Ofev®

Boehringer Ingelheim

1. NAME OF THE MEDICINAL PRODUCT

OFEV Soft Capsules 100 mg
OFEV Soft Capsules 150 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

OFEV 100 mg soft capsules

1 capsule contains 100 mg of nintedanib (= free base)
corresponding to 120.4 mg 1*H*-Indole-6-carboxylic acid, 2,3-dihydro-3-[[[4-[methyl[(4- methyl-1-piperazinyl)acetyl] amino]phenyl] amino]phenylmethylene]-2-oxo-, methyl ester, (3*Z*)-, ethanesulfonate (1:1) (= nintedanib esilate).

OFEV 150 mg soft capsules

1 capsule contains 150 mg of nintedanib (= free base)
corresponding to 180.6 mg 1*H*-Indole-6-carboxylic acid, 2,3-dihydro-3-[[[4-[methyl[(4- methyl-1-piperazinyl)acetyl] amino]phenyl]amino]phenylmethylene]-2-oxo-, methyl ester, (3*Z*)-, ethanesulfonate (1:1) (= nintedanib esilate).

Excipients

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

Capsule shell: Gelatine (porcine), glycerol 85%, titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172), black ink (Opacode®)

Black ink: Shellac glaze, iron oxide black (E172), propylene glycol (E1520)

3. PHARMACEUTICAL FORM

Soft capsule.

OFEV 100 mg soft capsules: Peach-colored, opaque, oblong, soft gelatin capsules, imprinted in black on one side with Boehringer Ingelheim company symbol and with“100”, and containing a bright yellow viscous suspension.

OFEV 150 mg soft capsules: Brown-colored, opaque, oblong, soft gelatin capsules, imprinted in black on one side with Boehringer Ingelheim company symbol and with“150”, and containing a bright yellow viscous suspension.

4. CLINICAL PARTICULARS

4.1 INDICATIONS

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

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

OFEV is indicated for the treatment of chronic fibrosing Interstitial Lung Diseases (ILDs) with a progressive phenotype [see section Clinical Trials]

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 DOSAGE AND ADMINISTRATION

Dosing in NSCLC

Treatment with OFEV should be initiated and supervised by a physician experienced in the use of anticancer therapies.
For posology, method of administration, and dose modifications of docetaxel, please refer to the corresponding product information for docetaxel.
The recommended dose of OFEV is 200 mg twice daily administered approximately 12 hours apart, on days 2 to 21 of a standard 21-day docetaxel treatment cycle.
OFEV must not be taken on the same day of docetaxel chemotherapy administration (= day 1).

The recommended maximum daily dose of 400 mg should not be exceeded.

Patients may continue therapy with OFEV after discontinuation of docetaxel for as long as clinical benefit is observed or until unacceptable toxicity occurs.

Dosing in IPF / chronic fibrosing ILDs with a progressive phenotype / SSc-ILD

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

The recommended dose of OFEV is 150 mg twice daily administered approximately 12 hours apart.
The recommended maximum daily dose of 300 mg should not be exceeded.

Dose adjustments

NSCLC

As initial measure for the management of adverse reactions (see Tables 1a and 1b), treatment with nintedanib should be temporarily interrupted until the specific adverse reaction has resolved to levels that allow continuation of therapy (to grade 1 or baseline).
Nintedanib treatment may be resumed at a reduced dose. Dose adjustments in 100 mg steps per day (i.e. a 50 mg reduction per dosing) based on individual safety and tolerability are recommended as described in Table 1a and Table 1b.

In case of further persistence of the adverse reaction(s), i.e. if a patient does not tolerate 100 mg twice daily, treatment with OFEV should be permanently discontinued. In case of specific elevations of aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) values to > 3 x upper limit normal (ULN) in conjunction with an increase of total bilirubin to ≥ 2 x ULN and alkaline phosphatase (ALKP) < 2 x ULN; (see Table 1b) treatment with OFEV should be interrupted. Unless there is an alternative cause established, OFEV should be permanently discontinued (see section ***Special Warnings and Precautions***).

Table1a: Recommended dose adjustments for OFEV (nintedanib) in case of diarrhoea, vomiting and other non-haematological or haematological adverse reactions except liver enzyme elevations (see Table 1b)

CTCAE* Adverse reaction	**Dose adjustment**
Diarrhoea ≥ grade 2 for more than 7 consecutive days despite anti-diarrhoeal treatment ***OR*** Diarrhoea ≥ grade 3 despite anti-diarrhoeal treatment	After treatment interruption and recovery to grade 1 or baseline, dose reduction from 200 mg twice daily to 150 mg twice daily and - if a 2nd dose reduction is considered necessary - from 150 mg twice daily to 100 mg twice daily.
Vomiting ≥ grade 2 ***AND/OR*** Nausea ≥ grade 3 despite anti-emetic treatment	
Other non-haematological or haematological adverse reaction of ≥ grade 3	

* CTCAE: Common Terminology Criteria for Adverse Events

Table 1b: Recommended dose adjustments for OFEV (nintedanib) in case of AST and/or ALT and bilirubin elevations

AST / ALT and bilirubin elevations	Dose adjustment
Elevation of AST and/or ALT values to > 2.5 x ULN in conjunction with total bilirubin elevation to ≥ 1.5 x ULN ***OR*** Elevation of AST and/or ALT values to > 5x ULN	After treatment interruption and recovery of transaminase-values to ≤ 2.5 x ULN in conjunction with bilirubin to normal, dose reduction from 200 mg twice daily to 150 mg twice daily and - if a 2nd dose reduction is considered necessary - from 150 mg twice daily to 100 mg twice daily.
Elevation of AST and/or ALT values to > 3 x ULN in conjunction with an increase of total bilirubin to ≥ 2 x ULN and ALKP < 2 x ULN	Unless there is an alternative cause established, OFEV should be permanently discontinued

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase
ALKP: Alkaline phosphatase; ULN: Upper limit normal

IPF / chronic fibrosing ILDs with a progressive phenotype / SSc-ILD

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

Dose modifications or interruptions may be necessary for liver enzyme elevations. For aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 times to < 5 times the upper limit of normal (ULN) without signs of severe liver damage, interrupt treatment or reduce OFEV to 100mg twice daily. Once liver enzymes have returned to baseline values, treatment with OFEV may be reintroduced at a reduced dosage (100mg twice daily), which subsequently may be increased to the full dosage (150mg twice daily) [***see section Special Warnings and Precautions, Adverse Reactions***].

Special populations

Paediatric population

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

Elderly patients (≥ 65 years)

No overall differences in safety and efficacy were observed for elderly patients. No adjustment of the initial dosing is required on the basis of a patient's age (see section ***Pharmacokinetics***). Patients ≥ 75 years may be more likely to require dose reduction to manage adverse effects.

Race

Based on population pharmacokinetic (-PK) analyses, no *a priori* dose adjustments of OFEV are necessary (see section Special Populations, ***Special Warnings and Precautions***, ***Pharmacokinetics***). 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 ***Pharmacokinetics***).

Renal impairment

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

IPF / chronic fibrosing ILDs with a progressive phenotype / SSc-ILD

Nintedanib is predominantly eliminated via biliary/faecal excretion (> 90 %). Exposure increased in patients with hepatic impairment (Child Pugh A, Child Pugh B; see section ***Pharmacokinetics*)**.

In patients with mild hepatic impairment (Child Pugh A), the recommended dose of OFEV is 100mg 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 ***Pharmacokinetics)***.

NSCLC

Nintedanib is predominantly eliminated via biliary/faecal excretion (> 90 %). Exposure increased in patients with hepatic impairment (Child Pugh A, Child Pugh B; see section ***Pharmacokinetics)***.

No adjustment of the starting dose is needed for patients with mild hepatic impairment (Child Pugh A) based on clinical data.

Limited safety data available from 9 patients with moderate hepatic impairment (Child Pugh B) are insufficient to characterize this population.
The safety, efficacy and pharmacokinetics of nintedanib have not been investigated in patients with severe hepatic impairment (Child Pugh C). Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with OFEV is not recommended (see sections ***Special Warnings and Precautions for Use*** and ***Pharmacokinetics***).

Method of Administration
OFEV capsules should be taken orally, preferably with food, swallowed whole with water, and should not be chewed. 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.
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

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

NSCLC
For contraindications of docetaxel please refer to the corresponding product information for docetaxel.

