1 NAME OF THE MEDICINE

nintedanib esilate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

OFEV are soft gelatin capsules for oral administration containing 100 mg or 150 mg nintedanib (as nintedanib esilate).

Excipients with known effect:

Each OFEV 100 mg capsule contains 1.2 mg of soya lecithin.

Each OFEV 150 mg capsule contains 1.8 mg of soya lecithin.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

OFEV 100 mg capsules are peach-coloured, opaque, oblong, soft gelatin capsules imprinted in black on one side with the Boehringer Ingelheim company logo and “100”. The capsules contain a bright yellow viscous suspension.

OFEV 150 mg capsules are brown-coloured, opaque, oblong, soft gelatin capsules imprinted in black on one side with the Boehringer Ingelheim company logo and “150”. The capsules contain a bright yellow viscous suspension.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

OFEV is indicated in combination with docetaxel for the treatment of patients with locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after failure of first line chemotherapy.

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

OFEV is also indicated for the treatment of other chronic fibrosing Interstitial Lung Diseases (ILDs) with a progressive phenotype.

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Method of administration

OFEV capsules should be taken orally, preferably with food, swallowed whole with water, and should not be chewed or crushed.

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.

NSCLC

Treatment with OFEV should be initiated and supervised by a physician experienced in the use of anticancer therapies.

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Special populations

Paediatric population

The safety and efficacy of OFEV in paediatric patients have not been studied in clinical trials.

Elderly patients (≥ 65 years)

No overall differences in safety and efficacy were observed for elderly patients compared to patients aged below 65 years. No adjustment of the initial dosing is required on the basis of a patient's age (see Section 5.2 Pharmacokinetic Properties).

Race

Based on population PK analyses, no *a priori* dose adjustments of OFEV are necessary (see Sections 4.4 Special Warnings and Precautions for Use, Special populations and 5.2 Pharmacokinetic Properties). Safety data for Black patients are limited.

Body weight

Based on population PK analyses, no a priori dose adjustments of OFEV are necessary (see Section 5.2 Pharmacokinetic Properties).

Renal impairment

Less than 1% of a single dose of nintedanib is excreted via the kidney (see Section 5.2 Pharmacokinetic Properties). 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 Pharmacokinetic Properties).

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 Pharmacokinetic Properties).

NSCLC

No adjustment of the starting dose is needed for patients with mild hepatic impairment based on clinical data (Child Pugh A, see Section 4.4 Special Warnings and Precautions for Use).

IPF, other chronic fibrosing ILDs with a progressive phenotype, and SSc-ILD

In patients with mild hepatic impairment (Child Pugh A), the recommended dose of OFEV is 100 mg twice daily approximately 12 hours apart. If adverse reactions occur, treatment interruption or treatment discontinuation should be considered.

4.3 CONTRAINDICATIONS

OFEV is contraindicated in patients with known hypersensitivity to nintedanib, peanut or soya, or to any of the excipients.

OFEV is contraindicated during pregnancy (see Section 4.6 Fertility, Pregnancy and Lactation).

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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 4.8 Adverse Effects (Undesirable Effects)). 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 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.

Gastrointestinal perforations

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. OFEV should therefore only be initiated at least 4 weeks after major, including abdominal, surgery. Therapy with OFEV should be permanently discontinued in patients who develop gastrointestinal perforation.

NSCLC

The frequency of gastrointestinal perforation was comparable between the treatment arms in the LUME-Lung 1 study. Particular caution should be exercised when treating patients with previous abdominal surgery or a recent history of a hollow organ perforation.

IPF, other chronic fibrosing ILDs with a progressive phenotype, and SSc-ILD

In the clinical trials no increased risk of gastrointestinal perforation was observed in OFEV treated patients. 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.

Neutropenia and sepsis

NSCLC

A higher frequency of neutropenia of CTCAE grade $\geq$ 3 was observed in patients treated with OFEV in combination with docetaxel as compared to treatment with docetaxel alone. Subsequent complications such as sepsis or febrile neutropenia have been observed. Febrile neutropenia was reported in 7.5% of patients in the combination arm compared to 4.5% of patients during treatment with docetaxel alone. Fatal sepsis was reported in 0.9% of patients treated with OFEV in combination with docetaxel. Fatal sepsis was not reported during treatment with docetaxel alone.

Blood counts should be monitored during therapy, in particular during the combination treatment with docetaxel. Frequent monitoring of complete blood counts should be performed at the beginning of each treatment cycle and around the nadir for patients receiving treatment

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with nintedanib in combination with docetaxel, and as clinically indicated after the administration of the last combination cycle.

Hepatic function

Use in hepatic impairment

Subjects with baseline AST, ALT or bilirubin levels > 1.5 times the upper limit of normal were excluded from the pivotal studies. Based on increased exposure, the risk for adverse events may be increased in patients with mild hepatic impairment (Child Pugh A; see Sections 4.2 Dose and Method of Administration and 5.2 Pharmacokinetic Properties). 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 5.2 Pharmacokinetic Properties).

Liver enzyme elevations and hyperbilirubinaemia

Cases of drug-induced liver injury have been observed with nintedanib treatment.

NSCLC

In the post-marketing period, severe liver injury with fatal outcome has been reported. Administration of nintedanib was associated with an elevation of liver enzymes (ALT, AST, ALP) gamma-glutamyltransferase (GGT)) and bilirubin. These increases were reversible upon dose reduction or interruption in the majority of cases. Liver related adverse events of grade ≥ 3 were reported in 15.3% of patients treated with the combination of OFEV and docetaxel compared to 1.8% of patients treated with docetaxel alone.

Transaminase, ALP and bilirubin levels should be investigated before the initiation of the combination treatment with OFEV plus docetaxel. The values should be monitored as clinically indicated or periodically during treatment, i.e. in the combination phase with docetaxel at the beginning of each treatment cycle and monthly in case OFEV is continued as monotherapy after discontinuation of docetaxel.

If relevant liver enzyme elevations are measured, interruption, dose reduction or discontinuation of the therapy with OFEV may be required (see Section 4.2 Dose and Method of Administration, Table 2). Alternative causes of the liver enzyme elevations should be investigated and respective action should be taken as necessary.

In case of specific changes in liver values (AST/ALT > 3 x ULN in conjunction with bilirubin ≥ 2 x ULN and ALP < 2 x ULN) treatment with OFEV should be interrupted. Unless there is an alternative cause established, OFEV should be permanently discontinued (see Section 4.2 Dose and Method of Administration, Table 2).

Female and Asian patients have a higher risk of elevations in liver enzymes. Nintedanib exposure increased linearly with patient age and was inversely correlated to weight which may also result in a higher risk of developing liver enzyme elevations (see Section 5.2 Pharmacokinetic Properties). Close monitoring is recommended in patients with these risk factors.

IPF, other chronic fibrosing ILDs with a progressive phenotype, and SSc-ILD

Patients with mild hepatic impairment (Child Pugh A) should be treated with a reduced dose of OFEV (see Sections 4.2 Dose and Method of Administration and 5.2 Pharmacokinetic Properties).

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. Administration of nintedanib was associated with elevations of liver enzymes (ALT, AST, ALP, gamma-glutamyl-

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transferase (GGT)) and bilirubin. In the INPULSIS trials, liver enzyme elevations were reported in 13.6% versus 2.6% of nintedanib patients treated with OFEV and placebo, respectively. In the SENSCIS trial, liver enzyme elevations were reported in 13.2% versus 3.1% of patients treated with OFEV and placebo, respectively. Elevations of liver enzymes were reversible and not associated with clinically manifest liver disease. The majority of hepatic events occur within the first three months of treatment. Therefore, hepatic transaminase and bilirubin levels should be investigated before the 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, ALP, 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 4.2 Dose and Method of Administration). 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 5.2 Pharmacokinetic Properties). Close monitoring is recommended in patients with these risk factors.

