

**EVIDENCE BRIEFING  
JANUARY 2019**

**Nintedanib for progressive fibrosing interstitial  
lung disease**

<b>NIHRI ID</b>	15059	<b>NICE ID</b>	9828
<b>Developer/Company</b>	Boehringer Ingelheim Ltd	<b>UKPS ID</b>	648033

**Licensing and market  
availability plans**

In phase III clinical development.

**SUMMARY**

Nintedanib is an oral medicinal product under clinical development for patients with progressive fibrosing interstitial lung disease (PF-ILD). ILDs belong to a group of over 200 rare conditions that affect the tissue and space around the air sacs of the lungs, where tissue becomes thickened, stiff and scarred over a period of time. PF-ILDs are a specific sub-type where there is a progressive scarring (fibrosis) of the lung tissue that results in worsening respiratory symptoms, lung function decline, limited response to immunomodulatory therapies, organ failure, decreased quality of life and, potentially, early death.

Nintedanib is already licensed for treating idiopathic pulmonary fibrosis which is a subtype of ILDs. Nintedanib acts by blocking specific enzymes and pathways that lead to the development of blood vessels within lung cells involved in the scarring process. This inhibits further growth of the scarring tissues resulting in slowing of the disease progression. This action has been shown to be similar in patients with idiopathic pulmonary fibrosis. If licensed, nintedanib may provide the first novel therapy for PF-ILD where limited treatment options currently exist.

## PROPOSED INDICATION

Progressive fibrosing interstitial lung disease (PF-ILD)<sup>1</sup>

## TECHNOLOGY

### DESCRIPTION

Nintedanib (Ofev) is a small molecule tyrosine kinase inhibitor including the receptors platelet-derived growth factor receptor (PDGFR)  $\alpha$  and  $\beta$ , fibroblast growth factor receptor (FGFR) 1-3, and vascular endothelial growth factor receptors (VEGFRs) 1-3. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these receptors and blocks the intracellular signalling. In addition nintedanib inhibits Flt-3 (Fms-like tyrosine-protein kinase), Lck (lymphocyte-specific tyrosine-protein kinase), Lyn (tyrosine-protein kinase lyn) and Src (proto-oncogene tyrosine-protein kinase src) kinases. Nintedanib inhibits the activation of FGFR and PDGFR signalling cascades which are critically involved in proliferation, migration and differentiation of lung fibroblasts/myofibroblasts, the hallmark cells in the pathology of idiopathic pulmonary fibrosis (IPF).<sup>2</sup>

Nintedanib is under clinical development for patients with progressive fibrosing interstitial lung disease (PF-ILD). In the phase III clinical trial (INBUILD; NCT02999178), nintedanib is administered by oral soft capsule 150mg twice daily for a duration of 52 weeks.<sup>1,3</sup>

### INNOVATION AND/OR ADVANTAGES

The PF-ILD clinical trial (INBUILD) is the first in the field of fibrosing lung diseases to group patients based on the clinical behaviour of their disease, rather than the diagnosis.<sup>4</sup> There are currently no therapies with proven efficacy for patients with PF-ILD.<sup>3</sup>

Based on clinical and mechanistic parallels between PF-ILD and IPF, and converging common pathways of progressing lung fibrosis, it is anticipated that nintedanib will elicit similar effects in the wider PF-ILD population (that is, by slowing the progression of the disease). This assumption is supported by preclinical data indicating that nintedanib impacts fundamental processes of lung fibrosis and that its antifibrotic activity is independent of the known or assumed aetiologies underlying the fibrosing lung disease.<sup>3,5,6,7,8</sup>

### DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Nintedanib (Ofev) is licensed in the EU for the treatment of IPF. Very common ( $\geq 1/10$ ) adverse reactions are detailed in the summary of product characteristics (SmPC) including: diarrhoea, nausea, abdominal pain, and hepatic enzyme increase.<sup>2</sup>

Nintedanib is in phase III clinical development in the EU and globally for ILD associated with Systemic Sclerosis (SSc-ILD).<sup>9</sup>