4.4 SPECIAL WARNINGS AND PRECAUTIONS

Gastrointestinal-Disorders

NSCLC

- *Diarrhoea*
  Diarrhoea was the most frequently reported gastro-intestinal event and appeared in close temporal relationship with the administration of docetaxel (see section ***Adverse Reactions***). In the clinical trial LUME-Lung 1 (see section ***Clinical trials***), the majority of patients had mild to moderate diarrhoea. 6.3 % of the patients had diarrhoea of grade ≥3 in combination treatment compared to 3.6 % treated with docetaxel alone. Diarrhoea should be treated at first signs with adequate hydration and anti-diarrhoeal medicinal products, e.g. loperamide, and may require interruption, dose reduction or discontinuation of therapy with OFEV (see section ***Dosage and Administration***).

- *Nausea and vomiting*
  Nausea and vomiting, mostly of mild to moderate severity, were frequently reported gastrointestinal adverse events (see section ***Adverse Reactions***). If symptoms persist despite appropriate supportive care (including anti-emetic therapy), dose reduction, treatment interruption or discontinuation of therapy with OFEV (see section ***Dosage and Administration***) may be required.

Diarrhoea and vomiting may lead to dehydration with or without electrolyte disturbances which may progress to renal function impairment. In the event of dehydration, administration of electrolytes and fluids is required. Plasma levels of electrolytes should be monitored, if relevant gastrointestinal adverse events occur.

IPF / chronic fibrosing ILDs with a progressive phenotype / SSc-ILD

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

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

- *Nausea and vomiting*
  Nausea and vomiting were frequently reported adverse events (see section ***Adverse Reactions***). In most patients with nausea and vomiting, the event was of mild to moderate intensity. In the INPULSIS trials, nausea led to discontinuation of nintedanib 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.

Hypertension

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

The use of VEGFR inhibitors may promote the formation of aneurysm and/or artery dissection. Serious cases of artery dissection have been reported in patients using VEGFR TKIs, including nintedanib. Before initiating OFEV, this risk should be carefully considered in patients with risk factors such as poorly controlled hypertension or a history of aneurysm.

Neutropenia and Sepsis

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A higher frequency of neutropenia of CTCAE grade > 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.

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

Hepatic Function

NSCLC

Based on increased exposure, the risk for adverse events may be increased in patients with mild hepatic impairment (Child Pugh A; see sections ***Dosage and Administration***, ***Pharmacokinetics***). Limited safety data are available in 9 patients with hepatocellular carcinoma and moderate hepatic impairment classified as Child Pugh B. Although no unexpected safety findings were reported in these patients, the data are insufficient to support a recommendation for treatment of patients with moderate hepatic impairment. The efficacy of nintedanib has not been investigated in patients with moderate hepatic impairment (Child Pugh B). The safety, efficacy and pharmacokinetics of nintedanib have not been studied in patients with severe hepatic impairment (Child Pugh C). Treatment with nintedanib is not recommended in patients with moderate or severe hepatic impairment (see section ***Dosage and Administration***).

Cases of drug-induced liver injury have been observed with nintedanib treatment. In the post-marketing period, severe liver injury with fatal outcome has been reported. Elevations of liver enzymes (ALT, AST, ALKP, gamma-glutamyltransferase (GGT)) and bilirubin were reversible upon dose

reduction or interruption in the majority of cases.

Transaminase, ALKP and bilirubin levels should be investigated upon 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 mono-therapy 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 ***Dosage and Administration/Table 1b***). 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 ALKP < 2 x ULN) treatment with OFEV should be interrupted. Unless there is an alternative cause established, OFEV should be permanently discontinued (see section ***Dosage and Administration/Table 1b***)

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 Pharmacokinetics). Close monitoring is recommended in patients with these risk factors

IPF / chronic fibrosing ILDs with a progressive phenotype / SSc-ILD

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. 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 ***Dosage and Administration***, ***Pharmacokinetics)***.

Cases of drug-induced liver injury have been observed with nintedanib treatment. In the post-marketing period, non-serious and serious cases of drug-induced liver injury, including severe liver injury with fatal outcome, have been reported. The majority of hepatic events occur within the first three months of treatment. Therefore, hepatic transaminase and bilirubin levels should be investigated upon initiation of treatment with OFEV, at regular intervals during the first three months of treatment and periodically thereafter (e.g. at each patient visit) or as clinically indicated.

Elevations of liver enzymes (ALT, AST, ALKP, gamma-glutamyltransferase (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. 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 a 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 result in a higher risk of developing liver enzyme elevations (see sections ***Pharmacokinetics***). Close monitoring is recommended in patients with these risk factors.

Special populations

NSCLC

In study 1199.13 (LUME-Lung 1), there was a higher frequency of serious adverse events in patients treated with nintedanib 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.

Renal Function

Cases of renal impairment/failure, in some cases with fatal outcome, have been reported with nintedanib use (see section: ***Adverse Reactions***). Patients should be monitored during nintedanib therapy, with particular attention to those patients exhibiting risk factors for renal impairment/failure. In case of renal impairment/failure, therapy adjustment should be considered (see section on dose adjustment).

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 ¾ 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 ***Dosage and Administration/Table 1a***).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.

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

- *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 develop 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 or phenprocoumon should be monitored regularly for changes in prothrombin time, INR, or clinical bleeding episodes.

IPF / chronic fibrosing ILDs with a progressive phenotype / 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 the clinical trials. Therefore these patients should only be treated with OFEV if the anticipated benefit outweighs the potential risk. In the post-marketing period non-serious and serious bleeding events, some of which were fatal, have been observed.

Arterial thromboembolic events

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 Idiopathic Pulmonary Fibrosis (IPF) when treated with nintedanib monotherapy.

IPF / chronic fibrosing ILDs with a progressive phenotype / 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.

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 / chronic fibrosing ILDs with a progressive phenotype / 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.

Gastrointestinal perforations and ischaemic colitis

Due to the mechanism of action nintedanib patients might have an increased risk of gastrointestinal perforations and ischaemic colitis. 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.

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 / *chronic fibrosing ILDs with a progressive phenotype* / 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.

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

Wound healing complication

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

Effect on QT interval

No QT prolongation was observed for nintedanib in the clinical trial program (see section ***Pharmacodynamic properties***). As several other tyrosine kinase inhibitors are known to exert an effect on QT, caution should be exercised when administering nintedanib in patients who may develop QTc prolongation.

Soya lecithin

OFEV soft capsules contain soya lecithin which may 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 (see section ***Contraindications).***

4.5 INTERACTIONS

P-glycoprotein (P-gp)

Nintedanib is a substrate of P-gp (see section ***Pharmacokinetics***). Co-administration with the potent P-gp inhibitor ketoconazole increased exposure to nintedanib 1.61-fold based on AUC and 1.83-fold based on C_{max} in a dedicated drug-drug interaction study.

In a drug-drug interaction study with the potent P-gp inducer rifampicin, exposure to nintedanib decreased to 50.3% based on AUC and to 60.3% based on C_{max} upon co-administration with rifampicin compared to administration of nintedanib alone.

If co-administered with OFEV, potent P-gp inhibitors (e.g. ketoconazole or erythromycin) may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability

of nintedanib. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV (see section ***Dosage and Administration)***.

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

Food

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

Cytochrome(CYP)-enzymes

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

Co-administration with other drugs

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

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

IPF / chronic fibrosing ILDs with a progressive phenotype / SSc-ILD
Co-administration of nintedanib with bosentan did not alter the pharmacokinetics of nintedanib (see section ***Pharmacokinetics***).

4.6 FERTILITY, PREGNANCY AND LACTATION

Fertility

NSCLC
Based on preclinical investigations, there is no evidence for impairment of male fertility (see section ***Toxicology***). From subchronic and chronic toxicity studies, there is no evidence that female fertility in rats is impaired at a systemic exposure level comparable with that at the maximum recommended human dose (MRHD) of 200 mg twice daily (see section ***Toxicology***).

IPF / chronic fibrosing ILDs with a progressive phenotype / SSc-ILD
Based on preclinical investigations there is no evidence for impairment of male fertility (see section

Toxicology). From subchronic and chronic toxicity studies, there is no evidence that female fertility in rats is impaired at a systemic exposure level comparable with that at the maximum recommended human dose (MRHD) of 150 mg twice daily (see section ***Toxicology***).

Contraception

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

Pregnancy

There is no information on the use of OFEV in pregnant women, but pre-clinical studies in animals have shown reproductive toxicity of this drug (see section ***Toxicology***). As nintedanib may cause foetal harm also in humans, it must not be applied during pregnancy (see section ***Contraindications***) and pregnancy testing must be conducted prior to treatment with OFEV and during treatment as appropriate.
Female patients should be advised to notify their doctor or pharmacist if becoming pregnant during therapy with OFEV.
If the patient becomes pregnant while receiving OFEV, treatment must be discontinued and the patient should be apprised of the potential hazard to the foetus.

