.32 (95% CI 0.16, 0.65; p = 0.0010). This indicates that the risk of having a first acute adjudicated 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.

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.

Additional data from the phase IV INJOURNEY trial with OFEV 150 mg twice daily and add-on pirfenidone:

Concomitant treatment with OFEV and pirfenidone has been investigated in an exploratory open-label, randomised trial of OFEV 150 mg twice daily with add-on pirfenidone (titrated to 801 mg three times a day) compared to OFEV 150 mg twice daily alone in 105 randomised 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 frequent and in line with the established safety profile of each component. Diarrhoea, nausea and vomiting were the most frequent adverse events reported in 20 (37.7%) versus 16 (31.4%), in 22 (41.5%) versus 6 (11.8%) and in 15 (28.3%) versus 6 (11.8%) patients, treated with pirfenidone added to OFEV versus nintedanib alone, respectively.

Mean (SE) absolute changes from baseline in FVC at week 12 were -13.3 (17.4) mL in patients treated with nintedanib with add-on pirfenidone ($n=48$) compared to -40.9 (31.4) mL in patients treated with nintedanib alone ($n=44$).

QT interval

In a dedicated 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.

Other chronic fibrosing Interstitial Lung Diseases (ILDs) with a progressive phenotype

The clinical efficacy of OFEV has been studied in patients with chronic fibrosing 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 (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 for the patient's relevant ILD.

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 was 17.4 months and the mean OFEV exposure over the whole trial was 15.6 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%).

The INBUILD trial was not designed or powered to provide evidence for a benefit of nintedanib in specific diagnostic subgroups. Consistent effects were demonstrated in subgroups based on the ILD diagnoses. The experience with nintedanib in very rare progressive fibrosing ILDs is limited.

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 7) corresponding to a relative treatment effect of 57.0%.

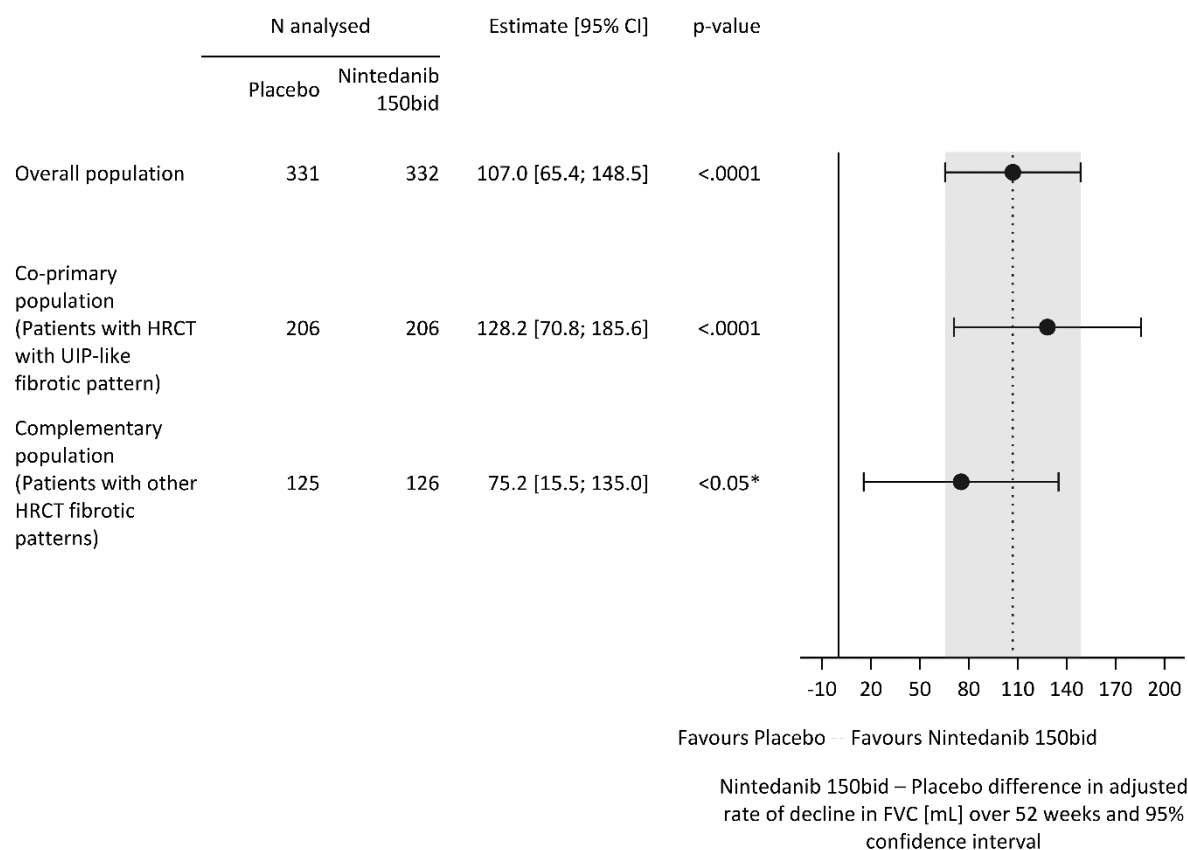
Table 7: Annual rate of decline in FVC (mL) over 52 weeks

