

## OFEV® MEDIA BACKGROUNDER

1. What is OFEV® (nintedanib\*)?
2. How does OFEV® (nintedanib\*) work?
3. Data overview
4. OFEV® (nintedanib\*) approval status

### 1. What is OFEV® (nintedanib\*)?

OFEV® (nintedanib\*) is a small molecule tyrosine kinase inhibitor (TKI) developed by Boehringer Ingelheim for idiopathic pulmonary fibrosis (IPF).<sup>1</sup> Nintedanib\* is currently approved in the US, the European Union, Japan and other territories for the treatment of IPF. Nintedanib\*, one capsule twice daily, consistently slows disease progression with approximately 50% reduction in FVC decline across a broad range of IPF patient types. \*\*<sup>2,3,4,5</sup>

### 2. How does OFEV® (nintedanib\*) work?

Nintedanib\* targets growth factor receptors, which have been shown to be involved in the mechanisms by which pulmonary fibrosis occurs. Most importantly nintedanib\* inhibits platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR) and vascular endothelial growth factor receptor (VEGFR).<sup>1,6,7</sup> It is believed that nintedanib\* reduces disease progression in IPF and slows the decline in lung function by blocking the signalling pathways that are involved in fibrotic processes.<sup>1,6,8</sup>

### 3. Data overview

Nintedanib\* has been studied in a comprehensive clinical trial programme including the Phase II TOMORROW dose finding trial, the Phase III INPULSIS®-1 and 2 trials as well as the open-label INPULSIS®-ON extension trial.

#### About the INPULSIS®-1 and -2 clinical trials

INPULSIS®-1 and -2 are two global Phase III trials which evaluated the efficacy and safety of nintedanib\* in the treatment of IPF. The trials were identical in design, e.g. with matching dosing, inclusion criteria and endpoints.<sup>9</sup>

\*Nintedanib is approved under the brand name OFEV® in the US, EU, Japan and other territories for use in patients with IPF. Nintedanib is under regulatory review by health authorities in other countries

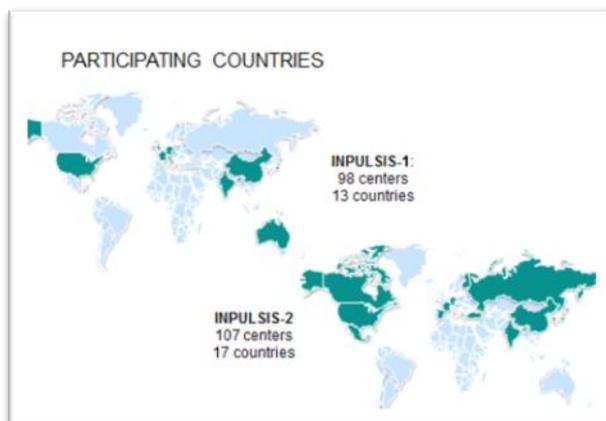
\*\*INPULSIS® recruited a broad range of patient types – similar to those seen in clinical practice including patients with early disease (FVC > 90% predicted), no honeycombing on HRCT and/or concomitant emphysema

‡Adjudicated exacerbations was a pre-specified sensitivity analysis in the pooled data set. Time to first investigator-reported exacerbation was a secondary endpoint which was met in TOMORROW and INPULSIS®-2 but not in INPULSIS®-1

Results from INPULSIS<sup>®</sup>-1 and -2 were presented at the American Thoracic Society (ATS) International Conference and published in the *New England Journal of Medicine* in May 2014.<sup>2</sup>

## INPULSIS<sup>®</sup> study design<sup>9</sup>

- Two randomised, double-blind, placebo-controlled, parallel-group trials in 1,066 patients recruited in 24 countries across the Americas, Europe, Asia and Australia
- 52-week treatment period followed by 4-week follow-up period
- 3:2 randomisation ratio for nintedanib\*:placebo
- Oral nintedanib\* 150 mg twice daily
- Dose interruption and/or dose reduction to 100 mg bid allowed to manage adverse events. After an adverse event had resolved, the dose could be reinstated at 150 mg twice daily



