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Newcastle University

Health Technology Briefing
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Nintedanib for treating interstitial lung disease in children aged 6 to 17 years old

Company/Developer	Boehringer Ingelheim Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 28315	NICE TSID: 11776	UKPS ID: 664962

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Nintedanib is a drug that is being investigated for use in patients aged 6 to 17 years old. Childhood ILD (chILD) is a group of over 200 rare lung conditions that are grouped together as they all share features such as inflammation that causes scaring in the lungs, resulting in irreversible breathing problems. Currently there are no licensed treatments for fibrosing ILD for children and adolescents.

Nintedanib works by attaching to proteins on the cells of the lungs, reducing inflammation and slowing damage to the lungs over time. Nintedanib is administered orally twice a day, along with standard of care medicines. If licensed nintedanib would be the first treatment available to this age group that treats the underlying mechanisms of ILD instead of the resulting symptoms. This would result in slowing disease progression from an earlier age, which could improve quality of life and reduce symptom severity.

Proposed Indication

Treatment of fibrosing interstitial lung disease (ILD) in children and adolescents aged 6 to 17 years old.[1]

Technology

Description

Nintedanib (Ofev, Vargatev, BIBF-1120) is a small molecule tyrosine kinase inhibitor that binds to platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, VEGFR 1-3, Lck (lymphocyte-specific tyrosine-protein kinase), Lyn (tyrosine-protein kinase lyn), Src (proto-oncogene tyrosine-protein kinase src), and CSF1R (colony stimulating factor 1 receptor) kinases. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these kinases and blocks the intracellular signalling cascades, which have been demonstrated to be involved in the pathogenesis of fibrotic tissue remodelling in interstitial lung diseases.[2]

Nintedanib is in clinical development for the treatment of patients aged 6 to 17 years old who have fibrosing ILD. In the phase III clinical trial (NCT04093024), nintedanib will be administered via twice daily oral capsule on top of standard-of-care (SOC) for 24 weeks, followed by a variable duration of Nintedanib, with dosing based on weight dependent allometric scaling.[1,3]

Key Innovation

In adult patients, nintedanib has been shown to slow the rate of decline of pulmonary function, improve health-related quality of life, and reduce the number of exacerbations.[4,5] Currently there are no medicinal products recommended by NICE for childhood ILD and these patients are treated with SOC treatments to treat the symptoms of the disease. The prognosis is variable but in some cases significantly impacts daily life, and is associated with a high degree or morbidity and mortality.[3,4,6] If licensed, nintedanib will become the first medicinal product approved for the treatment of children and adolescents aged 6 to 17 years with fibrosing ILD.

Regulatory & Development Status

Nintedanib currently has Marketing Authorisation in the EU/UK for the treatment of adults with:[7]

- Idiopathic pulmonary fibrosis
- Chronic fibrosis interstitial lung disease with a progressive phenotype
- Systemic sclerosis-associated interstitial lung disease
- Locally advanced, metastatic, or locally recurrent non-small cell lung cancer of adenocarcinoma histology after first-line chemotherapy (in combination with docetaxel)

Nintedanib is currently in phase II/III clinical trials for the treatment of various indications, including:[8]

- Ovarian cancer
- Peritoneal cancer
- Systemic scleroderma
- SARS-Cov-2 induced pulmonary fibrosis

Patient Group

Disease Area and Clinical Need

Childhood ILD (chILD) is a group of over 200 rare lung conditions found in infants, children and teenagers that are grouped together as they share some common features such as inflammation which can lead to fibrosis and scaring in the lungs.[9] Inflammation and subsequent fibrosis of the lungs reduces their elasticity, resulting in breathing difficulties which is the main symptom which characterises chILD, other symptoms include sunken ribs when breathing, noisy breathing, low growth rate, and clubbing of the fingers.[9,10] Some children are born with chILD but others develop the disease later in life. In some cases, the disease gets progressively worse over time, whereas other cases it improves over time. Over 70% of ILD cases in children have a known cause which includes factors such as: genetics, infections, or environmental causes such as exposure to chemicals or fumes.[9,10]

ILD in children is rare. Some studies have estimated the prevalence in the UK and Ireland to be around 3.6 cases per million, however the exact prevalence of ILD is difficult to estimate as data are usually for specific underlying conditions.[11,12] The most common types of chILD are due to defects in the NKX2.1 gene, mutations in the ABCA3 gene, or SFTPB gene mutations, and some common types of chILD include eosinophilic pneumonia, systemic lupus erythematosus, systemic sclerosis, but chILD can also occur due to things such as infections or toxic inhalation. Up to 11% of chILD cases remain unclassifiable with no known cause.[12]

Recommended Treatment Options

There are currently no NICE recommended treatments for ILD in patients under the age of 18. Common SOC treatments for chILD symptom management include oxygen therapy, and medication such as steroids or antibiotics to reduce inflammation or clear infections, but in extreme cases some children require lung transplantation.[6]

Clinical Trial Information

Trial	**InPedILD; NCT04093024, 2018-004530-14;** A Double Blind, Randomised, Placebo-controlled Trial to Evaluate the Dose-exposure and Safety of Nintedanib Per OS on Top of Standard of Care for 24 Weeks, Followed by Open Label Treatment With Nintedanib of Variable Duration, in Children and Adolescents (6 to 17 Year-old) With Clinically Significant Fibrosing Interstitial Lung Disease **Phase 3** – Completed **Location(s):** UK, 13 EU countries, USA, Canada, and other countries **Study completion date:** May 2022	**InPedILD-ON; NCT05285982, 2020-005554-23;** An Open-label Trial of the Long-term Safety and Tolerability of Nintedanib Per OS, on Top of Standard of Care, Over at Least 2 Years, in Children and Adolescents With Clinically Significant Fibrosing Interstitial Lung Disease (InPedILD™-ON) **Phase 3** – Recruiting **Location(s):** UK, 10 EU countries, USA and Canada **Primary completion date:** May 2026
Trial Design	Randomised, parallel assignment, double-blind, placebo-controlled	Non-randomised, parallel assignment, open label

Population	N= 39 (actual); Subjects with fibrosing interstitial lung disease; aged 6 to 17 years old	N= 60 (estimated); Subjects with fibrosing interstitial lung disease; aged 6 to 17 years old
Intervention(s)	Nintedanib (oral capsule)	Nintedanib (oral capsule)
Comparator(s)	Matched Placebo (oral capsule)	No active comparator
Outcome(s)	Primary Outcome Measures: • Area under the plasma concentration-time curve at steady state (AUCτ,ss) based on sampling at steady state (at week 2 and week 26) [time frame: week 2 and week 26] • Number (%) of patients with treatment-emergent adverse events at week 24 [time frame: week 24] See trial record for full list of other outcomes	Primary Outcome Measure: • Incidence of treatment emergent adverse events [time frame: up to 50 months]
Results (efficacy)	-	-
Results (safety)	-	-

Estimated Cost

Nintedanib is already marketed in the UK; the NHS indicative price of a pack of 100mg or 150mg capsules is £2151.10.[13]

Relevant Guidance

NICE Guidance

No relevant guidance identified.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract Paediatric Medicine: Respiratory. E03/S/g.

Other Guidance

- The chILD-EU Collaboration. European protocols for the diagnosis and initial treatment of interstitial lung disease in children. 2015.[14]
- American Thoracic Society. Clinical practice guideline: classification, evaluation, and management of childhood interstitial lung disease in infancy. 2013.[15]
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Additional Information

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