	Placebo	OFEV 150 mg twice daily
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). (**Error! Reference source not found.**)

Figure 2: Forest plot of the annual rate of decline in FVC (mL) over 52 weeks in the patient populations



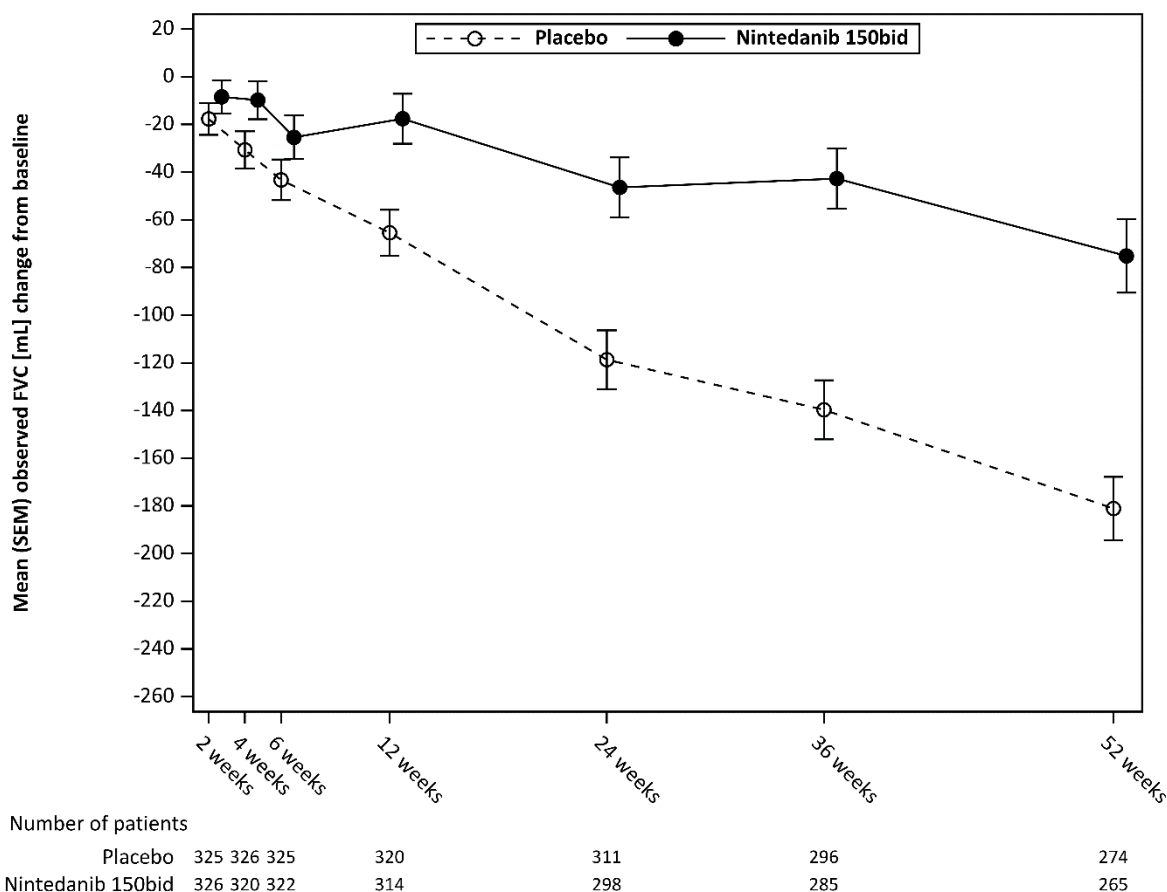
* nominal p-value (p=0.014)

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

Figure 3: 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 8).