## Key inclusion criteria:<sup>9</sup>

Included were patients aged  $\geq 40$  years with a diagnosis of IPF established within five years before randomisation. Participants were required to have a forced vital capacity (FVC)  $\geq 50\%$  predicted, a carbon monoxide diffusion capacity (DLco) of 30-79% predicted, and to have undergone a chest high-resolution computerised (HRCT) scan  $\leq 12$  months before screening. The diagnosis of IPF was established based on the central review of chest HRCT scans from all patients by an expert radiologist. Surgical lung biopsy specimens if available were also centrally evaluated by an expert pathologist.

## Primary endpoint<sup>9</sup>

\*Nintedanib is approved under the brand name OFEV<sup>®</sup> in the US, EU, Japan and other territories for use in patients with IPF. Nintedanib is under regulatory review by health authorities in other countries

\*\*INPULSIS<sup>®</sup> recruited a broad range of patient types – similar to those seen in clinical practice including patients with early disease (FVC  $> 90\%$  predicted), no honeycombing on HRCT and/or concomitant emphysema

‡Adjudicated exacerbations was a pre-specified sensitivity analysis in the pooled data set. Time to first investigator-reported exacerbation was a secondary endpoint which was met in TOMORROW and INPULSIS<sup>®</sup>-2 but not in INPULSIS<sup>®</sup>-1

The primary endpoint was the annual rate of decline in FVC (mL/year).

### Forced vital capacity (FVC):

FVC is a lung function test measuring the amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible. As IPF progresses, lung function gradually and irreversibly deteriorates and this is measured by FVC decline. For patients with IPF randomised to placebo arms of recent IPF clinical trials, the average annual decline in FVC is in the range of 150mL to 200mL, while in the general elderly population it is approximately 30–65 mL per year.<sup>10,11,12,13</sup> In the absence of another identifiable cause, a progressive decline of FVC in patients with IPF is regarded as a manifestation of disease progression.<sup>14</sup> In addition, declines in FVC % predicted of >5% and >10% over 6–12 months are associated with a reduced survival time.<sup>14,15,16,17</sup>

### Secondary endpoints<sup>9</sup>

The key secondary endpoints were:

- Time to first acute IPF exacerbation (investigator-reported) over 52 weeks
- Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score over 52 weeks (expressed in points). The SGRQ is a self-administered questionnaire originally developed for chronic obstructive lung disease assessing health-related quality of life (with a value of 0 indicating no impairment at all and a value of 100 indicating the worst possible health-related quality of life).

In a pre-specified sensitivity analysis for the pooled data set of the INPULSIS<sup>®</sup> trials, all exacerbations reported by the site investigators as adverse events were adjudicated as confirmed, suspected or no exacerbation in a blinded manner by an Independent Adjudication Committee before database lock.

### INPULSIS<sup>®</sup> results<sup>2</sup>

Nintedanib\*, one capsule twice daily, consistently slows disease progression with an ~50% reduction in FVC decline across a broad range of IPF patient types\*\* – including patients with early disease (FVC>90% predicted), no honeycombing on HRCT and/or concomitant emphysema.<sup>2,3,4,5</sup>

The annual rate of FVC decline in the two trials was:

- INPULSIS<sup>®</sup>-1: -114.7mL (nintedanib\*) vs. -239.9mL (placebo)
- INPULSIS<sup>®</sup>-2: -113.6mL (nintedanib\*) vs. -207.3mL (placebo)

\*Nintedanib is approved under the brand name OFEV<sup>®</sup> in the US, EU, Japan and other territories for use in patients with IPF. Nintedanib is under regulatory review by health authorities in other countries

\*\*INPULSIS<sup>®</sup> recruited a broad range of patient types – similar to those seen in clinical practice including patients with early disease (FVC > 90% predicted), no honeycombing on HRCT and/or concomitant emphysema