Breastfeeding/lactation

There is no information on the excretion of nintedanib and its metabolites in human milk. Pre-clinical studies showed that small amounts of nintedanib and its metabolites (≤ 0.5 % of the administered dose) were secreted into milk of lactating rats.
A risk to the newborns/infants cannot be excluded. Breastfeeding should be discontinued during treatment with OFEV.

NSCLC

For fertility, pregnancy and lactation information for docetaxel please refer to the corresponding product information for docetaxel.

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 REACTIONS

NSCLC

Summary of the safety profile

The safety data provided in the sections below are based on the global, double-blind randomized 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 and based on data observed during the nintedanib post-marketing period. The most frequently reported adverse drug reactions (ADRs) specific for OFEV were diarrhoea, increased liver enzyme values (ALT and AST) and vomiting. Table 2 provides a summary of the adverse reactions by System Organ Class (SOC).

For the management of selected adverse reactions, see section ***Special Warnings and Precautions***. Information about selected adverse reactions observed from the LUME-Lung 1 trial is described below.

Tabulated list of adverse reactions

Table 2 summarizes the frequencies of adverse drug reactions that were reported in the pivotal study LUME-Lung 1 for patients with NSCLC of adenocarcinoma tumour histology (n = 320).

The following terms are used to rank the ADRs by frequency:
very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).
Within each frequency grouping adverse reactions are presented in order of decreased seriousness.

Table 2: Summary of ADRs per frequency category

System Organ Class	**Very common (≥ 1/10)**	**Common (≥ 1/100 < 1/10)**	**Uncommon (≥ 1/1,000 < 1/100)**	**Not Known**
Infections and infestations		Febrile neutropenia, Abscesses, Sepsis		
Blood and lymphatic system disorders	Neutropenia (includes febrile neutropenia)	Thrombocytopenia		
Metabolism and nutrition disorders	Decreased appetite, Electrolyte imbalance	Dehydration Weight Decreased		
Nervous system disorders	Peripheral neuropathy	Headache [1)]		
Vascular disorders	Bleeding [1)]	Venous thromboembolism, Hypertension		Aneurysms and artery dissections

Gastrointestinal disorders	Diarrhoea, Vomiting, Nausea, Abdominal pain		Perforation [1)] Pancreatitis [2)]	
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 (including stomatitis), Rash, Alopecia [1)]	Pruritus		
Renal and Urinary disorders		Proteinuria		Renal failure

[1)] Frequency was not increased in patients treated with nintedanib plus docetaxel as compared to placebo plus docetaxel.

[2)] 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.

Description of selected adverse reactions

Diarrhoea

Diarrhoea occurred in 43.4 % (≥ grade 3: 6.3 %) of adenocarcinoma patients in the nintedanib arm. The majority of adverse reactions appeared in close temporal relationship with the administration of docetaxel. Most patients recovered from diarrhoea following treatment interruption, anti-diarrhoeal therapy and nintedanib dose reduction.

For recommended measures and dosing adjustments in case of diarrhoea, see sections ***Special Warnings and Precautions*** and ***Dosage and Administration***, respectively.

Liver enzyme elevations and hyperbilirubinaemia

Liver-related adverse reactions occurred in 42.8 % of nintedanib-treated patients. Approximately one third of these patients had liver-related adverse reactions of ≥ grade 3 severity. In patients with increased liver parameters, the use of the established stepwise dose reduction scheme was the appropriate measure and discontinuation of treatment was only necessary in 2.2 % of patients. In the majority of patients, elevations of liver parameters were reversible.

For information about special populations, recommended measures and dosing adjustments in case of liver enzyme and bilirubin elevations, see sections ***Special Warnings and Precautions*** and ***Dosage and Administration***, respectively.

Neutropenia, febrile neutropenia and sepsis

Sepsis and febrile neutropenia have been reported as subsequent complications of neutropenia. The rates of sepsis (1.3 %) and febrile neutropenia (7.5 %) were increased under treatment with nintedanib as compared to the placebo arm. It is important that the patient's blood counts are monitored during therapy, in particular during the combination treatment with docetaxel (see section ***Special Warnings and Precautions***).

Bleeding
Although bleeding is an expected adverse reaction of nintedanib due to its mechanism of action, the bleeding incidence was comparable between the 2 treatment groups (placebo: 11.1 %, nintedanib: 10.9 %) in adenocarcinoma patients.

Perforation
As expected via its mechanism of action perforation might occur in patients treated with nintedanib. However, the frequency of patients with gastrointestinal perforation was low.

Peripheral neuropathy
Peripheral neuropathy is also known to occur with docetaxel treatment. Peripheral neuropathy was reported in 16.5 % of patients in the placebo arm and in 19.1 % of patients in the nintedanib arm.

IPF / chronic fibrosing ILDs with a progressive phenotype / SSc-ILD

Summary of the safety profile
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 ***Clinical Trials***).

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

Tabulated list of adverse reactions

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

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

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

Table 3: Summary of ADRs per frequency category

System Organ Class	***Adverse Reactions***	***Frequency***		
		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
Renal and Urinary disorders	Renal Failure	Not known	Not known	Uncommon
	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

In clinical trials (see section ***Pharmacodynamic properties***), diarrhoea was the most frequent gastro-intestinal event reported. In most patients, the event was of mild to moderate intensity. More than two thirds of patients experiencing diarrhoea reported its first onset already during the first three months of treatment. In most patients, the events were managed by antidiarrhoeal therapy, dose reduction or treatment interruption (see section ***Special Warnings and Precautions***). An overview of the reported diarrhoea events in the clinical trials is listed in Table 4.

Table 4: Diarrhoea adverse events in clinical trials over 52 weeks

	INPULSIS		INBUILD		SENSCIS	
	Placebo	OFEV	Placebo	OFEV	Placebo	OFEV
Diarrhoea	18.4%	62.4%	23.9%	66.9%	31.6%	75.7%
Severe Diarrhoea	0.5%	3.3%	0.9%	2.4%	1.0%	4.2%
Diarrhoea leading to OFEV dose reduction	0%	10.7%	0.9%	16.0%	1.0%	22.2%
Diarrhoea leading to OFEV discontinuation	0.2%	4.4%	0.3%	5.7%	0.3%	6.9%

Hepatic enzyme increased

In the INPULSIS trials, liver enzyme elevations (see section ***Special Warnings and Precautions***) were reported in 13.6% versus 2.6% of patients treated with OFEV and placebo, respectively. In the INBUILD trial, liver enzyme elevations were reported in 22.6% versus 5.7% of 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.

For further information about special populations, recommended measures and dosing adjustments in case of diarrhoea and hepatic enzyme increased, refer additionally to sections ***Special Warnings and Precautions*** and ***Dosage and Administration***, respectively.

4.9 OVERDOSE

There is no specific antidote or treatment for OFEV overdose. The highest single dose of nintedanib administered in phase I studies was 450 mg once daily. In addition, 2 patients in the oncology programme had an overdose of maximum 600 mg twice daily 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 case of overdose, treatment should be interrupted and general supportive measures initiated as appropriate.

IPF

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents - Protein kinase inhibitor. ATC code: L01EX09

Mechanism of Action

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Nintedanib is a triple angiokinase inhibitor blocking vascular endothelial growth factor receptors (VEGFR 1-3), platelet-derived growth factor receptors (PDGFR α and ß) 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 (Flt)-3, lymphocyte-specific tyrosine-protein kinase (Lck) and proto-oncogene tyrosine-protein kinase Src (Src) are inhibited.

IPF / chronic fibrosing ILDs with a progressive phenotype / SSc-ILD

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

Pharmacodynamic effects

NSCLC

Tumour angiogenesis is an essential feature contributing to tumour growth, progression and metastasis formation and is predominantly triggered by the release of pro-angiogenic factors secreted by the tumour cell (i.e. VEGF and bFGF) to attract host endothelial as well as perivascular cells to facilitate oxygen and nutrient supply through the host vascular system. In preclinical disease models, nintedanib, as single agent, effectively interfered with the formation and maintenance of the tumour vascular system resulting in tumour growth inhibition and tumour stasis. In particular, treatment of tumour xenografts with nintedanib led to a rapid reduction in tumour micro vessel density, pericytes vessel coverage and tumour perfusion.
Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) measurements showed an anti-angiogenic effect of nintedanib in humans. It was not clearly dose dependent, but most responses were seen at doses of ≥ 200 mg. Logistic regression revealed a statistically significant association of the anti-angiogenic effect to nintedanib exposure. DCE-MRI effects were seen 24-48 h after the first drug intake and were preserved or even increased after continuous treatment over several weeks. No correlation of the DCE-MRI response and subsequent clinically significant reduction in target lesion size was found, but DCE-MRI response was associated with disease stabilization.