Table 8: 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

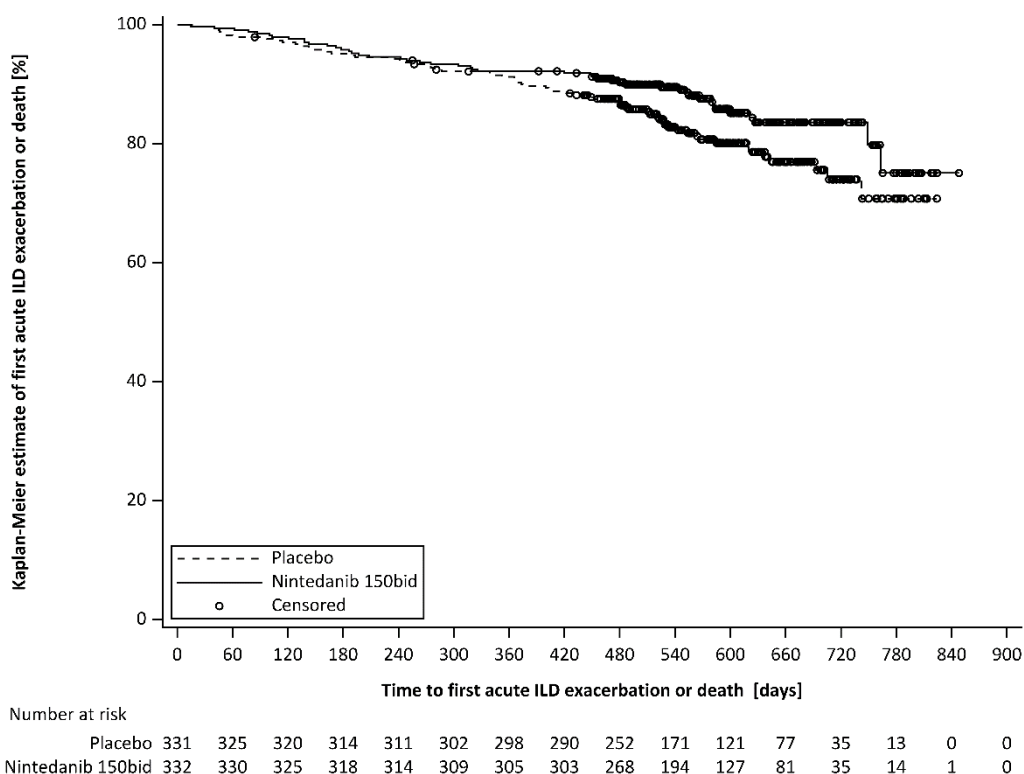
10% threshold		
Number (%) of FVC responders ¹	169 (51.1)	197 (59.3)
Comparison vs placebo		
Odds ratio ²		1.42
95% CI		(1.04, 1.94)
Nominal p-value		0.0268
¹ Responder patients are those with no relative decline greater than 5% or greater than 10% in FVC % predicted, depending on the threshold and with an FVC evaluation at 52 weeks (patients with missing data at Week 52 were considered as non-responders).		
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 4).

Figure 4: 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 ($\geq 10\%$ absolute decline of FVC % predicted) or death

In the INBUILD trial, the risk of progression ($\geq 10\%$ 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 ($\geq 10\%$ 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 ($\geq 10\%$ 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 (K-BILD) 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).

Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD)

The clinical efficacy of OFEV has been studied 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 (46.5% mycophenolate mofetil, 1.9% mycophenolate sodium, 0.5% mycophenolic acid). 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 (Table9) corresponding to a relative treatment effect of 43.8%.