Haemorrhage

NSCLC

VEGFR inhibition might be associated with an increased risk of bleeding. In the clinical trial LUME-Lung 1 with OFEV, the frequency of bleeding in both treatment arms was comparable. Mild to moderate epistaxis represented the most frequent bleeding event. There were no imbalances of respiratory or fatal bleedings and no intracerebral bleeding was reported. The majority of fatal bleeding events were tumour-associated.

In the post-marketing period non-serious and serious bleeding events, some of which were fatal, have been observed. In patients who experience grade 3/4 bleeding events, the benefits and risks of continuing treatment with OFEV should be carefully weighed and discontinuation of OFEV may be considered. If treatment with OFEV is resumed, a reduced daily dose is recommended (see Section 4.2 Dose and Method of Administration, Table 1).

Patients with recent pulmonary bleeding (> 2.5 mL of red blood) as well as patients with centrally located tumours with radiographic evidence of local invasion of major blood vessels or radiographic evidence of cavitary or necrotic tumours have been excluded from clinical trials. Therefore, it is not recommended to treat these patients with OFEV.

Brain metastasis

Stable brain metastasis: No increased frequency of cerebral bleeding in patients with adequately pre-treated brain metastases which were stable for ≥ 4 weeks before start of treatment with OFEV was observed. However, such patients should be closely monitored for signs and symptoms of cerebral bleeding.

Active brain metastasis: Patients with active brain metastasis were excluded from clinical trials and are not recommended for treatment with OFEV.

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Therapeutic anticoagulation

There are no data available for patients with inherited predisposition to bleeding or for patients receiving a full dose of anticoagulative treatment prior to start of treatment with OFEV. In patients on chronic low dose therapy with low molecular weight heparins or acetylsalicylic acid, no increased frequency of bleeding was observed. Patients who developed thromboembolic events during treatment and who required anticoagulant treatment were allowed to continue OFEV and did not show an increased frequency of bleeding events. Patients taking concomitant anticoagulation, such as warfarin should be monitored regularly for changes in prothrombin time, INR, or clinical bleeding episodes.

IPF, other chronic fibrosing ILDs with a progressive phenotype, and SSc-ILD

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 8.3% for SENSCIS). 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 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 clinical trials. Cases of haemorrhage have been reported in postmarketing 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

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.

NSCLC

The frequency of arterial thromboembolic events was comparable between the two treatment arms in the phase III study 1199.13 (LUME-Lung 1). Patients with a recent history of myocardial infarction or stroke were excluded from this study. However, an increased frequency of arterial thromboembolic events was observed in patients with IPF when treated with nintedanib monotherapy.

IPF, other chronic fibrosing ILDs with a progressive phenotype, and SSc-ILD

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 groups. In the 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.

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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 nintedanib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Venous thromboembolism

NSCLC

Patients treated with OFEV have an increased risk of venous thromboembolism including deep vein thrombosis. Patients should be closely monitored for thromboembolic events. OFEV should be discontinued in patients with life-threatening venous thromboembolic reactions.

IPF, other chronic fibrosing ILDs with a progressive phenotype, and SSc-ILD

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.

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.

Pulmonary hypertension

Other chronic fibrosing ILDs with a progressive phenotype and SSc-ILD

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

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 4.3 Contraindications).

Special populations

In study 1199.13 (LUME-Lung 1), there was a higher frequency of serious adverse events in patients treated with OFEV plus docetaxel with a body weight of less than 50 kg compared to patients with a weight ≥ 50 kg; however the number of patients with a body weight of less than 50 kg was small. Therefore close monitoring is recommended in patients weighing < 50 kg.

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Docetaxel

For precautions related to docetaxel please refer to the corresponding product information for docetaxel.

Use in the elderly

See Sections 4.2 Dose and Method of Administration, Special populations, Elderly patients (≥ 65 years) and 5.2 Pharmacokinetic Properties, Intrinsic and Extrinsic Factors; Special Populations, Age.

Paediatric Use

See Sections 4.2 Dose and Method of Administration, Special populations, Paediatric population and 5.2 Pharmacokinetic Properties, Intrinsic and Extrinsic Factors; Special Populations, Age.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

P-glycoprotein (P-gp)

Nintedanib is a substrate of P-gp (see Section 5.2 Pharmacokinetic Properties). 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 by 50 % based on AUC and by 40 % 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 4.2 Dose and Method of 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 5.2 Pharmacokinetic Properties).

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

Co-administration with other drugs

The potential for interactions of nintedanib with hormonal contraceptives was not explored.

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NSCLC

Co-administration of nintedanib with docetaxel (75 mg/m²) did not alter the pharmacokinetics of either drug to a relevant extent.

IPF, other chronic fibrosing ILDs with a progressive phenotype, and SSc-ILD

For co-administration of nintedanib with pirfenidone (see Section 5.2 Pharmacokinetic Properties).

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Based on preclinical investigations, there is no evidence for impairment of male fertility. A study of male fertility and early embryonic development up to implantation in rats at 100 mg/kg/day did not reveal effects on the male reproductive tract and male fertility. In the same species, nintedanib reduced female fertility at 100 mg/kg/day (slightly above the clinical exposure on an AUC basis), and increased early resorptions at ≥ 20 mg/kg/day (below clinical exposure based on AUC). Ovarian follicles and corpora lutea (increased luteinised follicles and increased number and decreased size of corpora lutea) were adversely affected in mice and rats at subclinical exposures.

Use in pregnancy - Pregnancy Category D

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.

As nintedanib may cause fetal harm also in humans, it must not be used during pregnancy (see Section 4.3 Contraindications) 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 fetus.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV and to use highly effective contraceptive methods during and at least 3 months after the last dose of OFEV. It is currently unknown whether nintedanib may reduce the effectiveness of hormonal contraceptives, and therefore, women using hormonal contraceptives must add a barrier method.

NSCLC

In rats, embryo-fetal lethality and teratogenic effects were observed at an exposure significantly lower (below the level of quantification, at 2.5 mg/kg/day) than at the maximal recommended human dose (MRHD) of 200 mg twice daily.

In rabbits, embryo-fetal lethality and teratogenic effects were observed at 15 mg/kg/day with an exposure approximately 4 times higher than at the MHRD but equivocal effects on the embryo-fetal development of the axial skeleton and the heart were noted already at an exposure below than at the MRHD of 200 mg twice daily.

IPF, other chronic fibrosing ILDs with a progressive phenotype, and SSc-ILD

In rats, embryo-fetal lethality and teratogenic effects were observed at an exposure significantly lower (below the level of quantification, at 2.5 mg/kg/day) than at the maximal recommended human dose (MRHD) of 150 mg twice daily.

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In rabbits, embryo-fetal lethality and teratogenic effects were observed at 15 mg/kg/day with an exposure approximately 5 times higher than at the MHRD but equivocal effects on the embryo-fetal development of the axial skeleton and the heart were noted already at an exposure below that at the MRHD of 150 mg twice daily.

Fetal abnormalities included brachydactyly, major artery anomalies (missing, additional, altered position or size), abnormal heart shape, missing urogenital organs (kidneys, ureter, uterus, ductus deferens, ovaries), vertebral anomalies (missing, fused, displaced, cleft, asymmetrical ossification), and rib anomalies (flat, thickened, additional, fused).

Use in 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/or its metabolites (≤ 0.5% of the administered dose) were secreted into milk of lactating rats.

Decreased postnatal viability during the first 4 postnatal days was observed in rats dosed with 10 mg/kg/day nintedanib from gestation day 6 to postnatal day 20 (exposure less than the clinical exposure based on AUC).

Because of the potential for serious adverse effects in breastfeeding infants, breastfeeding should be discontinued during treatment with OFEV.

4.7 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

Summary of the safety profile

NSCLC

The safety data provided below are based on the global, double-blind randomised pivotal phase III trial 1199.13 (LUME-Lung 1) comparing treatment with OFEV plus docetaxel against placebo plus docetaxel in patients with locally advanced, or metastatic, or recurrent NSCLC after first-line chemotherapy. Adverse events in all patients occurring in at least 10% of patients in either treatment arm in the pivotal trial LUME-Lung 1 are summarised in Table 3.