IPF / chronic fibrosing ILDs with a progressive phenotype / SSc-ILD

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

CLINICAL TRIALS

Non-Small Cell Lung Cancer (NSCLC)

Efficacy in the pivotal phase III trial LUME-Lung 1

The efficacy and safety of OFEV was investigated in 1314 patients with locally advanced, metastatic or recurrent NSCLC after one prior line of chemotherapy. 'Locally recurrent' was defined as local re-occurrence of the tumour without metastases at study entry. The trial including 658 patients (50.1 %) with adenocarcinoma, 555 patients (42.2 %) with squamous cell carcinoma, and 101 patients (7.7 %) with other tumour histologies.

Patients were randomized (1:1) to receive nintedanib 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). Randomization was stratified according to Eastern Cooperative Oncology Group (ECOG) status (0 *vs*. 1), bevacizumab pretreatment (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.

The primary endpoint was progression-free survival (PFS) as assessed by an independent review committee (IRC). 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 5, the addition of nintedanib 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. Overall survival 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 nintedanib 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.

Table 5: Efficacy results for study LUME-Lung 1 for patients with adenocarcinoma tumour histology

	Nintedanib + Docetaxel	Placebo + Docetaxel
Progression free survival (PFS)* - primary analysis		
Patients, n	277	285
Number of Deaths or Progressions, n (%)	152 (54.9)	180 (63.2)
Median PFS [months]	4.0	2.8
HR (95% CI)	0.77 (0.62; 0.96)	
Stratified Log-Rank Test p-value**	0.0193	
Progression free survival (PFS)* - follow-up analysis**		
Patients, n	322	336
Number of Deaths or Progressions, n (%)	255 (79.2)	267 (79.5)
Median PFS [months]	4.2	2.8
HR (95% CI)	0.84 (0.71; 1.00)	
Stratified Log-Rank Test p-value**	0.0485	
Disease control [%]	60.2	44.0
Odds ratio (95% CI)[+]	1.93 (1.42; 2.64)	
p-value[+]	< 0.0001	
Objective response [%]	4.7	3.6
Odds ratio (95% CI)[+]	1.32 (0.61; 2.93)	
p-value[+]	0.4770	
Tumour shrinkage [%]**°**	-7.76	-0.97
p-value**°**	0.0002	
Overall Survival (OS)***		
Patients, n	322	336
Number of Deaths, n (%)	259 (80.4)	276 (82.1)
Median OS [months]	12.6	10.3
HR (95% CI)	0.83 (0.70; 0.99)	
Stratified Log-Rank Test p-value*	0.0359	

HR: hazard ratio; CI: confidence interval

***** Primary PFS analysis performed when 713th PFS events had been observed based on IRC-assessment in the overall ITT population (332 events in adenocarcinoma patients).

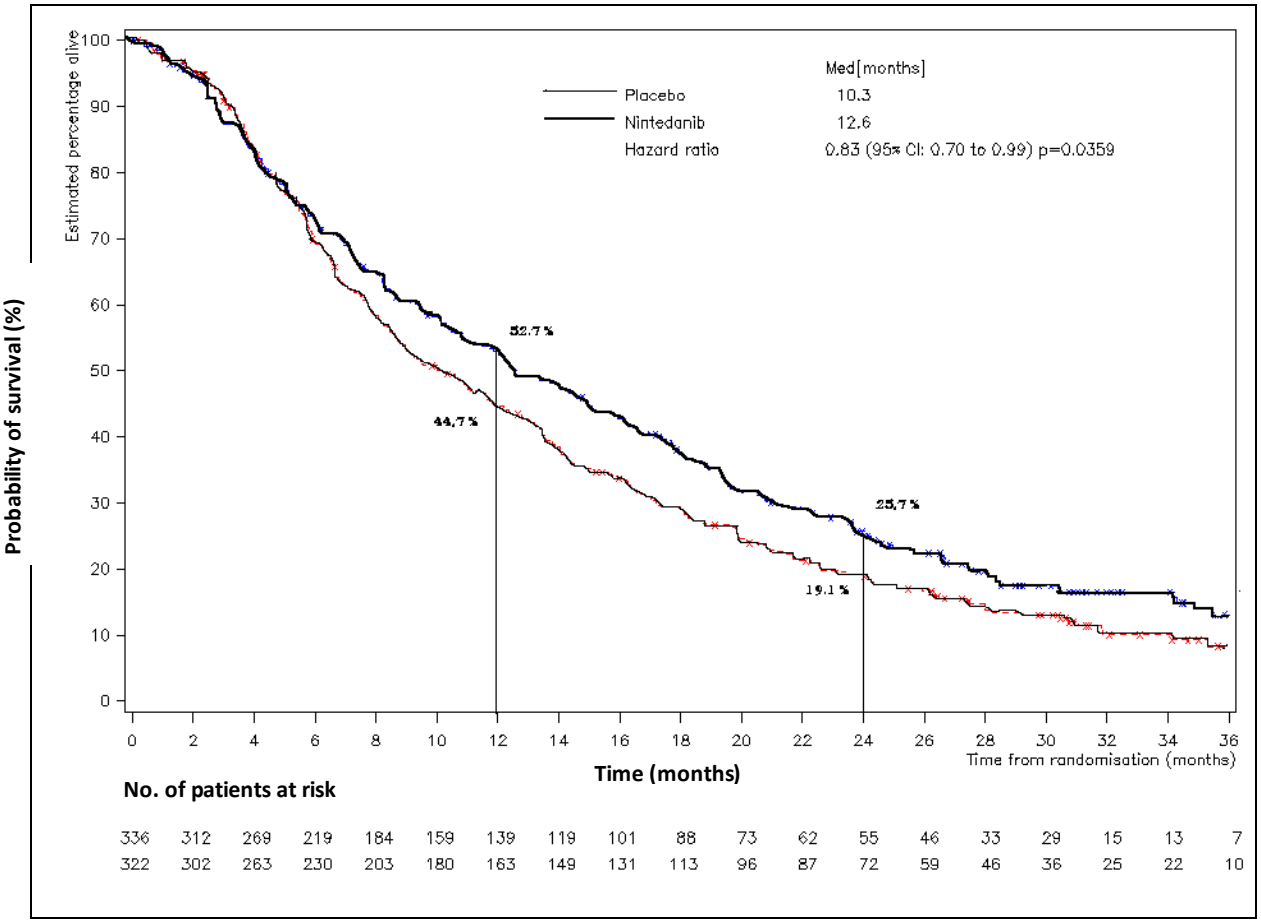
****** Stratified by baseline ECOG PS (0 versus 1), brain metastases at baseline (yes versus no) and prior treatment with bevacizumab (yes versus no).

*** OS analysis and follow-up PFS-analysis performed when 1121 death cases had been observed in the overall ITT population (535 events in adenocarcinoma patients).

[+] Odds ratio and p-value were obtained from a logistic regression model adjusted for baseline ECOG Performance Score (0 versus 1).
[°] Adjusted mean of best-% change from baseline and p-value generated from an ANOVA model adjusting for baseline ECOG PS (0 versus 1), brain metastases at baseline (yes versus no) and prior treatment with bevacizumab (yes versus no).

A statistically significant improvement in OS favouring treatment with nintedanib 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).

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



An 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 nintedanib 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 (nintedanib: 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 %); nintedanib: 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.

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 and INPULSIS-2). 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 randomized in a 3:2 ratio to treatment with OFEV 150 mg or placebo twice daily for 52 weeks.
The primary endpoint was the annual rate of decline in Forced Vital Capacity (FVC). The key secondary endpoints were change from baseline in Saint George's Respiratory Questionnaire (SGRQ) total score at 52 weeks and time to first acute IPF exacerbation.