‡Adjudicated exacerbations was a pre-specified sensitivity analysis in the pooled data set. Time to first investigator-reported exacerbation was a secondary endpoint which was met in TOMORROW and INPULSIS<sup>®</sup>-2 but not in INPULSIS<sup>®</sup>-1

Nintedanib\* also reduced the risk of adjudicated acute exacerbations<sup>‡</sup> by 68%. IPF exacerbations – events of acute respiratory worsening with no known cause – can significantly impact the course of the disease, often leading to death within a few months.<sup>18</sup> In one year, approximately 5–14% of all IPF patients may experience an exacerbation.<sup>14,19</sup> The impact of treatment on the reduction of IPF exacerbations can be crucial given that approximately 50% of patients hospitalised for an acute IPF exacerbation die during hospitalisation.<sup>18</sup> **Fehler! Textmarke nicht definiert.**

There was a significant, albeit small benefit of nintedanib\* versus placebo in change in SGRQ total score in INPULSIS<sup>®</sup>-2, but no significant difference between groups in INPULSIS<sup>®</sup>-1.

In both trials, the most common adverse events were of gastrointestinal nature, of mild to moderate intensity, generally manageable, and rarely leading to treatment discontinuation. The most frequent adverse event in the nintedanib\* groups was diarrhoea, which was reported in 62% vs. 19% (INPULSIS<sup>®</sup>-1) and 63% vs. 18% (INPULSIS<sup>®</sup>-2) of patients in the nintedanib\* vs. placebo groups, respectively. Less than 5% of patients in the nintedanib\* groups of INPULSIS<sup>®</sup>-1 and INPULSIS<sup>®</sup>-2 discontinued treatment due to this event. Side effects can be effectively managed in most patients. The proportion of patients with serious adverse events was similar in all groups.

Further analyses from the two INPULSIS<sup>®</sup> Phase III clinical trials confirmed the effect of nintedanib\* on slowing disease progression in a broad range of IPF patient types. One analysis confirmed that patients taking anti-acid medications at baseline also benefited from the effect of nintedanib\* on FVC decline.<sup>20</sup> Anti-acid medications are commonly given to patients with IPF to manage gastroesophageal reflux disease. In addition, another analysis showed that the effect of nintedanib\* on FVC decline was independent of the use of corticosteroid medication at baseline.<sup>21</sup>

### Open-label extension trial (INPULSIS<sup>®</sup>-ON) *The effect and safety of nintedanib\* long-term*

More than 90% of eligible patients who participated in the INPULSIS<sup>®</sup> trials opted to continue with nintedanib\* treatment as part of an open-label extension trial which is currently ongoing.<sup>22</sup> INPULSIS<sup>®</sup>-ON is a single arm study. Patients with idiopathic pulmonary fibrosis (IPF) on placebo in the INPULSIS<sup>®</sup> trials initiated treatment with nintedanib\* in the extension trial and patients treated with nintedanib\* continued to receive treatment.

\*Nintedanib is approved under the brand name OFEV<sup>®</sup> in the US, EU, Japan and other territories for use in patients with IPF. Nintedanib is under regulatory review by health authorities in other countries

\*\*INPULSIS<sup>®</sup> recruited a broad range of patient types – similar to those seen in clinical practice including patients with early disease (FVC > 90% predicted), no honeycombing on HRCT and/or concomitant emphysema

‡Adjudicated exacerbations was a pre-specified sensitivity analysis in the pooled data set. Time to first investigator-reported exacerbation was a secondary endpoint which was met in TOMORROW and INPULSIS<sup>®</sup>-2 but not in INPULSIS<sup>®</sup>-1

The interim analysis of the INPULSIS<sup>®</sup> extension trial (INPULSIS<sup>®</sup>-ON) showed that the change from baseline in forced vital capacity (FVC) in patients treated with nintedanib\* at 48 weeks of the extension trial was comparable to what was observed at 52 weeks in the INPULSIS<sup>®</sup> trials.<sup>23</sup> The analysis suggests that the effect of nintedanib\* on slowing disease progression is maintained in the long-term. Long-term nintedanib\* treatment in the INPULSIS<sup>®</sup>-ON extension study also confirmed manageable safety and tolerability profile for more than 3 years.<sup>23</sup>