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Table 4 summarises the frequencies of adverse drug reactions (ADRs) by System Organ Class (SOC) that were reported in the pivotal study LUME-Lung 1 for patients with NSCLC of adenocarcinoma tumour histology (n = 320) and based on data observed during the nintedanib post-marketing period. The following terms are used to rank the ADRs by frequency: very common (≥ 1/10), common (≥ 1/100 < 1/10), uncommon (≥ 1/1,000 < 1/100). Within each frequency grouping adverse reactions are presented in order of decreased seriousness. The most frequently reported adverse reactions specific for OFEV were diarrhoea, increased liver enzyme values (ALT and AST) and vomiting.

Table 4: Summary of ADRs per frequency category

System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 < 1/10)	Uncommon (≥ 1/1,000 < 1/100)
Infections and infestations		Febrile neutropenia[1], Abscesses, Sepsis[1]	
Blood and lymphatic system disorders	Neutropenia[1] (includes febrile neutropenia)	Thrombocytopenia	
Metabolism and nutrition disorders	Decreased appetite, Electrolyte imbalance	Dehydration Weight decreased	
Nervous system disorders	Peripheral neuropathy[1]	Headache[2]	
Vascular disorders	Bleeding[2]	Venous thromboembolism, Hypertension	
Gastrointestinal disorders	Diarrhoea, Vomiting, Nausea, Abdominal pain		Perforation[2] Pancreatitis[3]
Hepatobiliary disorders	Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased	Hyperbilirubinaemia, Gamma-Glutamyltransferase increased	Drug-induced liver injury
Skin and subcutaneous tissue disorders	Mucositis[1] (including stomatitis), Rash, Alopecia[2]	Pruritus	
Renal and urinary disorders		Proteinuria[2]	

[1] Please also refer to the product information for docetaxel

[2] Frequency was not increased in patients treated with nintedanib plus docetaxel as compared to placebo plus docetaxel. For all other ADRs, the frequency was higher in patients treated with nintedanib plus docetaxel compared to placebo plus docetaxel.

[3] Events of pancreatitis have been reported in patients taking nintedanib for the treatment of IPF and NSCLC. The majority of these events were reported for patients in the IPF indication.

OFEV has been studied in clinical trials including 1529 patients suffering from IPF, 663 patients with other chronic fibrosing Interstitial Lung Diseases (ILDs) with a progressive phenotype, and 576 patients with 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).

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

Adverse events occurring in at least 5% of patients in either treatment arm in the pivotal trials INPULSIS-1 and INPULSIS-2 are summarised in Table 5.

Adverse events occurring in at least 5% of patients in either treatment arm in the pivotal trial SENSCIS are summarised in Table 6.

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Table 6: Adverse events occurring in at least 5% of patients in either treatment arm in SENSCIS – by SOC and preferred term – TS

	Placebo n (%)	Nintedanib 150 mg twice daily n (%)
Patients	288 (100.0)	288 (100.0)
Patients with any AE	276 (95.8)	283 (98.3)
Gastrointestinal disorders	164 (56.9)	254 (88.2)
Diarrhoea	91 (31.6)	218 (75.7)
Nausea	39 (13.5)	91 (31.6)
Vomiting	30 (10.4)	71 (24.7)
Abdominal pain	21 (7.3)	33 (11.5)
Abdominal pain upper	13 (4.5)	20 (6.9)
Gastrooesophageal reflux disease	22 (7.6)	12 (4.2)
Infections and infestations	183 (63.5)	180 (62.5)
Nasopharyngitis	49 (17.0)	36 (12.5)
Upper respiratory tract infection	35 (12.2)	33 (11.5)
Urinary tract infection	23 (8.0)	24 (8.3)
Bronchitis	24 (8.3)	16 (5.6)
Influenza	15 (5.2)	12 (4.2)
Respiratory tract infection	15 (5.2)	5 (1.7)
Respiratory, thoracic and mediastinal disorders	111 (38.5)	101 (35.1)
Cough	52 (18.1)	34 (11.8)
Dyspnoea	25 (8.7)	21 (7.3)
Musculoskeletal and connective tissue disorders	87 (30.2)	100 (34.7)
Arthralgia	19 (6.6)	17 (5.9)
Back pain	12 (4.2)	16 (5.6)
Skin and subcutaneous tissue disorders	94 (32.6)	96 (33.3)
Skin ulcer	50 (17.4)	53 (18.4)
Investigations	48 (16.7)	86 (29.9)
Weight decreased	12 (4.2)	34 (11.8)
Alanine aminotransferase increased	3 (1.0)	21 (7.3)
Gamma-glutamyltransferase increased	4 (1.4)	17 (5.9)
Aspartate aminotransferase increased	1 (0.3)	15 (5.2)
General disorders and administration site conditions	72 (25.0)	77 (26.7)
Fatigue	20 (6.9)	31 (10.8)
Pyrexia	13 (4.5)	17 (5.9)
Nervous system disorders	59 (20.5)	60 (20.8)
Headache	24 (8.3)	27 (9.4)
Dizziness	12 (4.2)	17 (5.9)
Metabolism and nutrition disorders	22 (7.6)	44 (15.3)
Decreased appetite	12 (4.2)	27 (9.4)

Adverse events occurring in at least 5% of patients in either treatment arm in the pivotal trial INBUILD are summarised in Table 7.

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Table 7: Adverse events occurring in at least 5% of patients over 52 weeks in either treatment arm in INBUILD – by SOC and preferred term – TS

	Placebo n (%)	Nintedanib 150 mg twice daily n (%)
Patients	331 (100.0)	332 (100.0)
Patients with any AE	296 (89.4)	317 (95.5)
Gastrointestinal disorders	149 (45.0)	268 (80.7)
Diarrhoea	79 (23.9)	222 (66.9)
Nausea	31 (9.4)	96 (28.9)
Vomiting	17 (5.1)	61 (18.4)
Abdominal pain	8 (2.4)	34 (10.2)
Abdominal pain upper	6 (1.8)	30 (9.0)
Constipation	25 (7.6)	23 (6.9)
Infections and infestations	185 (55.9)	177 (53.3)
Nasopharyngitis	40 (12.1)	44 (13.3)
Bronchitis	47 (14.2)	41 (12.3)
Upper respiratory tract infection	19 (5.7)	24 (7.2)
Urinary tract infection	13 (3.9)	20 (6.0)
Pneumonia	20 (6.0)	19 (5.7)
Respiratory, thoracic and mediastinal disorders	144 (43.5)	128 (38.6)
Dyspnoea	44 (13.3)	36 (10.8)
Cough	44 (13.3)	33 (9.9)
Interstitial lung disease	39 (11.8)	16 (4.8)
Investigations	56 (16.9)	114 (34.3)
Alanine aminotransferase increased	12 (3.6)	43 (13.0)
Weight decreased	11 (3.3)	41 (12.3)
Aspartate aminotransferase increased	12 (3.6)	38 (11.4)
Gamma-glutamyltransferase increased	7 (2.1)	19 (5.7)
General disorders and administration site conditions	85 (25.7)	86 (25.9)
Fatigue	20 (6.0)	33 (9.9)
Asthenia	10 (3.0)	18 (5.4)
Oedema peripheral	20 (6.0)	12 (3.6)
Musculoskeletal and connective tissue disorders	87 (26.3)	77 (23.2)
Back pain	16 (4.8)	19 (5.7)
Arthralgia	20 (6.0)	10 (3.0)
Metabolism and nutrition disorders	38 (11.5)	69 (20.8)
Decreased appetite	17 (5.1)	48 (14.5)
Nervous system disorders	54 (16.3)	69 (20.8)
Headache	23 (6.9)	35 (10.5)
Hepatobiliary disorders	10 (3.0)	38 (11.4)
Hepatic function abnormal	3 (0.9)	19 (5.7)

Table 8 summarises the frequencies of ADRs by MedDRA SOC that were reported in the nintedanib group pooled from the two placebo-controlled Phase III clinical trials of 52 weeks duration in 638 IPF patients, the placebo-controlled Phase III clinical trial of 52 weeks duration in 663 patients with other chronic fibrosing ILDs with a progressive phenotype, the placebo-controlled Phase III clinical trial of 52 weeks duration in 288 SSc-ILD patients and data observed during the post-marketing experience.

