# NINTEDANIB MEDIA BACKGROUNDER

1. What is nintedanib?
2. How does nintedanib work?
3. Data overview
4. International treatment guidelines for IPF

## 1. What is nintedanib?

Nintedanib* (OFEV▼®) is a small molecule tyrosine kinase inhibitor (TKI) developed by Boehringer Ingelheim for idiopathic pulmonary fibrosis (IPF).[1] Nintedanib* is currently approved in the US, the European Union, Japan and other countries for the treatment of IPF. It is an oral treatment, given as one capsule twice daily. It has been demonstrated to slow disease progression with an approximately 50% reduction compared with placebo in the lung function decline (as measured by forced vital capacity) across a range of IPF patient types.[1-7] The difference in annual rate of FVC decline between nintedanib and placebo groups in the pooled INPULSIS® trials was 109.9 mL/year.** [2]

## 2. How does nintedanib work?

Nintedanib* targets growth factor receptors, which have been shown to be involved in the mechanisms by which pulmonary fibrosis occurs.[1,8] Most importantly nintedanib* inhibits platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR) and vascular endothelial growth factor receptor (VEGFR).[8-10] 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. [9-11]

## 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. [2,12]

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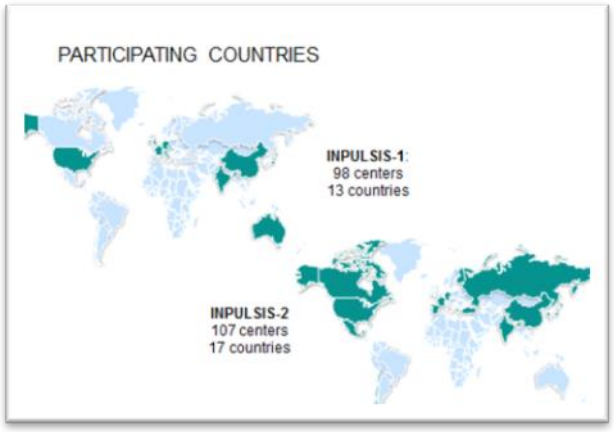
**INPULSIS® recruited a range of patient types – including patients with early disease (FVC > 90% predicted), no honeycombing on HRCT and/or concomitant emphysema

The first results from INPULSIS®-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.[2]

## INPULSIS® study design[12]

- 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
- Temporary treatment interruption and/or dose reduction to 100 mg bid allowed to manage adverse events. After an adverse event had resolved, the dose could be reinstituted at 150 mg twice daily




## Key inclusion criteria[12]

Included were patients aged ≥40 years with a diagnosis of IPF established within five years before randomisation. Participants were required to have a forced vital capacity (FVC) ≥ 50% predicted, a carbon monoxide diffusion capacity (DLco) of 30-79% predicted, and to have undergone a chest high-resolution computerised (HRCT) scan ≤ 12 months before screening. The diagnosis of IPF was confirmed 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[12]

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

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## 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 150 mL to 200 mL, while in the general elderly population it is approximately 30–65 mL per year.[13-16] In the absence of another identifiable cause, a progressive decline of FVC in patients with IPF is regarded as a manifestation of disease progression.[17] In addition, declines in FVC % predicted of >5% and >10% over 6–12 months are associated with a reduced survival time.[17-20]

## Secondary endpoints[12]

The key secondary endpoints were:

- Time to first investigator-reported acute IPF exacerbation 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).

## INPULSIS® results[2]

In the pre-specified pooled analysis of the two trials, nintedanib* reduced the decline in FVC by approximately 50% compared with placebo: the difference in annual rate of FVC decline between nintedanib and placebo groups was 109.9 ml/year.[2]

The annual rate of FVC decline in the two trials was:[2]

- INPULSIS®-1: -114.7 mL (nintedanib*) vs. -239.9 mL (placebo)
- INPULSIS®-2: -113.6 mL (nintedanib*) vs. -207.3 mL (placebo)

Nintedanib* showed a favourable but statistically non-significant trend in the pooled INPULSIS® -1 and -2 data for time to first investigator-reported exacerbation. There was a statistically significant increase in the pre-specified sensitivity analysis of time to first adjudicated exacerbation.[2]

- Time to first investigator-reported exacerbation (pooled): Hazard ratio (HR): 0.64; 95% confidence interval (CI): 0.39 to 1.05; p=0.08
- Time to first adjudicated acute exacerbation (pooled): HR: 0.32; 95% CI: 0.16 to 0.65; p=0.001

In a post hoc analysis of the data from both INPULSIS® -1 and -2 and TOMORROW (in patients with the licensed 150 mg starting dose) a statistically significant reduction in the risk of suffering one or more exacerbation as reported by the treated physician was seen.[21]

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

In both trials, the most common adverse events were of gastrointestinal nature, of mild to moderate intensity, generally manageable, and only led to treatment discontinuation in 7.6% of the group treated with nintedanib*. [1,2] The most frequent adverse event in the nintedanib* groups was diarrhoea, which was reported in 62% vs. 19% (INPULSIS®-1) and 63% vs. 18% (INPULSIS®-2) of patients in the nintedanib* vs. placebo groups, respectively. Less than 5% of patients in the nintedanib* groups of INPULSIS®-1 and INPULSIS®-2 discontinued treatment due to this event. Side effects can be effectively managed in most patients.[1,2] The proportion of patients with serious adverse events was similar in all groups.