Table 9: Annual rate of decline in FVC (mL) over 52 weeks

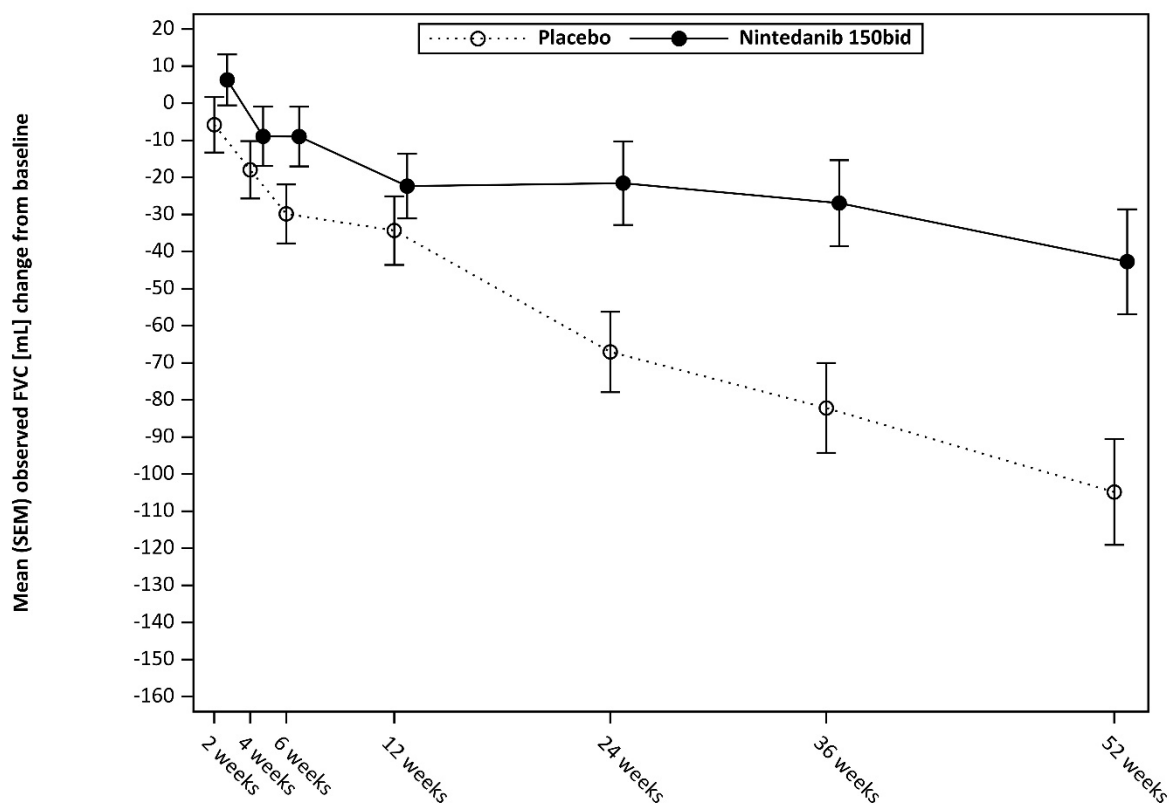
	Placebo	OFEV 150 mg twice daily
Number of analysed patients	288	287
Rate ¹ (SE) of decline over 52 weeks	-93.3 (13.5)	-52.4 (13.8)
Comparison vs placebo		
Difference ¹		41.0
95% CI		(2.9, 79.0)
p-value		<0.05
¹ Based on a random coefficient regression with fixed categorical effects of treatment, ATA 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 5 and Table 10) and rate of decline in FVC in % predicted over 52 weeks (Table 11) 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 SENSICIS) suggested that the on treatment effect of OFEV on slowing progression of SSc-ILD persisted beyond 52 weeks.

Figure 5: Mean (SEM) observed FVC change from baseline (mL) over 52 weeks



Number of patients

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

bid = twice daily

Table 10: 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		46.4
95% CI		(8.1, 84.7)
p-value		<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 11: 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		1.15
95% CI		(0.09, 2.21)
p-value		<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).

Paediatric population

Treatment of paediatric patients with nintedanib for fibrosing Interstitial Lung Diseases (ILDs) is not registered.

5.2 Pharmacokinetics properties

Absorption

Nintedanib reached maximum plasma concentrations approximately 2 - 4 h after oral administration as soft gelatine capsule under fed conditions (range 0.5 - 8 h). 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.

Nintedanib exposure increased dose-proportionally in the dose range of 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 h; fed: 3.98 h).

In an in vitro study, mixing nintedanib capsules with a small amount of apple sauce or chocolate pudding for up to 15 minutes did not have any impact on the pharmaceutical quality. Therefore, taking the capsules with soft food would not be expected to alter the clinical effect when taken immediately.