These data are being presented at the European Respiratory Society International Congress on 29 September 2015 at 2.45 p.m. in Room 4.1.:

- Interim analysis of nintedanib in an open-label extension of the INPULSIS<sup>®</sup> trials (INPULSIS<sup>®</sup>-ON)

#### OFEV<sup>®</sup> (nintedanib\*) approval status (up to 31<sup>st</sup> August 2015)

- The FDA approved OFEV<sup>®</sup> (nintedanib\*) for the treatment of IPF on 15 October 2014
- The European Commission approved OFEV<sup>®</sup> (nintedanib\*) for the treatment of IPF in the European Union on 15 January 2015
- Health Canada approved OFEV<sup>®</sup> (nintedanib\*) for the treatment of IPF on 25 June 2015
- The Ministry of Health, Labour and Welfare in Japan approved OFEV<sup>®</sup> (nintedanib\*) for the treatment of IPF on 3 July 2015
- Swissmedic in Switzerland approved OFEV<sup>®</sup> (nintedanib\*) for the treatment of IPF and to slow disease progression on 13 August 2015

\*Nintedanib is approved under the brand name OFEV<sup>®</sup> in the US, EU, Japan and other territories for use in patients with IPF. Nintedanib is under regulatory review by health authorities in other countries

\*\*INPULSIS<sup>®</sup> recruited a broad range of patient types – similar to those seen in clinical practice including patients with early disease (FVC > 90% predicted), no honeycombing on HRCT and/or concomitant emphysema

#Adjudicated exacerbations was a pre-specified sensitivity analysis in the pooled data set. Time to first investigator-reported exacerbation was a secondary endpoint which was met in TOMORROW and INPULSIS<sup>®</sup>-2 but not in INPULSIS<sup>®</sup>-1

## References:

- <sup>1</sup> Richeldi L, *et al.* Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N Engl J Med.* 2011;365:1079-1087.
- <sup>2</sup> Richeldi, L, *et al.* Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med.* 2014;370:2071-82.
- <sup>3</sup> Cottin V, Taniguchi H, Richeldi L, *et al.* Effect of baseline emphysema on reduction in FVC decline with nintedanib in the INPULSIS trials. Abstract presented at the 18th International Colloquium on Lung and Airway Fibrosis; Mont Tremblant, Canada, September 20-24, 2014. Available at: <http://iclaf.com/conference/index.php/2014/ICLAF/paper/view/151>. Accessed June 11, 2015.
- <sup>4</sup> Kolb M, Richeldi L, Kimura T, Stowasser S, Hallmann C, du Bois RM. Effect of baseline FVC on decline in lung function with nintedanib in patients with IPF: results from the INPULSIS® trials. Poster presented at the 110th American Thoracic Society Conference; Denver, Colorado, May 15–20, 2015.
- <sup>5</sup> Raghu G, Wells A, Nicholson AG, *et al.* Consistent effect of nintedanib on decline in FVC in patients across subgroups based on HRCT diagnostic criteria: results from the INPULSIS® trials in IPF. Poster presented at the 110th American Thoracic Society Conference; Denver, Colorado, May 15–20, 2015.
- <sup>6</sup> Selman M, *et al.* Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications for therapy. *Ann Intern Med.* 2001;134:136-51.
- <sup>7</sup> Hilberg F, *et al.* BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. *Cancer Res.* 2008;68:4774-4782.
- <sup>8</sup> Wollin L, *et al.* Antifibrotic and Anti-inflammatory Activity of the Tyrosine Kinase Inhibitor Nintedanib in Experimental Models of Lung Fibrosis. *J Pharmacol Exp Ther.* 2014;349:209–220.
- <sup>9</sup> Richeldi L, *et al.* Design of the INPULSIS® Trials: Two phase 3 trials of nintedanib in patients with idiopathic pulmonary fibrosis. *Respir Med.* 2014;108:1023-30.
- <sup>10</sup> Griffith KA, *et al.* Predictors of Loss of Lung Function in the Elderly. The Cardiovascular Health Study. *Am J Respir Crit Care Med.* 2001;163:61–68.
- <sup>11</sup> Janssens JP. Aging of the Respiratory System: Impact on Pulmonary Function Tests and Adaption to Exertion. *Clin Chest Med.* 2005;26:469-84, vi-vii.
- <sup>12</sup> Alexeeff SE, *et al.* Statin Use Reduces Decline in Lung Function. VA Normative Aging Study. *Am J Respir Crit Care Med.* 2007;176:742-7.
- <sup>13</sup> Brändli O, *et al.* Lung function in healthy never smoking adults: reference values and lower limits of normal of a Swiss population. *Thorax.* 1996;51:277-283.
- <sup>14</sup> Raghu G, *et al.* An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management. *Am J Respir Crit Care Med.* 2011;183:788–824.
- <sup>15</sup> Jegal Y, *et al.* Physiology Is a Stronger Predictor of Survival than Pathology in Fibrotic Interstitial Pneumonia. *Am J Respir Crit Care Med.* 2005;171:639–44.
- <sup>16</sup> Zappala CJ, *et al.* Marginal decline in forced vital capacity is associated with a poor outcome in idiopathic pulmonary fibrosis. *Eur Respir J.* 2010;35:830–6.
- <sup>17</sup> du Bois RM, *et al.* Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. *Am J Respir Crit Care Med.* 2011 Dec 15;184:1382-9.