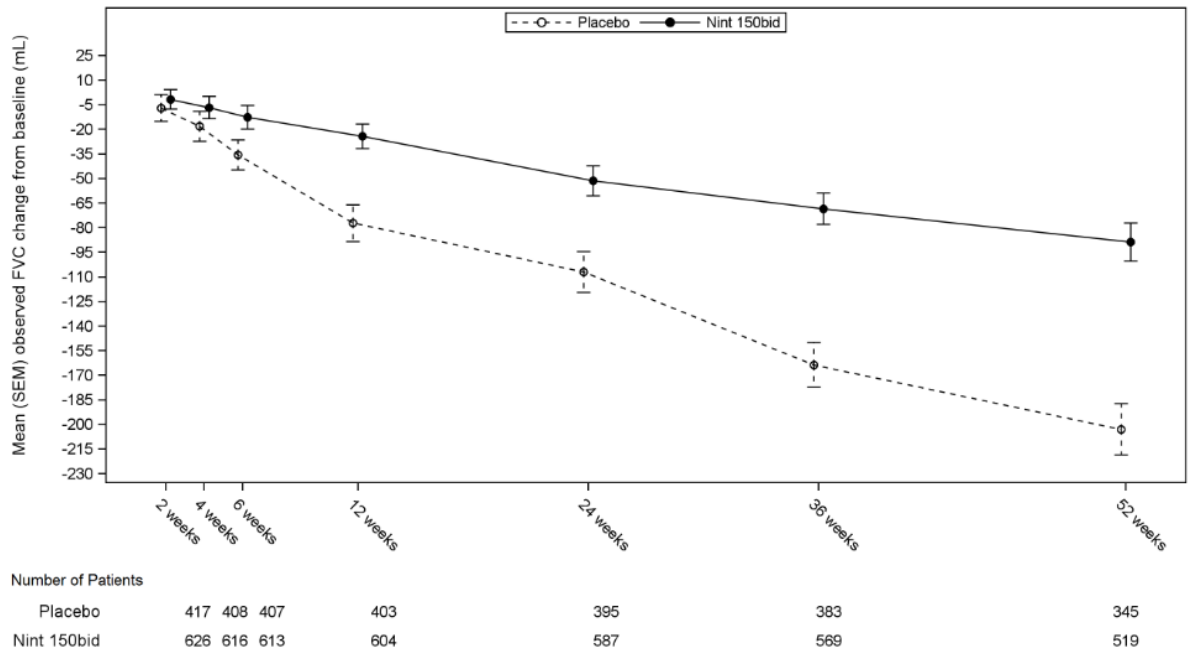
Annual rate of decline in FVC
The annual rate of decline of FVC (in mL) was significantly reduced in patients receiving OFEV compared to patients receiving placebo. The treatment effect was consistent in both trials. See Table 6 for individual and pooled study results.

Table 6: Annual rate of decline in FVC (mL) in trials INPULSIS-1, INPULSIS-2 and their pooled data - treated set

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

The robustness of the effect of OFEV in reducing the annual rate of decline in FVC was confirmed in all pre-specified sensitivity analyses. In addition, similar effects were observed on other lung function endpoints e.g. change from baseline in FVC at week 52 and FVC responder analyses providing further substantiation of the effects of OFEV on slowing disease progression. See Figure 2 for the evolution of change from baseline over time in both treatment groups, based on the pooled analysis of studies. INPULSIS-1 and INPULSIS-2.

Figure 2: 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 7 for individual and pooled study results.

Table 7: 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		0.0007		0.1833		0.0007

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

[2]Based on a logistic regression

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

In both INPULSIS trials, the risk of progression was statistically significantly reduced for patients treated with OFEV compared with placebo. In the pooled analysis, the HR was 0.60 indicating a 40% reduction in the risk of progression for patients treated with OFEV compared with placebo, see Table 8.

Table 8: Frequency of patients with ≥ 10% absolute decline of FVC % predicted or death over 52 weeks and time to progression in trials INPULSIS-1, INPULSIS-2, and their pooled data -

treated set

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

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

Change from baseline in SGRQ total score at week 52

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

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

Time to first acute IPF exacerbation

In the INPULSIS-2 trial, the risk of first acute IPF exacerbation over 52 weeks was significantly reduced in patients receiving OFEV compared to placebo, in the INPULSIS-1 trial there was no difference 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 9 for individual and pooled study results.

Table 9: Time to first acute exacerbation over 52 weeks based on investigator-reported events in

trials INPULSIS-1, INPULSIS-2, and their pooled data - treated set

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

[1] Based on data collected up to 372 days (52 weeks + 7 day margin).

[2] Based on a Log-rank test.

[3] Based on a Cox's regression model.

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

Survival analysis

In the pre-specified pooled analysis of survival data of the INPULSIS trials, overall mortality over 52 weeks was lower in the OFEV group (5.5%) compared with the placebo group (7.8%). The analysis of time to death resulted in a HR of 0.70 (95% CI 0.43, 1.12; p =0.1399). The results of all survival endpoints (such as on-treatment mortality and respiratory mortality) showed a consistent numerical difference in favour of OFEV (see Table 10).

Table 10: 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 a 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).

Chronic fibrosing Interstitial Lung Diseases (ILDs) with a progressive phenotype (PF-ILD)

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

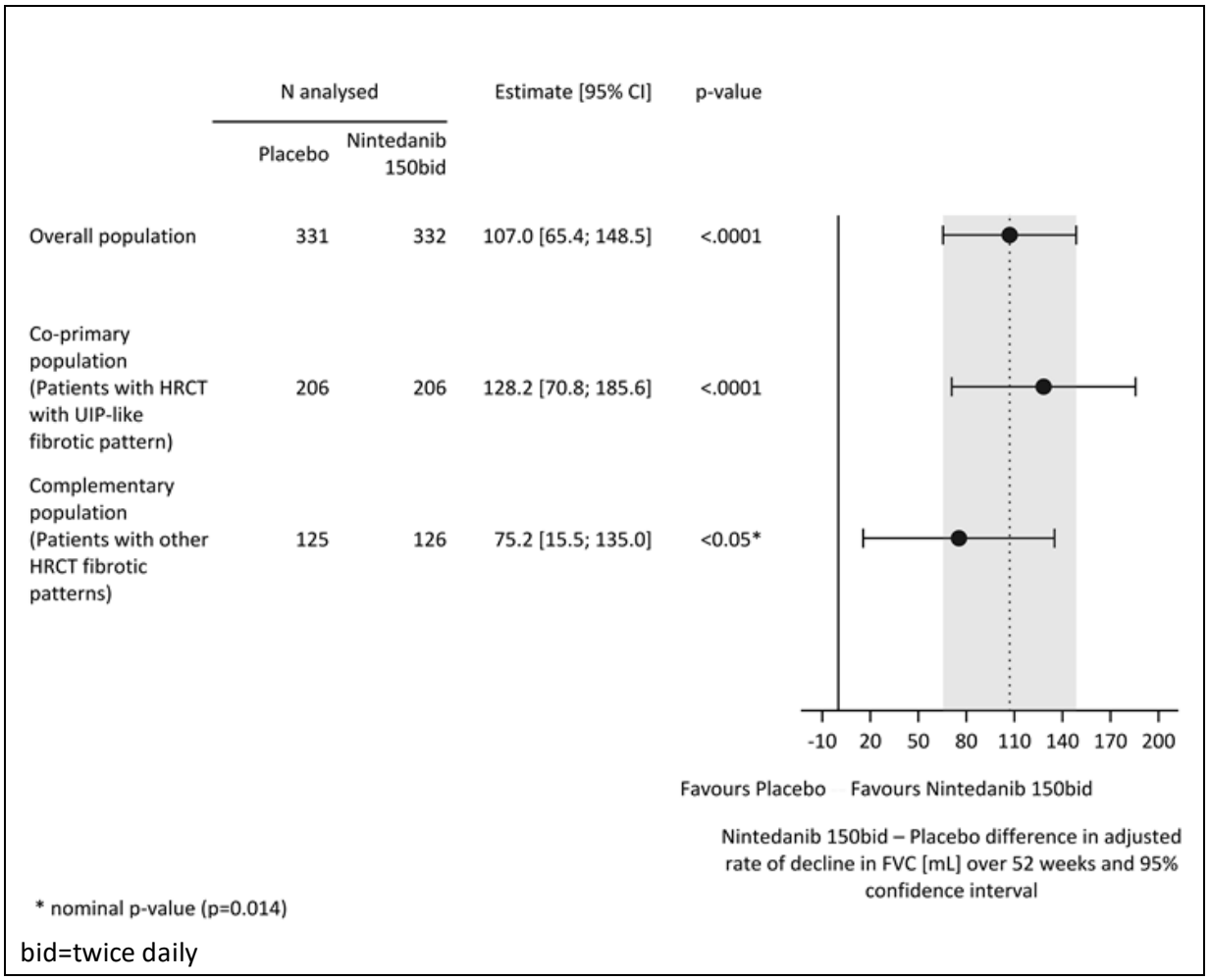
Table 11: Annual rate of decline in FVC (mL) over 52 weeks

	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). (Figure 3)