Distribution

Nintedanib follows at least bi-phasic disposition kinetics. After intravenous infusion, a high volume of distribution (V_{ss} : 1,050 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 uridine 5'-diphospho-glucuronosyltransferase enzymes (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. Nintedanib, BIBF 1202, and BIBF 1202 glucuronide did not inhibit or induce CYP enzymes in preclinical studies, either. Drug-drug interactions between nintedanib and CYP substrates, CYP inhibitors, or CYP inducers are therefore not expected.

Elimination

Total plasma clearance after intravenous infusion was high (CL: 1,390 mL/min, 28.8 % gCV). Urinary excretion of unchanged active substance within 48 h was about 0.05 % of the 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 %).

Linearity/non-linearity

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_T . Nintedanib trough concentrations remained stable for more than one year.

Transport

Nintedanib is a substrate of P-gp. For the interaction potential of nintedanib with this transporter, see section 4.5. 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.

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 ng/mL (relative standard error: 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 4.4).

Population pharmacokinetic analysis in 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.

PopPK analyses indicated moderate effects on exposure to nintedanib depending on age, body weight, and race (see below). Based on the high inter-individual variability of exposure observed in the clinical trials these effects are not considered clinically relevant (see section 4.4).

Age

Exposure to nintedanib increased linearly with age. $AUC_{\tau,ss}$ decreased by 16 % for a 45-year old patient and increased by 13 % for a 76-year old patient 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. Based on a PopPK model, an increase in nintedanib exposure of approximately 20 - 25% was observed in patients ≥ 75 years compared with patients under 65 years.

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 (5th percentile) and decreased by 19 % for a 100 kg patient (95th 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 patient 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 C_{max} and AUC was 2.2-fold higher in volunteers with mild hepatic impairment (Child Pugh A; 90% CI 1.3 – 3.7 for C_{max} 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 C_{max} (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

In a dedicated pharmacokinetic study, concomitant treatment of nintedanib with pirfenidone was investigated in patients with IPF. Group 1 received a single dose of 150 mg nintedanib before and after uptitration to 801 mg pirfenidone three times a day at steady state. Group 2 received steady state treatment of 801 mg pirfenidone three times a day and had a PK profiling before and after at least 7 days of co-treatment with 150 mg nintedanib twice daily. In group 1, the adjusted geometric mean ratios (90% confidence interval (CI)) were 93% (57% - 151%) and 96% (70% - 131%) for C_{max} and AUC_{0-tz} of nintedanib, respectively (n=12). In group 2, the adjusted geometric mean ratios (90% CI) were 97% (86% - 110%) and 95% (86% - 106%) for $C_{max,ss}$ and $AUC_{\tau,ss}$ of pirfenidone, respectively (n=12).

Based on these results, there is no evidence of a relevant pharmacokinetic drug-drug interaction between nintedanib and pirfenidone when administered in combination.

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 C_{max} and AUC_{0-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.

5.3 Preclinical Safety Data

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

In rats, embryo-foetal lethality and teratogenic effects were observed at exposure levels below human exposure at the 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 were observed at an exposure approximately 3 times higher than at the MRHD but equivocal effects on the embryo-foetal development of the axial skeleton and the heart were noted already at an exposure below that at the MRHD of 150 mg twice daily.

In a pre- and postnatal development study in rats, effects on pre- and post-natal development were seen at an exposure below the MRHD.

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, 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Capsule fill: Medium chain triglycerides, hard fat, soya lecithin (E322)

Capsule shell: Gelatin, glycerol 85 %, titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to the packaging for information on shelf-life.

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Aluminium/aluminium blisters containing 10 capsules each.

100mg: Box of 60 or 120 capsules

150mg: Box of 60 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Manufactured by:

Catalent Germany Eberbach GmbH

Gammelsbacher Str. 2

69412 Eberbach

GERMANY

Packaged by:

Boehringer Ingelheim Pharma GmbH & Co. KG

Binger Straße 173

55216 Ingelheim am Rhein

GERMANY

For:

Boehringer Ingelheim International GmbH

Ingelheim am Rhein

GERMANY

8. PRODUCT REGISTRATION NUMBER

MAL16065014ACRZ: OFEV Soft Capsules 100 mg

MAL16065015ACRZ: OFEV Soft Capsules 150 mg

9. DATE OF REVISION

16 Oct 2024

Store in a safe place out of the reach of children!
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