## PATIENT GROUP

### DISEASE BACKGROUND

ILD encompasses a large group of over 200 rare and ultra-rare lung disorders with poorly understood aetiologies, with no widely accepted single classification.<sup>4,10</sup> Although these conditions are rare, a proportion of patients with ILDs may develop a progressive-fibrosing phenotype. IPF is the most

widely studied and most common ILD. It is characterised by progressive fibrosis, lung scarring and a radiological pattern known as usual interstitial pneumonia. There are a number of converging common pathways of progressing lung fibrosis between IPF and other fibrosing ILDs that may present a progressive phenotype (such as hypersensitivity pneumonitis, rheumatoid arthritis-associated ILD and unclassifiable disease). PF-ILD is the umbrella term for this group of patients based on their common disease behaviour.<sup>4,11,12,13,14</sup>

IPF can be used as a model when considering other ILDs with a progressive-fibrosing phenotype.<sup>3,15</sup> In patients with PF-ILD, the natural history appears to follow a course similar to IPF, with worsening of respiratory symptoms, lung function, health-related quality of life and functional status and with early mortality, despite treatment with currently available non-approved immunomodulatory therapies.<sup>3</sup> Risk factors reported to be associated with IPF include cigarette smoking, environmental exposures, microbial pathogens and genetics.<sup>15,16</sup>

## CLINICAL NEED AND BURDEN OF DISEASE

Despite global distribution, the proportion of patients who develop a progressive phenotype across different ILDs is not well known. This may be related to a number of reasons that includes the rare and ultra-rare nature of most of the ILDs, the heterogeneous nature of the aetiology (often unknown), the complexity of diagnosis (and subsequent recording of cases), the low numbers of patients diagnosed and the methods employed to retrospectively analyse patient databases.<sup>15</sup>

## PATIENT TREATMENT PATHWAY

### PATIENT PATHWAY

Early and accurate diagnosis of ILDs can be challenging, and it is difficult to predict disease progression. The differential diagnosis of ILDs requires a multidisciplinary approach, usually involving pulmonologists, radiologists and pathologists.<sup>11,17</sup> Evaluations include clinical presentation, specific history assessment, smoking status, lung function evolution, serological test results, imaging and, if required, lung biopsy. In nearly all cases, high-resolution computed tomography (HRCT) is the primary tool for diagnosis.<sup>11,12,16,18</sup>

The commonalities of ILDs that may present a progressive-fibrosing phenotype suggest the potential for a common treatment pathway. Most patients will have a combination of inflammation and fibrosis, and the effectiveness of immunomodulatory therapy varies between conditions.<sup>3,11</sup> Given the negative associated prognosis, further epidemiological studies are warranted to help identify ILD patients who may develop a progressive-fibrosing phenotype and enable effective clinical management.<sup>15</sup>

### CURRENT TREATMENT OPTIONS

With the exceptions of nintedanib and pirfenidone, which are licensed only for patients with IPF, there is no approved therapy for patients with PF-ILD.<sup>3,19,20</sup>

### PLACE OF TECHNOLOGY

If licensed, nintedanib will provide the first treatment option for patients with PF-ILD (other than IPF), who currently have no effective therapies available.