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).

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Table 8: Summary of ADRs per frequency category in IPF patients, other chronic fibrosing ILDs with a progressive phenotype and SSc-ILD.

System Organ Class	Adverse reaction	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
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 (ALT) increased	Common	Very common	Common
	Aspartate aminotransferase (AST) increased	Common	Common	Common
	Gamma-glutamyltransferase (GGT) increased	Common	Common	Common
	Blood alkaline Phosphatase (ALP) 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

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Renal and urinary disorders	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 preferrred term.

[2] Non-serious and serious bleeding events, some of which were fatal, have been observed in the post-marketing period.

For the management of selected adverse reactions please also refer to Section 4.4 Special Warnings and Precautions for Use.

Post marketing experience

Vascular disorders

Cases of aneurysms and artery dissections, sometimes fatal, have been reported with VEGFR pathway inhibitors.

4.9 OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

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 (IPF), 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-tyrosine kinase inhibitors.

ATC code: L01XE31.

Mechanism of Action

NSCLC

Nintedanib is a triple angiokinase inhibitor blocking vascular endothelial growth factor receptors (VEGFR 1-3), platelet-derived growth factor receptors (PDGFR α and β) and fibroblast growth factor receptors (FGFR 1-3) kinase activity. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these receptors and blocks the intracellular signalling which is crucial for the proliferation and survival of endothelial as well as perivascular cells (pericytes and vascular smooth muscle cells). In addition Fms-like tyrosine-protein kinase-3 (Flt-3), lymphocyte-specific tyrosine-protein kinase (Lck), tyrosine-protein kinase Lyn (Lyn) and proto-oncogene tyrosine-protein kinase Src (Src) are inhibited.

IPF, other chronic fibrosing ILDs with a progressive phenotype, and SSc-ILD

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Patients were randomised (1:1) to receive OFEV 200 mg orally twice daily in combination with 75 mg/m^2 of i.v. docetaxel every 21 days (n = 655) or placebo orally twice daily in combination with 75 mg/m^2 of docetaxel every 21 days (n = 659). OFEV was not given on day 1 of each cycle, i.e. the day when docetaxel was given. Randomisation was stratified according to Eastern Cooperative Oncology Group (ECOG) status (0 vs. 1), bevacizumab pre-treatment (yes vs. no), brain metastasis (yes vs. no) and tumour histology (squamous vs. non-squamous tumour histology).

Patient characteristics were balanced between treatment arms within the overall population and within the adenocarcinoma patients. In the overall population 72.7% of the patients were male. The majority of patients were non-Asian (81.6%), the median age was 60.0 years, the baseline ECOG performance status was 0 (28.6%) or 1 (71.3%); one patient had a baseline ECOG performance status of 2. 5.8% of the patients had stable brain metastasis at study entry and 3.8% had prior bevacizumab treatment.

The disease stage was determined at the time of diagnosis using Union Internationale Contre le Cancer (UICC) / American Joint Committee on Cancer (AJCC) Edition 6 or Edition 7. In the overall population, 16.0% of the patients had disease stage < IIIB/IV, 22.4% had disease stage IIIB and 61.6% had disease stage IV. 9.2% of the patients entered the study with locally recurrent disease stage as had been evaluated at baseline. For patients with tumour of adenocarcinoma histology, 15.8% had disease stage < IIIB/IV, 15.2% had disease stage IIIB and 69.0% had disease stage IV. 5.8% of the adenocarcinoma patients entered the study with locally recurrent disease stage as had been evaluated at baseline. 'Locally recurrent' was defined as local re-occurrence of the tumour without metastases at study entry.

The primary endpoint was progression-free survival (PFS) as assessed by an independent review committee (IRC) based on the intent-to-treat (ITT) population and tested by histology. Overall survival (OS) was the key secondary endpoint. Other efficacy outcomes included objective response, disease control, change in tumour size and health-related quality of life.

As shown in Table 9, the addition of OFEV to docetaxel led to a statistically significant reduction in the risk of progression or death by 21% for the overall population (HR 0.79; 95% CI: 0.68 - 0.92; p = 0.0019) as determined by the IRC. This result was confirmed in the follow-up PFS analysis (HR 0.85, 95% CI: 0.75 - 0.96; p = 0.0070) which included all events collected at the time of the final OS analysis. OS analysis in the overall population did not reach statistical significance (HR 0.94; 95% CI: 0.83 – 1.05). Of note, pre-planned analyses according to histology showed statistically significant difference in OS between treatment arms in the adenocarcinoma population only.

The addition of OFEV to docetaxel led to a statistically significant reduction in the risk of progression or death by 23% for the adenocarcinoma population (HR 0.77; 95% CI: 0.62 – 0.96). In line with these observations, related study endpoints such as disease control and change in tumour size showed significant improvements.

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Table 9: Efficacy results for study LUME-Lung 1 for all patients and for patients with adenocarcinoma tumour histology

	All patients		Adenocarcinoma tumour histology	
	OFEV (n = 565)	**Placebo (n = 569)**	**OFEV (n = 277)**	**Placebo (n = 285)**
Progression free survival*				
Number of Deaths or Progressions, n (%)	339 (60.0)	375 (65.9)	152 (54.9)	180 (63.2)
Median PFS [months]	3.4	2.7	4.0	2.8
HR (95% CI)**	0.79 (0.68, 0.92)		0.77 (0.62, 0.96)	
Stratified Log-Rank Test p-value**	0.0019		0.0193	
Disease control [%]	48.5	37.6	60.6	43.9
Odds ratio (95% CI)+	1.56 (1.23, 1.98)		1.98 (1.41, 2.77)	
p-value+	0.0002		<0.0001	
Objective response [%]	3.4	1.9	4.3	3.5
Odds ratio (95% CI)+	1.77 (0.85, 3.89)		1.25 (0.53, 3.01)	
p-value+	0.1283		0.6122	
Overall Survival***	**(n= 655)**	**(n= 659)**	**(n= 322)**	**(n= 336)**
Number of OS events, n (%)	564 (86.1)	557 (84.5)	259 (80.4)	276 (82.1)
Median OS [months]	10.1	9.1	12.6	10.3
HR (95% CI)	0.94 (0.83, 1.05)		0.83 (0.70, 0.99)	
Stratified Log-Rank Test p-value*	0.2720		0.0359	

* Primary PFS analysis based on a total of 713th PFS events in the overall population. Recruitment was ongoing when the primary analysis was conducted.

** Stratified by baseline ECOG PS (0 *vs*. 1), brain metastases at baseline (yes vs. no) and prior treatment with bevacizumab (yes *vs*. no) and in the all patients population additionally stratified by tumour histology (squamous *vs*. non−squamous).

*** OS analysis based on a total of 1121 deaths in the overall population

\+ Odds ratio and p-value are obtained from a logistic regression model adjusted for baseline ECOG Performance Score (0 *vs*. 1) and in the all patients population it is additionally adjusted by tumour histology (squamous vs. non-squamous).

A statistically significant improvement in OS favouring treatment with OFEV plus docetaxel was demonstrated in patients with adenocarcinoma with a 17% reduction in the risk of death (HR 0.83, p = 0.0359) and a median OS improvement of 2.3 months (10.3 vs. 12.6 months, Figure 1).