Sub-group analysis of the trial results demonstrated the consistency of the effect of nintedanib on FVC decline across a range of IPF patient types** – including patients with minimal lung function impairment (FVC>90% predicted), no honeycombing on HRCT and/or concomitant emphysema. [1-7]

## Open-label extension trial (INPULSIS®–ON)

### *The effect and safety of nintedanib* long-term*

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

An interim analysis of INPULSIS®-ON indicates that the change from baseline in FVC in patients continuing treatment with nintedanib* in the extension trial between baseline and week 48 and between weeks 48 and 96 was comparable to what was observed in patients on active treatment with nintedanib* in the 52 week INPULSIS® parent trials.[23] The analysis suggests that nintedanib* may have a long-term effect on slowing disease progression. Average total exposure of patients treated with nintedanib* in INPULSIS® and INPULSIS®-ON trials was approximately 3 years (35.7 months).[23] Long-term treatment with nintedanib* (up to 51 months) had a manageable safety and tolerability profile, consistent with the findings of the INPULSIS® studies and with no new safety signals identified. [23]

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## 4. International treatment guidelines for IPF

The 2015 international evidence-based IPF guideline, jointly developed by an international committee including the American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society (JRS) and the Latin American Thoracic Association (ALAT), provides physicians with updated treatment recommendations for patients with IPF.

The guideline gave a conditional recommendation for the use of nintedanib* in patients with IPF. The conditional recommendation means that the majority of individuals in this situation would want the suggested course of action, but many would not.[24] Clinicians should recognise that different choices will be appropriate for individual patients and are encouraged to discuss preferences with their patients when making treatment decisions. [24]

The committee noted the high value of the potential benefit of nintedanib* on patient-important outcomes such as disease progression as measured by rate of FVC decline and mortality, and a lower value on potentially significant adverse effects and the expected cost of treatment. In comparison to more selective tyrosine kinase inhibitors, the committee noted that nintedanib* appears to have some benefit in terms of patient important outcomes in IPF, though no significant effect on overall mortality was seen.[24]

**ERS abstract information:** Crestani B, et al. Long term treatement with nintedanib in patients with IPF: an update from INPULSIS ®-ON. Abstract presented at the ERS International Congress 2016, London, September 3 - 7, 2016.

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## References:


1. OFEV® Summary of Product Characteristics. Boehringer Ingelheim Limited. August 2016.
2. Richeldi, L, et al. Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis. N Engl J Med. 2014;370:2071-82.
3. 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 August 2016.
4. 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.
5. 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.
6. Costabel U, Inoue Y, Richeldi L, et al. Efficacy of Nintedanib in Idiopathic Pulmonary Fibrosis Across Pre-specified Subgroups in INPULSIS®. AM J Respir Crit Care Med. 2015: doi: 10.1164/rccm.201503-05620C.
7. Keating GM. Nintedanib: A Review of Its Use in Patients with Idiopathic Pulmonary Fibrosis. Drugs. 2015 Jul;75(10):1131-40. doi: 10.1007/s40265-015-0418-6.
8. Hilberg F, et al. BIBF 1120: Triple Angiokinase Inhibitor with Sustained Receptor Blockade and Good Antitumor Efficacy. Cancer Res. 2008;68:4774-4782.
9. 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.
10. Richeldi L., et al. Efficacy of a Tyrosine Kinase Inhibitor in Idiopathic Pulmonary Fibrosis. N Engl J Med. 2011 Sep 22;365(12):1079-87. doi: 10.1056/NEJMoa1103690.
11. 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.
12. 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.
13. 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.
14. 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.
15. 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.
16. 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.
17. 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.
18. 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.
19. 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.
20. 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.
21. Richeldi L, et al. Pooled analysis of data from the TOMORROW and INPULSIS® trials. Resp Med 02/2016. DOI: 10.1016/ j.rmed.2016.02.001. Available at: http://www.resmedjournal.com/article/S0954-6111(16)30019-1/abstract.
22. Clinical Trials www.clinicaltrials.gov (NCT01619085) Accessed August 2016.
23. Crestani B, et al. Long term Treatement with Nintedanib in Patients with IPF: an Update from INPULSIS ®-ON. Abstract Presented at the ERS International Congress 2016, London, September 3 - 7, 2016.
24. Raghu G, et al; An Official ATS/ERS/JRS/ALAT Clinical Practice Guidelines: Treatment of Idiopathic Pulmonary Fibrosis: Executive Summary. American Journal of Respiratory and Critical Care Medicine Volume 192 (2)238 – 248, July 2015.


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