## CLINICAL TRIAL INFORMATION

<b>Trial</b>	INBUILD, <a href="#">NCT02999178</a> , EudraCT 2015-003360-37; nintedanib vs placebo; phase III
<b>Sponsor</b>	Boehringer Ingelheim
<b>Status</b>	Ongoing
<b>Source of Information</b>	abstract <sup>3</sup> , trial registry <sup>1,21</sup>
<b>Location</b>	EU (incl UK), USA, Canada and other countries
<b>Design</b>	Randomised, placebo-controlled, double-blind
<b>Participants</b>	<p>n=663; pts aged ≥18 years are eligible for the trial if they have a physician-diagnosed fibrosing ILD, such as connective tissue disease (CTD)-associated ILD, chronic fibrosing hypersensitivity pneumonitis (HP), idiopathic non-specific interstitial pneumonia (INSIP), unclassifiable idiopathic interstitial pneumonia (IIP), environmental/ occupational lung disease or sarcoidosis, present with features of diffuse fibrosing lung disease of &gt;10% extent on HRCT and meet the protocol criteria for progression within 24 months of screening, as assessed by the investigator.</p> <p>The criteria for evidence of progression are worsening lung function (clinically significant, ≥10% relative decline in forced vital capacity (FVC)) or worsening lung function (≥5–&lt;10% relative decline in FVC) together with worsening respiratory symptoms and/or evidence of increasing fibrosis on chest imaging, despite treatment with unapproved medications used in clinical practice to treat ILD.</p>
<b>Schedule</b>	Randomised 1:1 to either oral nintedanib 150mg or matching placebo twice daily. The dose of the study drug may be reduced to 100mg twice daily or interrupted temporarily to manage adverse events. The study consists of two parts: part A and part B. In part A, patients attend study visits at wks 2, 4, 6, 12, 18, 24, 30, 36, 44 and 52. Part B visits take place thereafter every 16 wks.
<b>Follow-up</b>	The duration of part A is 52 wks. Part B is a variable treatment period beyond 52 wks. In part B, pts continue on blinded, randomised treatment (nintedanib or placebo) until the end of the trial or until a reason for treatment withdrawal is met. The blinded trial will end once the last randomised patient reaches the wk 52 visit and the benefit-risk profile of the nintedanib treatment over 52 wks has been assessed. If the benefit-risk assessment is deemed positive, all patients will have the option of receiving open-label nintedanib.
<b>Primary Outcomes</b>	<ul style="list-style-type: none"> <li>Annual rate of decline in Forced Vital Capacity (FVC) [Time Frame: 52 wks]</li> </ul>
<b>Secondary Outcomes</b>	<p>Main secondary outcomes:</p> <ul style="list-style-type: none"> <li>Absolute change from baseline in King's Brief Interstitial Lung Disease Questionnaire (K-BILD) total score at wk 52</li> <li>Time to first acute ILD exacerbation or death over 52 wks</li> <li>Time to death over 52 wks</li> </ul> <p>Other secondary outcomes:</p> <ul style="list-style-type: none"> <li>Time to death due to respiratory cause over 52 wks</li> <li>Time to progression (defined as equal or more than 10% absolute decline in FVC % predicted) or death over 52 wks</li> <li>Proportion of pts with a relative decline from baseline in FVC % predicted of more than 10% at wk 52</li> </ul>

	<ul style="list-style-type: none"> <li>• Proportion of pts with a relative decline from baseline in FVC % predicted of more than 5% at wk 52</li> <li>• Absolute change from baseline in Living with Pulmonary Fibrosis (L-PF) Symptoms dyspnoea domain score at wk 52</li> <li>• Absolute change from baseline in L-PF Symptoms cough domain score at wk 52</li> </ul>
<b>Key Results</b>	-
<b>Adverse effects (AEs)</b>	-
<b>Expected reporting date</b>	Estimated primary completion date May 2019

## ESTIMATED COST

Nintedanib (Ofev) is already marketed in the UK for IPF; 60 x 100mg capsules and 60 x 150mg capsules both have a NHS indicative price of £2151.10 (hospital only).<sup>22</sup>

## ADDITIONAL INFORMATION

## RELEVANT GUIDANCE

### NICE GUIDANCE

- NICE proposed technology appraisal. Nintedanib for treating interstitial lung disease caused by systemic sclerosis (ID1420). Expected publication date TBC.
- NICE technology appraisal. Nintedanib for treating idiopathic pulmonary fibrosis (TA379). January 2016.
- NICE technology appraisal. Pirfenidone for treating idiopathic pulmonary fibrosis (TA504). February 2018.

### NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Service Specification: Interstitial Lung Disease Service Adult. 17009/S

### OTHER GUIDANCE

- No relevant guidance identified.

## REFERENCES

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**NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.**