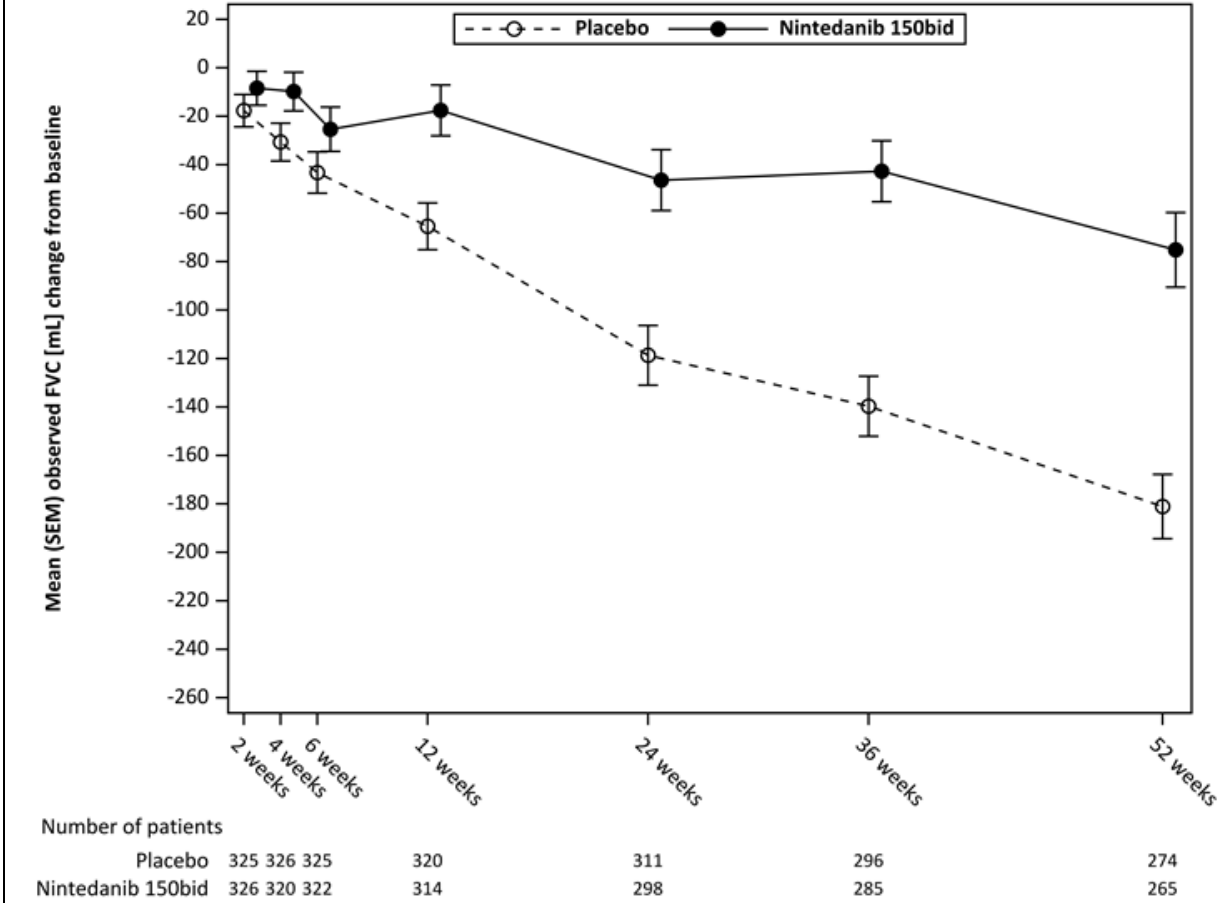
Figure 3: Forest plot of the annual rate of decline in FVC (mL) over 52 weeks in the patient populations



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

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

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



bid=twice daily

In addition, favourable effects of OFEV were observed on the adjusted mean absolute change from baseline in FVC % predicted at week 52.The adjusted mean absolute change from baseline to week 52 in FVC % predicted was lower in the nintedanib group (-2.62%) than in the placebo group (-5.86%).
The adjusted mean difference between the treatment groups was 3.24 (95% CI: 2.09, 4.40, nominal p<0.0001).

FVC responder analysis

The proportion of FVC responders, defined as patients with a relative decline in FVC % predicted no greater than 5%, was higher in the OFEV group as compared to placebo. Similar results were observed in analyses using a threshold of 10% (Table 12).

Table 12: 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).

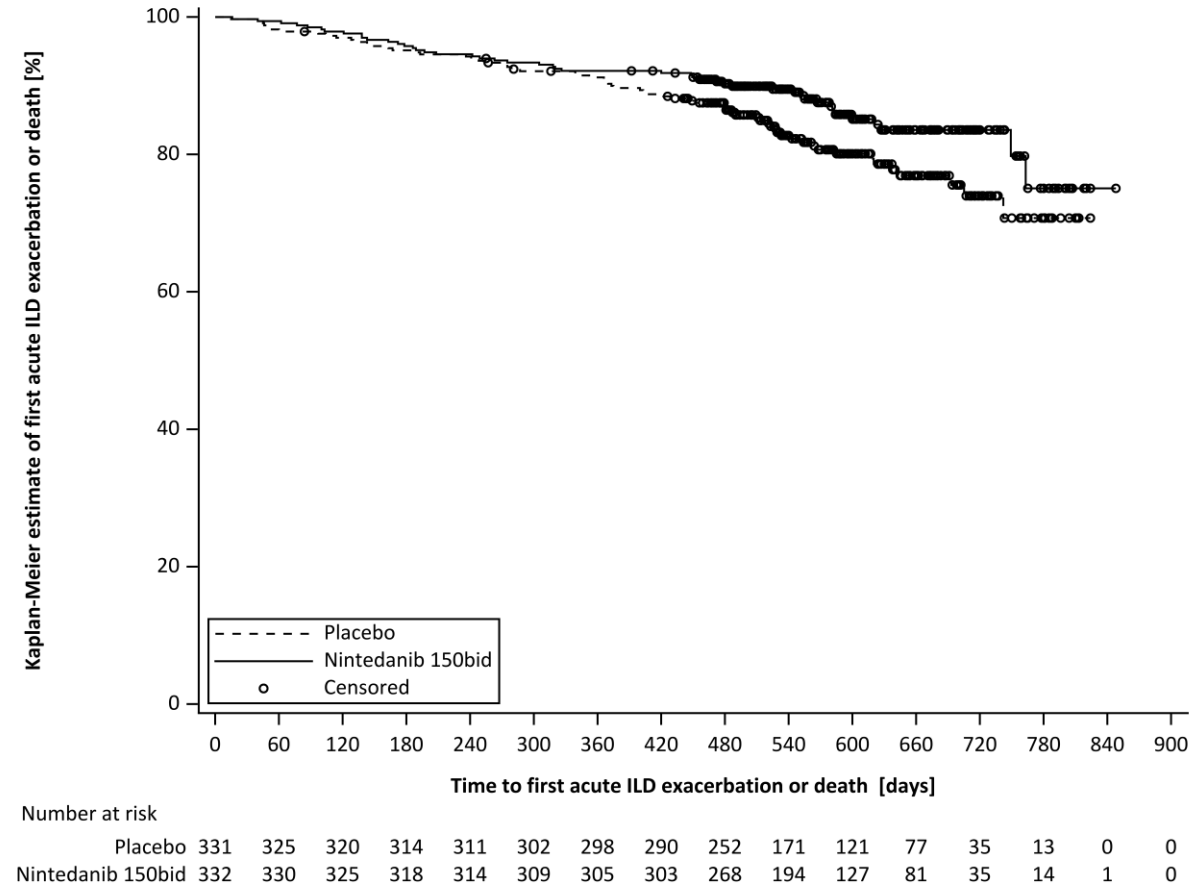
[2]Based on a logistic regression model with continuous covariate baseline FVC % predicted and binary covariate HRCT pattern

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 5).

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



bid=twice daily

Survival analysis

The proportion of patients who died over 52 weeks was 4.8% in the OFEV group compared to 5.1% in the placebo group. The HR was 0.94 (95% CI: 0.47, 1.86; nominal p=0.8544).

In the analysis of data over the whole trial, the risk of death was lower in the OFEV group compared to the placebo group. The HR was 0.78 (95% CI: 0.50, 1.21; nominal p=0.2594), indicating a 22% reduction in the risk of death in patients receiving OFEV compared to placebo.

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

In the INBUILD trial, the risk of progression (≥ 10% absolute decline of FVC % predicted) or death was reduced for patients treated with OFEV. The proportion of patients with an event over 52 weeks was 25.6% in the OFEV group and 37.5% in the placebo group. The HR was 0.65 (95% CI: 0.49, 0.85; nominal p=0.0017).

