

THE INPULSIS™ TRIALS

NINTEDANIB* IN IDIOPATHIC PULMONARY FIBROSIS (IPF)

MEDIA BACKGROUNDER

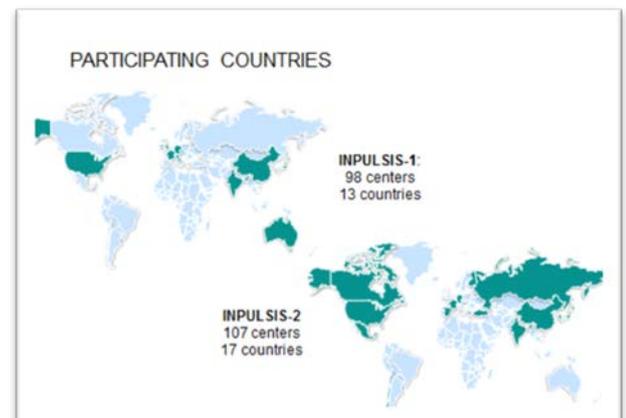
About the INPULSIS™-1 and -2 clinical trials

INPULSIS™-1 and -2 are two global Phase III trials evaluating the efficacy and safety of nintedanib* in the treatment of idiopathic pulmonary fibrosis (IPF). The trials are identical in design, e.g. with matching dosing, inclusion criteria, and endpoints.¹

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 design¹

- 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 150mg twice daily
- Dose interruption and or / dose reduction to 100mg 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:¹

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) $\geq 50\%$ 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 established based on the central review of chest HRCT scans from all patients by an expert radiologist. Surgical lung biopsy specimens were also centrally evaluated if available by an expert pathologist.

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Primary endpoint

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.^{3,4,5,6} In the absence of another identifiable cause, a progressive decline of FVC in patients with IPF is regarded as a manifestation of disease progression.⁷ In addition, declines in FVC % predicted of >5% and >10% over 6–12 months are associated with a reduced survival time.^{7,8,9,10}

Secondary endpoints¹

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™ trials, all exacerbations reported by the site investigators as adverse events were adjudicated as confirmed, suspected or no exacerbations in a blinded manner by an Adjudication Committee before database lock.

Clinically meaningful endpoints

Boehringer Ingelheim worked closely with regulatory authorities to determine the appropriate study design and clinically meaningful endpoints for the INPULSIS™ trials.

Currently, the most valid and broadly used endpoint in IPF is the lung function parameter FVC that has been shown to be a robust, relevant and responsive measure.¹⁰ The primary endpoint of annual rate of decline in FVC was selected based on consultations with both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

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Long-term lung function data together with supportive data on other clinically meaningful secondary endpoints (e.g. exacerbations) is vital when assessing treatment outcomes and disease progression in IPF. 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.¹¹ Approximately 5-14% of all IPF patients may experience an exacerbation.^{7,12}

INPULSIS™ results

Nintedanib*, one capsule twice a day, slowed disease progression by reducing the annual rate of decline in lung function by approximately 50% in a broad range of IPF patient types – including patients with early disease (FVC>90% pred), no honeycombing on HRCT and/or concomitant emphysema.

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

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

Nintedanib* also reduced adjudicated acute exacerbations** by 68%. This can be crucial given that approximately 50% of patients hospitalised for an acute IPF exacerbation die during hospitalisation.

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 rarely leading to treatment discontinuation.

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.

The proportion of patients with serious adverse events was similar in all groups.

**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

Open-label extension trial

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.¹³

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Nintedanib* in IPF

Nintedanib* is a small molecule tyrosine kinase inhibitor (TKI) in development by Boehringer Ingelheim for idiopathic pulmonary fibrosis (IPF).¹⁴ It targets growth factor receptors, which have been shown to be potentially involved in pathomechanisms of pulmonary fibrosis, most importantly the platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR) and vascular endothelial growth factor receptor (VEGFR).^{15,16} Nintedanib* has the potential to reduce disease progression in IPF by slowing the decline of lung function, by blocking the signaling pathways that are involved in fibrotic processes.^{16,17} Nintedanib* is also in clinical development as a treatment option for cancer, including non-small cell lung cancer, ovarian cancer, colorectal cancer and hepatocellular carcinoma.

Nintedanib* in IPF has been accepted for filing by the US Food and Drug Administration (FDA) and granted priority review designation as well as Breakthrough Therapy designation. In Europe, nintedanib* has been validated and granted accelerated assessment by the European Medicines Agency (EMA).

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References:

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