\*Nintedanib is approved under the brand name OFEV® in the US, EU, Japan and other territories for use in patients with IPF. Nintedanib is under regulatory review by health authorities in other countries

\*\*INPULSIS® recruited a broad range of patient types – similar to those seen in clinical practice including patients with early disease (FVC > 90% predicted), no honeycombing on HRCT and/or concomitant emphysema

‡Adjudicated exacerbations was a pre-specified sensitivity analysis in the pooled data set. Time to first investigator-reported exacerbation was a secondary endpoint which was met in TOMORROW and INPULSIS®-2 but not in INPULSIS®-1

<sup>18</sup> Song JW, *et al.* Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. *Eur Respir J.* 2011;37:356-363.

<sup>19</sup> Collard H.R., *et al.* Acute Exacerbations of Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med.* 2007;176:636-643.

<sup>20</sup> Raghu G, *et al.* Effect of anti-acid medication on reduction in FVC decline with nintedanib. Abstract presented at the ERS International Congress 2015, Amsterdam, September 26 – 30, 2015

<sup>21</sup> Cottin V, *et al.* Effect of baseline corticosteroid medication on reduction in FVC decline with nintedanib. Abstract presented at the ERS International Congress 2015, Amsterdam, September 26 – 30, 2015

<sup>22</sup> Clinical Trials [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT01619085) Accessed January 2015.

<sup>23</sup> Crestani B, *et al.* Interim analysis of nintedanib in an open-label extension of the INPULSIS trials (INPULSIS-ON). Abstract presented at the ERS International Congress 2015, Amsterdam, September 26 – 30, 2015

\*Nintedanib is approved under the brand name OFEV<sup>®</sup> in the US, EU, Japan and other territories for use in patients with IPF. Nintedanib is under regulatory review by health authorities in other countries

\*\*INPULSIS<sup>®</sup> recruited a broad range of patient types – similar to those seen in clinical practice including patients with early disease (FVC > 90% predicted), no honeycombing on HRCT and/or concomitant emphysema

‡Adjudicated exacerbations was a pre-specified sensitivity analysis in the pooled data set. Time to first investigator-reported exacerbation was a secondary endpoint which was met in TOMORROW and INPULSIS<sup>®</sup>-2 but not in INPULSIS<sup>®</sup>-1