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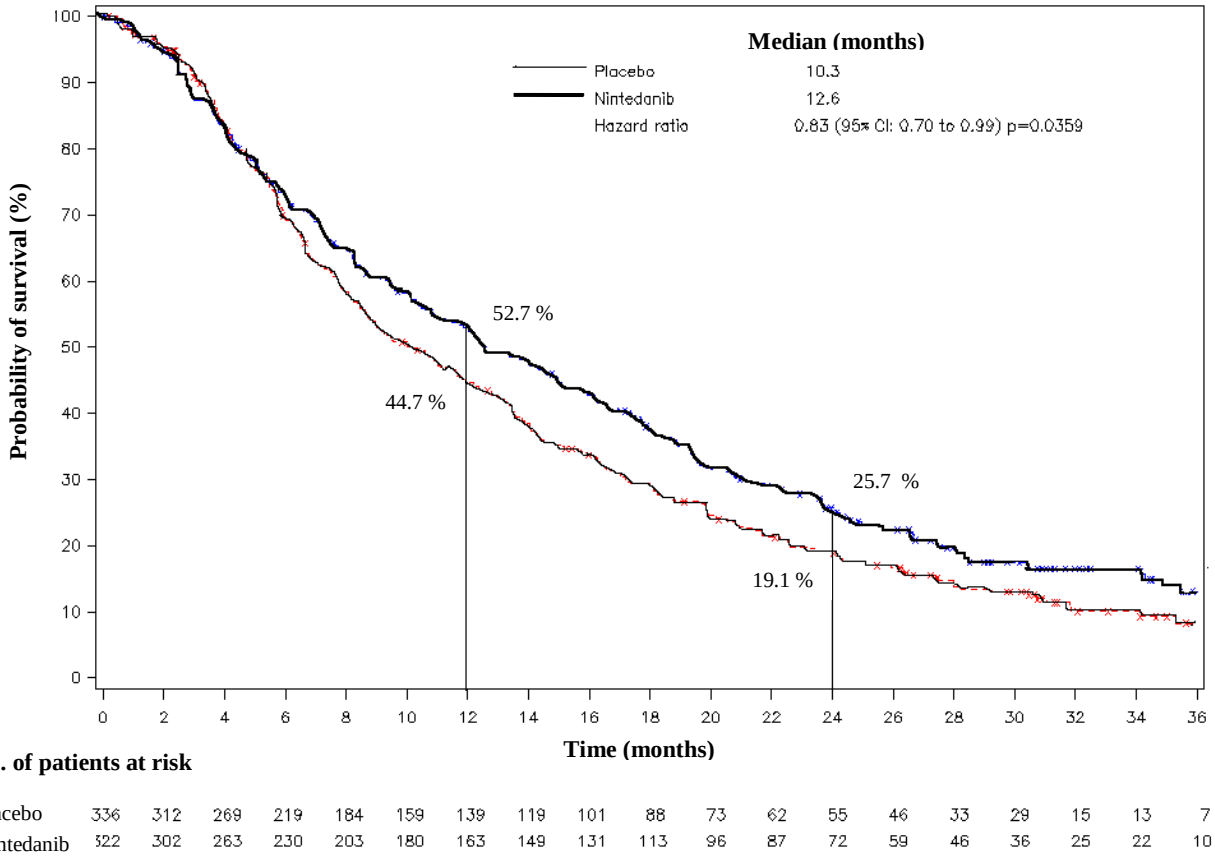
Figure 1: Kaplan-Meier Curve for overall survival for patients with adenocarcinoma tumour histology by treatment group in trial LUME-Lung 1



No. of patients at risk

Placebo	336	312	269	219	184	159	139	119	101	88	73	62	55	46	33	29	15	13	7
Nintedanib	322	302	263	230	203	180	163	149	131	113	96	87	72	59	46	36	25	22	10

A pre-specified evaluation was performed in the population of adenocarcinoma patients considered to have entered the study with a particularly poor treatment prognosis, namely, patients who progressed during or shortly after 1st line therapy prior to study entry. This population included those adenocarcinoma patients identified at baseline as having progressed and entered the study less than 9 months since start of their first-line therapy. Treatment of these patients with OFEV in combination with docetaxel reduced the risk of death by 25%, compared with placebo plus docetaxel (HR 0.75; 95% CI: 0.60 - 0.92; p = 0.0073). Median OS improved by 3 months (OFEV: 10.9 months; placebo: 7.9 months).

In a post-hoc analysis in adenocarcinoma patients having progressed and entered the study ≥ 9 months since start of their first-line therapy the difference did not reach statistical significance (HR for OS: 0.89, 95% CI 0.66 – 1.19).

The proportion of adenocarcinoma patients with stage < IIIB/IV at diagnosis was small and balanced across treatment arms (placebo: 54 patients (16.1%); OFEV: 50 patients, (15.5%)). The HR for these patients for PFS and OS was 1.24 (95% CI: 0.68, 2.28) and 1.09 (95% CI: 0.70, 1.70), respectively. However, the sample size was small, there was no significant interaction and the CI was wide and included the HR for OS of the overall adenocarcinoma population.

Quality of Life

Treatment with OFEV did not significantly change the time to deterioration of the pre-specified symptoms cough, dyspnoea and pain. Patients receiving OFEV plus docetaxel reported a statistically significant, small deterioration in the symptom assessment of diarrhoea used in

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the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire QLQ-C30. This finding did not compromise patients' self-reported Global health status/Quality of life. Patients receiving OFEV plus docetaxel reported statistically significant improvements in other individual lung cancer symptoms (e.g. pain in chest and pain in arm and shoulder).

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 and INPULSIS-2). The studies enrolled subjects with FVC ≥ 50% of predicted and DL_{CO} corrected for haemoglobin 30-79% of predicted at baseline. 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 10 for individual and pooled study results.

Table 10: 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.

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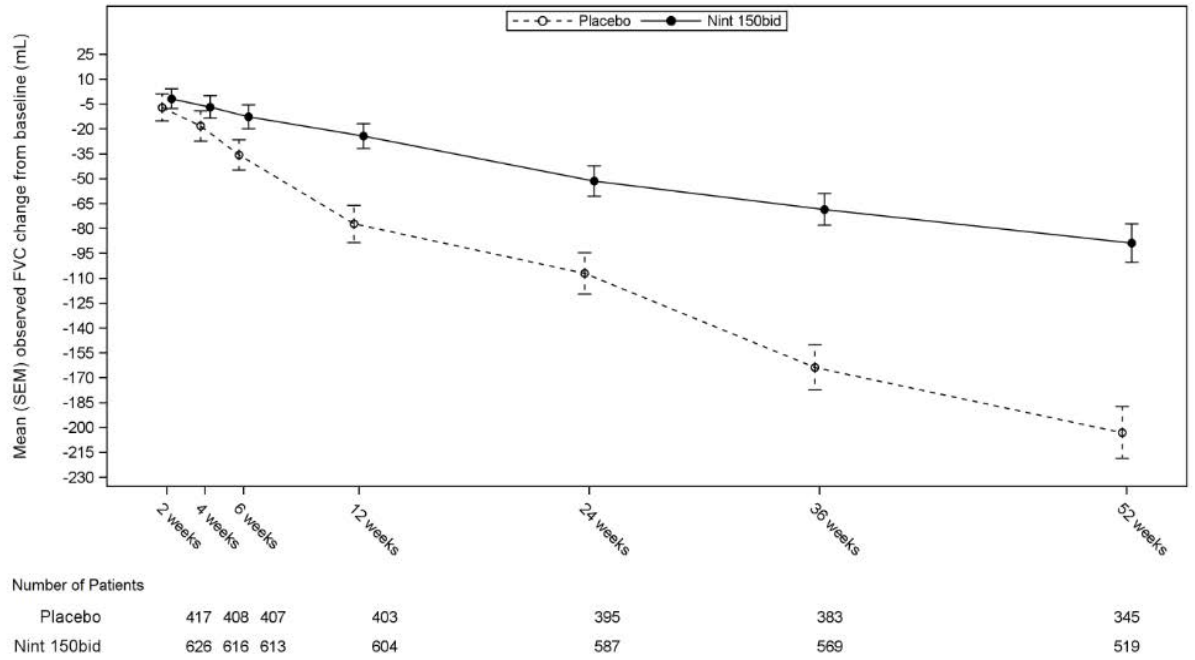
The robustness of the effect of OFEV in reducing the annual rate of decline in FVC was confirmed in all pre-specified sensitivity analyses.