In the analysis of data over the whole trial, the proportion of patients with an event of progression (≥ 10% absolute decline of FVC % predicted) or death was 40.4 % in the OFEV group and 54.7 % in the placebo

group. The HR was 0.66 (95% CI: 0.53, 0.83; p= 0.0003), indicating a 34% reduction in the risk of progression (≥ 10% absolute decline of FVC % predicted) or death in patients receiving OFEV compared to placebo.

Quality of life

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

- Absolute change from baseline in King's Brief Interstitial Lung Disease Questionnaire (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 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 (Table 13) corresponding to a relative treatment effect of 43.8%.

Table 13: Annual rate of decline in FVC (mL) over 52 weeks

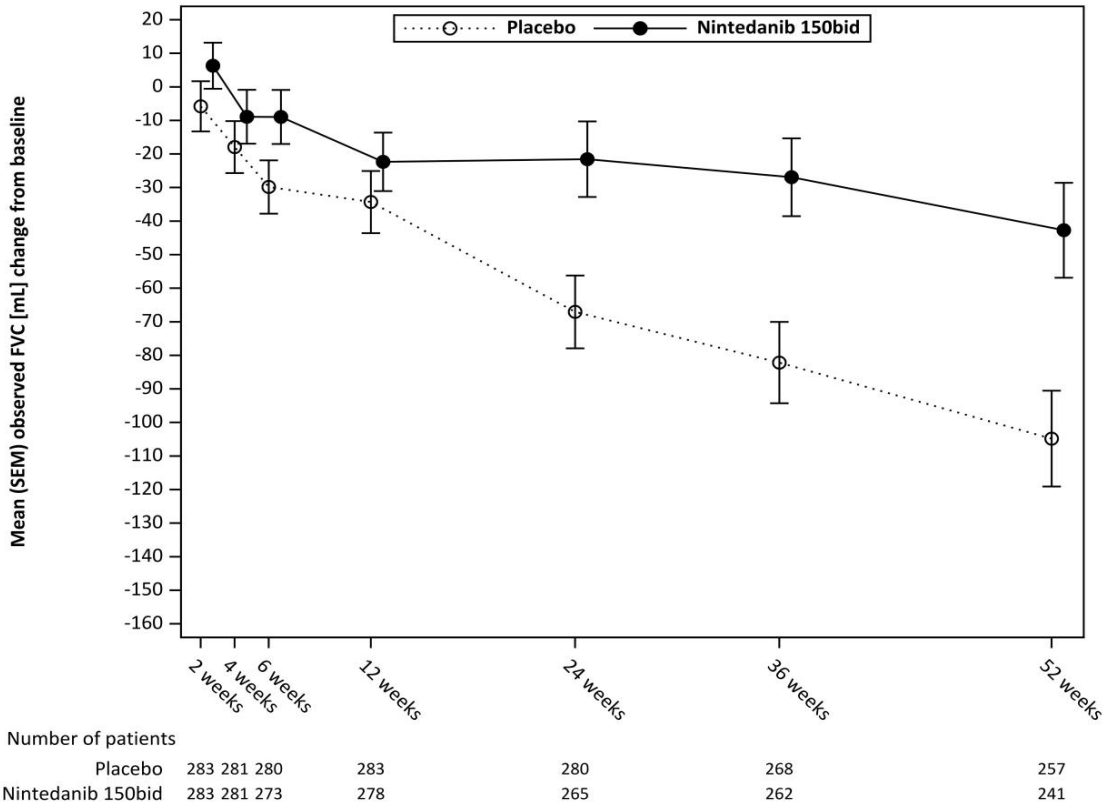
	Placebo	OFEV 150mg twice daily
Number of analysed patients	288	287
Rate[1] (SE) of decline over 52 weeks	-93.3 (13.5)	-52.4 (13.8)
Comparison vs placebo		
Difference[1] 95%CI p-value		41.0 (2.9, 79.0) <0.05
[1]Based on a random coefficient regression with fixed categorical effects of treatment, ATA status, 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 6 and Table 14) and rate of decline in FVC in % predicted over 52 weeks (Table 15) 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 14: Absolute change from baseline in FVC (mL) at week 52

	Placebo	OFEV 150mg 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

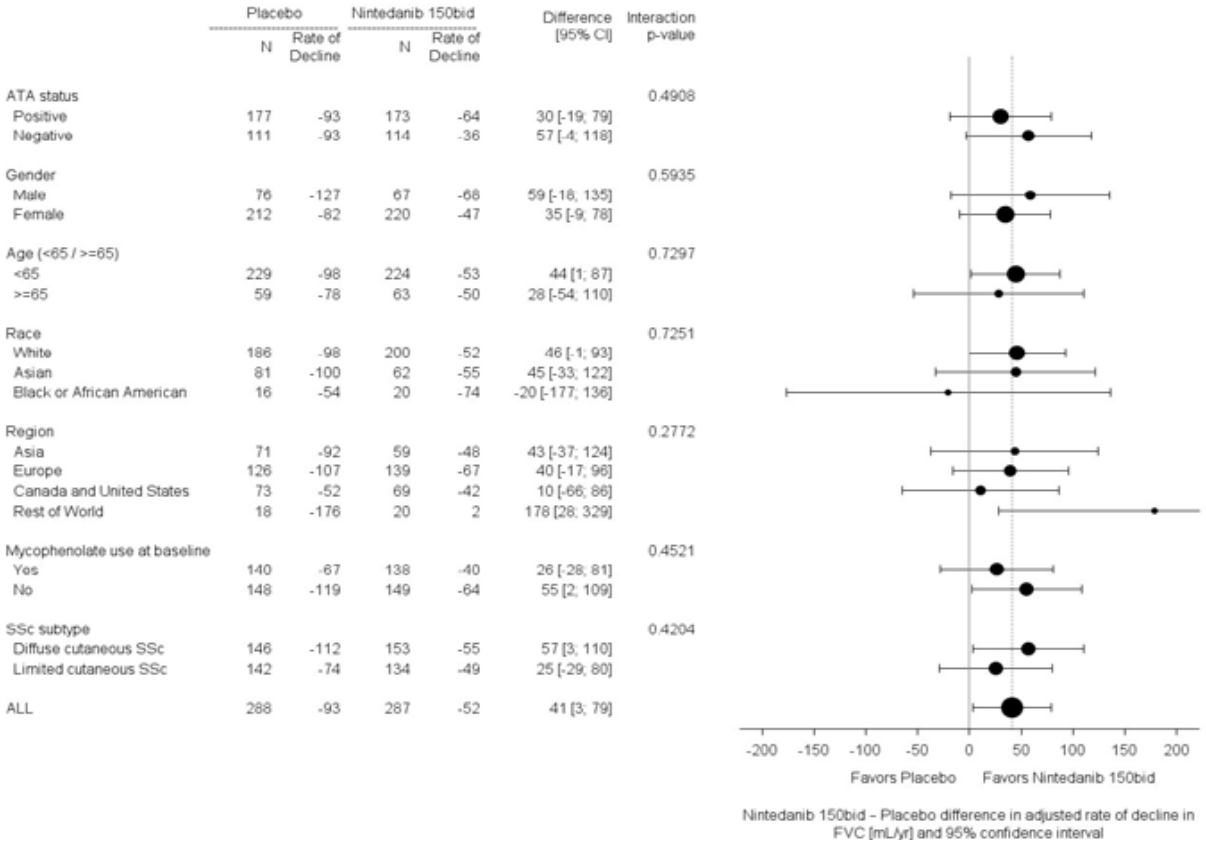
[1]Based on MMRM, with fixed categorical effects of ATA status, visit, treatment-by-visit interaction, baseline-by-visit interaction, age, gender and height. Visit was the repeated measure. Within-patient errors were modelled by unstructured variance-covariance structure. Adjusted mean was based on all analysed patients in the model (not only patients with a baseline and measurement at Week 52)

Table 15: Annual rate of decline in FVC (% predicted) over 52 weeks

	Placebo	OFEV 150mg twice daily
Number of analysed patients	288	287
Rate[1] (SE) of decline over 52 weeks	-2.6 (0.4)	-1.4 (0.4)
Comparison vs placebo		
Difference[1] 95% CI p-value		1.15 (0.09, 2.21) <0.05
[1]Based on a random coefficient regression with fixed categorical effects of treatment, ATA status, fixed continuous effects of time, baseline FVC [% pred], and including treatment-by-time and baseline-by-time interactions. Random effect was included for patient specific intercept and time. Within-patient errors were modelled by an unstructured variance-covariance matrix. Inter-individual variability was modelled by a variance-components variance-covariance matrix		

The annual rate of decline in FVC over 52 weeks was investigated in pre-specified subgroups by ATA status, gender, age, race, region, mycophenolate use at baseline, and SSc subtype. Overall, the analyses indicated a consistent treatment effect of nintedanib across all subgroups assessed.