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



bid = twice daily
SEM = standard error of the mean

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 11 for individual and pooled study results.

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 12.

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Table 12: 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

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 nintedanib group; the difference between the treatment groups was modest, but statistically significant (-2.69; 95% CI: -4.95, -0.43; p=0.0197). The clinical significance of this finding is unknown.

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. The clinical significance of this finding is unknown.

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 13 for individual and pooled study results.

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Table 13: 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 '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 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

The INPULSIS trials were not statistically powered for overall mortality. In a pre-specified pooled analysis, overall mortality over 52 weeks was numerically lower in the OFEV group (5.5%) compared with the placebo group (7.8%). The difference did not reach statistical significance. 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 14).

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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 ≥10%, FVC decline ≥ 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%).

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

Table 15: 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

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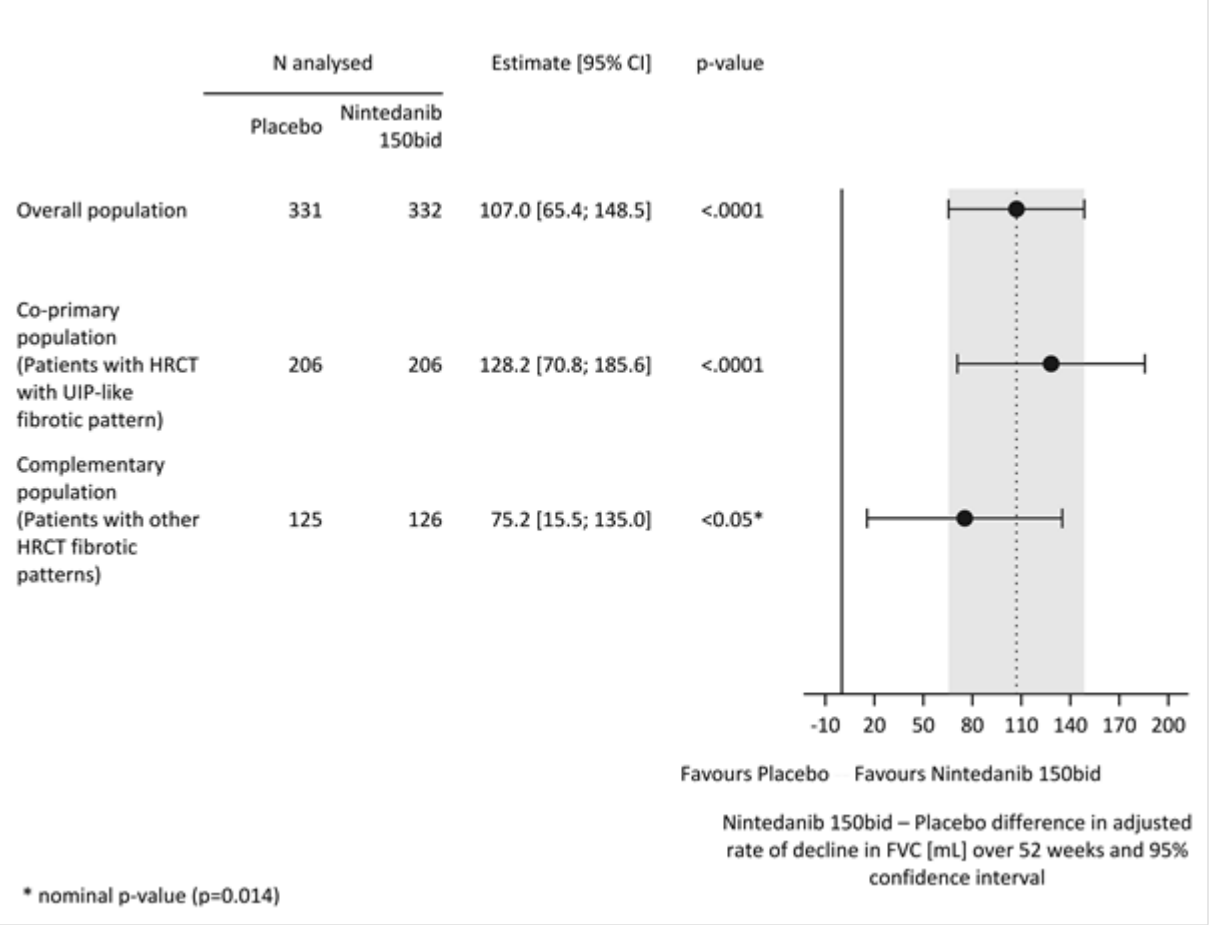
Similar results were observed in the co-primary population of patients with HRCT with UIP-like fibrotic pattern: the annual rate of decline in FVC was -211.1 mL/year in the placebo group (n=206) and -82.9 mL/year in the OFEV group (n=206). The difference between the treatment groups was 128.2 mL/year (95% CI: 70.8, 185.6; p<0.0001). Further, the treatment effect of annual rate of decline in FVC (mL) over 52 weeks was consistent in the complementary population of patients with other HRCT fibrotic patterns. (Figure 3).

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



bid = twice daily

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). The trial was not designed or powered to provide evidence for a benefit of nintedanib in specific diagnostic subgroups.

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

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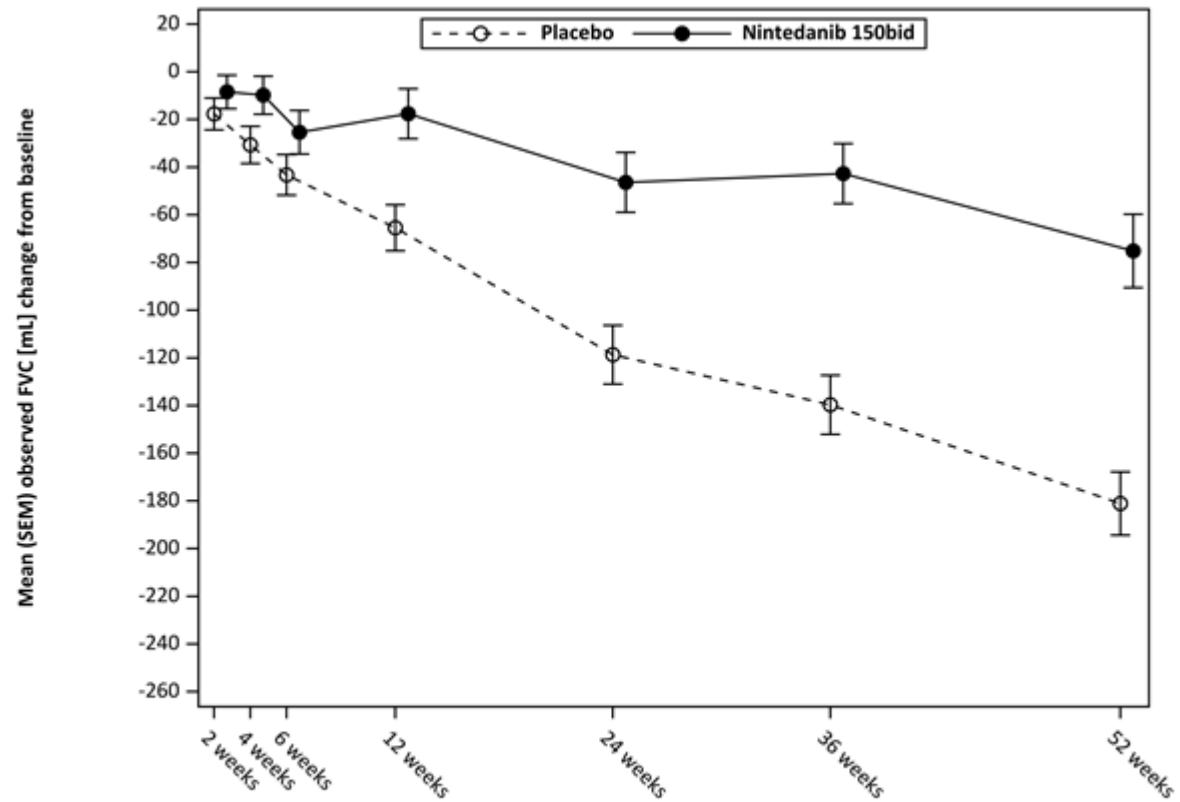
Figure 4: Mean (SEM) observed FVC change from baseline (mL) over 52 weeks



bid = twice daily

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).

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 16).

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Table 16: 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)
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)

[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. 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 (Figure 5)).

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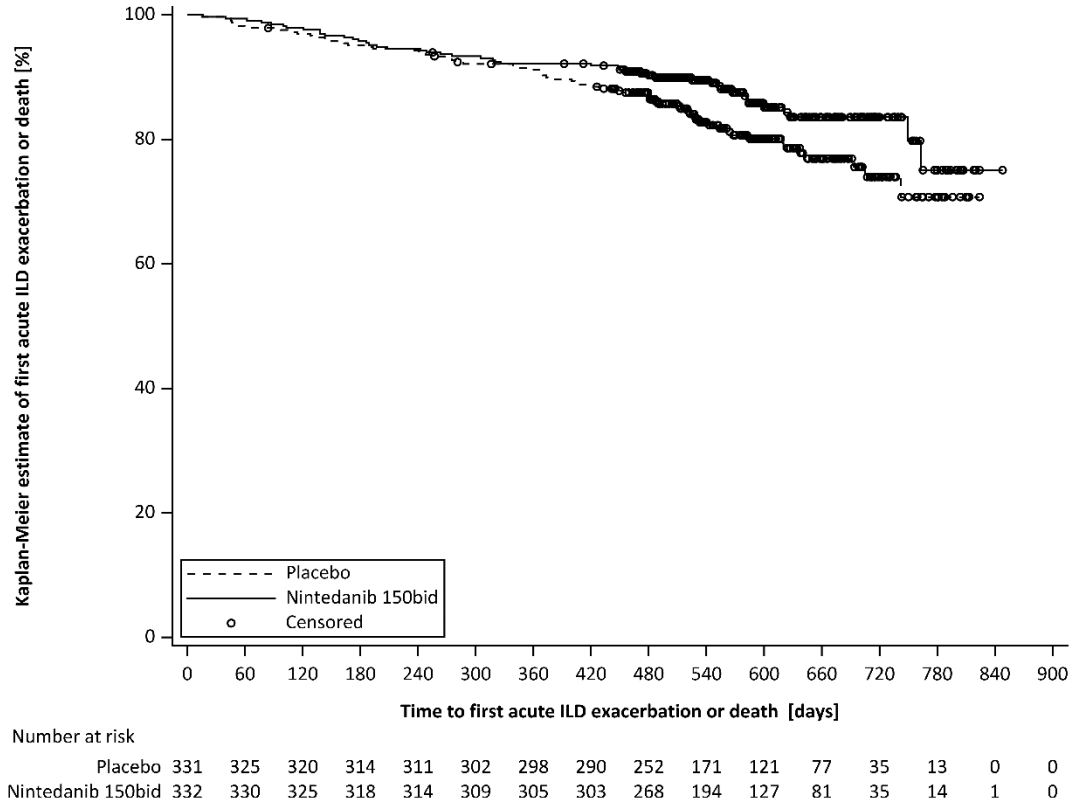
Figure 5: Kaplan–Meier plot of time to first acute ILD exacerbation or death over the whole trial



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. 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).

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 who died or progressed over 52 weeks was 25.6% in the OFEV group compared to 37.5% in the placebo group.

In the analysis of data over the whole trial, the risk of death or progression was lower in the OFEV group compared to the placebo group. The HR was 0.66 (95% CI: 0.53, 0.83).

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)

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- 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).

The adjusted mean absolute change from baseline in Living with Pulmonary Fibrosis (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). 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).

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. 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 17) corresponding to a relative treatment effect of 43.8%.

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Table 17: 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). The exploratory subgroup analysis of the annual rate of decline in FVC by mycophenolate use at baseline is presented in Table 18.

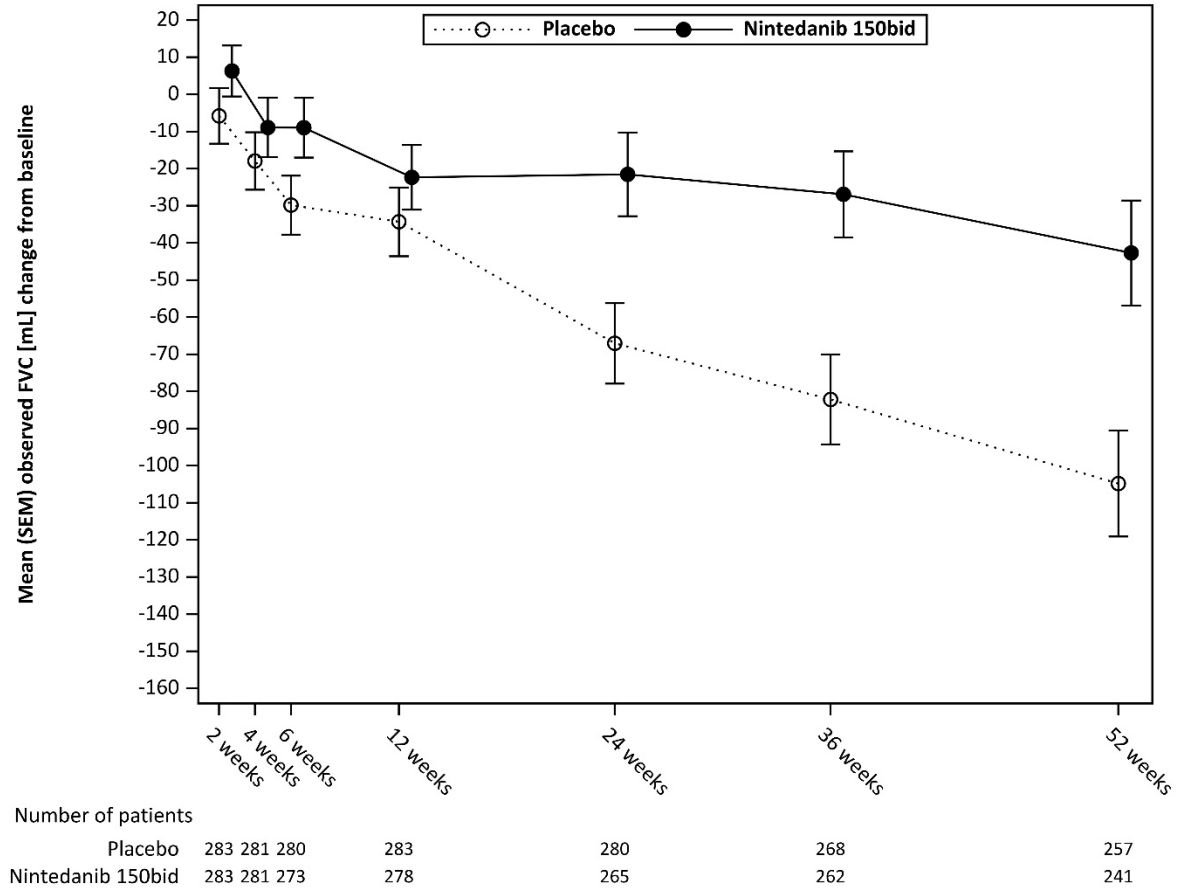
Table 18: Rate of decline in FVC [mL/yr] over 52 weeks by mycophenolate use at baseline

Mycophenolate use at baseline	Placebo		Nintedanib 150 mg bid		Difference (95% CI)
	N	Rate of Decline	N	Rate of Decline	
Yes	140	-66.5	138	-40.2	26.3 (-27.9; 80.6)
No	148	-119.3	149	-63.9	55.4 (2.3; 108.5)

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 6 and Table 19) and rate of decline in FVC in % predicted over 52 weeks (Table 20) 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 6: Mean (SEM) observed FVC change from baseline (mL) over 52 weeks



bid = twice daily

Table 19: 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)

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Table 20: 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).