Figure 7: Forest plot of the rate of decline in FVC [% predicted/year] over 52 weeks in subgroups in the SENSCIS trial – treated set



	Placebo		Nintedanib 150bid		Difference [95% CI]	Interaction p-value
	N	Rate of Decline	N	Rate of Decline		
ATA status						0.4908
Positive	177	-93	173	-64	30 [-19; 79]	
Negative	111	-93	114	-36	57 [-4; 118]	
Gender						0.5935
Male	76	-127	67	-68	59 [-18; 135]	
Female	212	-82	220	-47	35 [-9; 78]	
Age (<65 / >=65)						0.7297
<65	229	-98	224	-53	44 [1; 87]	
>=65	59	-78	63	-50	28 [-54; 110]	
Race						0.7251
White	186	-98	200	-52	46 [-1; 93]	
Asian	81	-100	62	-55	45 [-33; 122]	
Black or African American	16	-54	20	-74	-20 [-177; 136]	
Region						0.2772
Asia	71	-92	59	-48	43 [-37; 124]	
Europe	126	-107	139	-67	40 [-17; 96]	
Canada and United States	73	-52	69	-42	10 [-66; 86]	
Rest of World	18	-176	20	2	178 [28; 329]	
Mycophenolate use at baseline						0.4521
Yes	140	-67	138	-40	26 [-28; 81]	
No	148	-119	149	-64	55 [2; 109]	
SSc subtype						0.4204
Diffuse cutaneous SSc	146	-112	153	-55	57 [3; 110]	
Limited cutaneous SSc	142	-74	134	-49	25 [-29; 80]	
ALL	288	-93	287	-52	41 [3; 79]	

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).

Quality of Life

NSCLC

Treatment with nintedanib did not significantly change the time to deterioration of the pre-specified symptoms cough, dyspnoea and pain, but resulted in a significant deterioration in the diarrhoea symptom scale. Nevertheless, the overall treatment benefit of nintedanib was observed without adversely affecting self-reported quality of life.

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
However, 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 PHARMACOKINETICS

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

Absorption

Nintedanib reached maximum plasma concentrations approximately 2 - 4 hours after oral administration as soft gelatine capsule under fed conditions (range 0.5 - 8 hours). The absolute bioavailability of a 100 mg dose was 4.69% (90 % CI: 3.615 - 6.078) in healthy volunteers. Absorption and bioavailability are decreased by transporter effects and substantial first-pass metabolism.
Dose proportionality was shown by increase of nintedanib exposure (dose range 50 - 450 mg once daily and 150 - 300 mg twice daily). Steady state plasma concentrations were achieved within one week of dosing at the latest.
After food intake, nintedanib exposure increased by approximately 20 % compared to administration under fasted conditions (CI: 95.3 - 152.5%) and absorption was delayed (median t_{max} fasted: 2.00 hours; fed: 3.98 hours).
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 during the terminal phase (V_{SS}: 1050 L, 45.0% gCV) was observed.
The *in vitro* protein binding of nintedanib in human plasma was high, with a bound fraction of 97.8%. Serum albumin is considered to be the major binding protein. Nintedanib is preferentially distributed in plasma with a blood to plasma ratio of 0.869.

Biotransformation

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

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In preclinical in vivo experiments, BIBF 1202 did not show efficacy despite its activity at target receptors of the substance.

Elimination

Total plasma clearance after intravenous infusion was high (CL: 1390 mL/min, 28.8 % gCV). Urinary excretion of the unchanged active substance within 48 hours was about 0.05 % of 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 %).

Exposure-response relationship

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In exploratory pharmacokinetic (PK)-adverse event analyses, higher exposure to nintedanib tended to be associated with liver enzyme elevations, but not with gastrointestinal adverse events.
PK-efficacy analyses were not performed for clinical endpoints. Logistic regression revealed a statistically significant association between nintedanib exposure and DCE-MRI response.

IPF / chronic fibrosing ILDs with a progressive phenotype */ SSc-ILD*

Exposure–response analyses of patient 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 ***Special Warnings and Precautions***).

Intrinsic and Extrinsic Factors; Special Populations

The PK properties of nintedanib were similar in healthy volunteers, patients with IPF, patients with other chronic fibrosing ILDs with a progressive phenotype, patients with SSc-ILD, and cancer patients. Based on results of Population PK (PopPK) analyses and descriptive investigations, exposure to nintedanib was not influenced by sex (body weight corrected), mild and moderate renal impairment (estimated by creatinine clearance), liver metastases, ECOG performance score, alcohol consumption, or P-gp genotype. Population PK analyses indicated moderate effects on exposure to nintedanib depending onage, 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 ***Special warnings and precautions***).

Age

Exposure to nintedanib increased linearly with age. $AUC_{\tau,SS}$ decreased by 16 % for a 45-year old patient (5^{th} percentile) and increased by 13 % for a 76-year old patient (95^{th} percentile) relative to a patient with the median age of 62 years. The age range covered by the analysis was 29 to 85 years; approximately 5 % of the population was older than 75 years.
Studies in paediatric populations have not been performed.
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 (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 geometric mean exposure to nintedanib was 33 % higher in Chinese, Taiwanese, and Indian patients while it was 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

IPF

In a dedicated pharmacokinetic study, concomitant treatment of OFEV with pirfenidone was investigated in patients with IPF. Group 1 received a single dose of 150 mg OFEV 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 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). 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 $AUC_{0\text{-}tz}$ 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%; $AUC_{0\text{-}tz}$) for ethinylestradiol and 101% (90% - 113%; C_{max}) and 96% (91% - 102%; $AUC_{0\text{-}tz}$) for levonorgestrel, respectively (n=15), indicating that co-administration of nintedanib has no relevant effect on the plasma exposure of ethinylestradiol and levonorgestrel.

Drug-Drug Interaction Potential

Metabolism

Drug-drug interactions between nintedanib and CYP substrates, CYP inhibitors, or CYP inducers are

not expected, since nintedanib, BIBF 1202, and BIBF 1202 glucuronide did not inhibit or induce CYP enzymes preclinically nor was nintedanib metabolized by CYP enzymes to a relevant extent.

Transport

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

5.3 TOXICOLOGY

General toxicology

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

Reproduction toxicity

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A study of male fertility and early embryonic development up to implantation in rats did not reveal effects on the male reproductive tract and male fertility.
In rats, embryo-foetal lethality and teratogenic effects were observed at exposure levels below human exposure at the maximum recommended human dose (MRHD) 200 mg twice daily. Effects on the development of the axial skeleton and on the development of the great arteries were also noted at subtherapeutic exposure levels.
In rabbits, embryo-foetal lethality and teratogenic effects comparable to those in rats were observed at an exposure slightly higher than in rats.
In rats, small amounts of radiolabelled nintedanib and/or its metabolites were excreted into the milk (≤ 0.5 % of the administered dose).
From the 2-year carcinogenicity studies in mice and rats, there was no evidence for a carcinogenic potential of nintedanib.
Genotoxicity studies indicated no mutagenic potential for nintedanib.

IPF / chronic fibrosing ILDs with a progressive phenotype */ SSc-ILD*

A study of male fertility and early embryonic development up to implantation in rats did not reveal effects on the male reproductive tract and male fertility.
In rats, embryo-foetal lethality and teratogenic effects were observed at exposure levels below human exposure at the maximum recommended human dose (MRHD) of 150 mg twice daily. Effects on the development of the axial skeleton and on the development of the great arteries were also noted at subtherapeutic exposure levels.
In rabbits, embryo-foetal lethality and teratogenic effects comparable to those in rats were observed at an exposure slightly higher than in rats.
In rats, small amounts of radiolabelled nintedanib and/or its metabolites were excreted into the milk (≤ 0.5 % of the administered dose).
From the 2-year carcinogenicity studies in mice and rats, there was no evidence for a carcinogenic potential of nintedanib.
Genotoxicity studies indicated no mutagenic potential for nintedanib.

6. PHARMACEUTICAL PARTICULARS

6.1 STORAGE CONDITION

Do not store above 25°C.
Store in the original package in order to protect from moisture.

6.2 CONTAINER CLOSURE SYSTEM

Aluminium/Aluminium Blisters containing 10 capsules each

OFEV Soft Capsules 100mg: 6 strips x 10's and 12 strips x 10's
OFEV Soft Capsules 150mg: 6 strips x 10's

Not all pack sizes may be marketed.

7. MANUFACTURER

Manufactured by:
Catalent Germany Eberbach GmbH
Gammelsbacher Str. 2
69412 Eberbach

fors

Boehringer Ingelheim International GmbH
Ingelheim am Rhein
Germany

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