Effect on QT interval

QT/QTc measurements were recorded and analysed from a dedicated study comparing nintedanib monotherapy against sunitinib monotherapy in patients with renal cell carcinoma. In this study single oral doses 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.

NSCLC

No thorough QT-trial of nintedanib administered in combination with docetaxel was conducted.

Paediatric population

No clinical trials have been conducted in children and adolescents.

5.2 PHARMACOKINETIC PROPERTIES

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

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administrations was 1.04-fold for Cmax and 1.38-fold for AUCτ. 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: 0.953 – 1.525) and absorption was delayed (median t_{max} fasted: 2.00 hours; fed: 3.98 hours).

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.

Metabolism

The prevalent metabolic reaction for nintedanib is hydrolytic cleavage by esterases resulting in the free acid moiety BIBF 1202. BIBF 1202 is subsequently glucuronidated by UGT enzymes, namely UGT 1A1, UGT 1A7, UGT 1A8, and UGT 1A10 to BIBF 1202 glucuronide.

Only a minor extent of the biotransformation of nintedanib consisted of CYP pathways, with CYP 3A4 being the predominant enzyme involved. The major CYP-dependent metabolite could not be detected in plasma in the human ADME (absorption, distribution, metabolism and excretion) study. *In vitro*, CYP-dependent metabolism accounted for about 5% compared to about 25% ester cleavage.

Excretion

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 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 hours (gCV % approximately 50%).

Exposure-response relationship

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In exploratory PK - adverse event analyses, higher exposure to nintedanib tended to be associated with liver enzyme elevations, but not with gastrointestinal adverse events.

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PK-efficacy analyses were not performed for clinical endpoints. Logistic regression revealed a statistically significant association between nintedanib exposure and DCE-MRI response.

IPF, other chronic fibrosing ILDs with a progressive phenotype, and SSc-ILD

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 diarrhoea of any intensity, even if plasma exposure as risk determining factor could not be ruled out (see Section 4.4 Special Warnings and Precautions for Use).

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 analyses and descriptive investigations, exposure to nintedanib was not influenced by gender (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 the intrinsic and extrinsic factors age, body weight, and race which are described in the following. 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 Special Warnings and Precautions for Use).

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 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,

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respectively, compared to healthy volunteers. Subjects with severe hepatic impairment (Child Pugh C) have not been studied.

Concomitant treatment with pirfenidone

IPF

In a dedicated pharmacokinetic study, concomitant treatment of OFEV with pirfernidone was investigated in patients with IPF. Group 1 received a single dose of 150 mg OFEV before and after up-titration 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 OFEV 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 $AUC_{0\text{-}tz}$ 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).

Due to the wide confidence intervals of the PK parameters, statistically a pharmacokinetic drug-drug interaction cannot be ruled out but 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 $AUC_{0\text{-}tz}$ of nintedanib, respectively (n=13), indicating that co-administration of nintedanib with bosentan did not alter the pharmacokinetics of nintedanib.

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 metabolised 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 4.5 Interactions with other medicines and other forms of interactions. Nintedanib was shown not to be 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. *In vitro* studies also showed that nintedanib was a substrate of OCT-1, which is of low clinical relevance.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Nintedanib was not genotoxic in the bacterial reverse mutation assay, *in vitro* mouse lymphoma cell forward mutation assay, and *in vivo* rat micronucleus assay.

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Carcinogenicity

There was no evidence of carcinogenicity in a 103-week study in mice at oral doses of nintedanib up to 30 mg/kg/day, or in a 104-week study in rats at oral doses up to 10 mg/kg/day, resulting in approximately 2.5 and 0.15 times the human exposure (AUC) at the maximum recommended human dose (MRHD) of 200 mg twice daily, respectively.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each OFEV capsule also contains medium chain triglycerides, hard fat and lecithin.

The capsule shell contains gelatin, glycerol 85%, titanium dioxide, iron oxide red (CI 77491), iron oxide yellow (CI 77492).

The black printing ink (Opacode® Type S-1-17823) contains shellac, ethanol, propylene glycol, and iron oxide black (CI 77499).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Store in the original package in order to protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

OFEV 100 mg capsules are packaged in aluminium/aluminium blisters containing 10 capsules per blister. OFEV 100 mg are supplied in packs of 60 capsules.

OFEV 150 mg capsules are packaged in aluminium/aluminium blisters containing 10 capsules per blister. OFEV 150 mg are supplied in packs of 60 capsules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Nintedanib esilate is a bright yellow powder. The octanol-water partition coefficient (log P_{ow}) for nintedanib esilate free base was determined to be 3.6, which demonstrates the lipophilic character of the molecule. Due to the ionisable groups in nintedanib esilate, the lipophilicity profile is strongly pH dependent. At physiological pH (pH = 7.4), the apparent partition coefficient (log *D*) was calculated to 3.0. The molecule is less lipophilic in the acidic pH range (log D ≤ 1 for pH < 5).

Nintedanib esilate is soluble in water. A saturated solution in water was found to have a concentration of 2.8 mg/mL and exhibited an intrinsic pH of 5.7. The solubility of nintedanib esilate is strongly pH dependent with an increased solubility at acidic pH, particularly for pH < 3. The highest solubility of nintedanib esilate in organic solvents is observed in methanol

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and *N*-methylpyrrolidone. The best solubility in pharmaceutically relevant co-solvents is observed in propylene glycol.

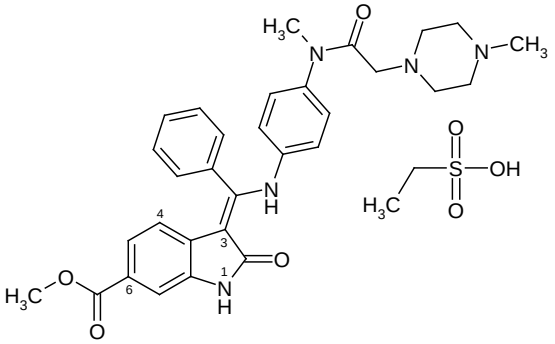
Chemical Structure

Chemical name: 1*H*-Indole-6-carboxylic acid, 2,3-dihydro-3-[[[4-[methyl[-(4-methyl-1-piperazinyl)acetyl]amino]phenyl]amino]phenylmethylene]-2-oxo-, methyl ester, (3*Z*)-, ethanesulfonate (1:1)

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

Molecular weight: 649.76

Structural formula:



CAS Number

656247-18-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

1 September 2015

10 DATE OF REVISION

05 January 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.1	New indication ‘other chronic fibrosing ILDs with a progressive phenotype’

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4.2	Addition of reference to the new indication 'other chronic fibrosing ILDs with a progressive phenotype'
4.4	Update of information related to the new indication 'other chronic fibrosing ILDs with a progressive phenotype' based on INBUILD trial. Addition of nephrotic range proteinuria, aneurysms and artery dissections.
4.8	Addition of adverse events and adverse reactions information for the new indication 'other chronic fibrosing LDs with a progressive phenotype'. Addition of proteinuria, aneurysms and artery dissections adverse drug reactions.
5.1	Addition of clinical trial results from the INBUILD trial for the new indication 'other chronic fibrosing ILDs with a progressive phenotype'
5.2	Addition of reference to the new indication 'other chronic fibrosing ILDs with a progressive phenotype'