NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
January 2024

Inhaled treprostinil for treating pulmonary hypertension with interstitial lung disease including combined pulmonary fibrosis and emphysema

Company/Developer	Ferrer International S. A
☐ New Active Substance	☒ Significant Licence Extension (SLE)

NIHRIO ID: 29488	NICE ID: Not applicable	UKPS ID: 669601

Licensing and Market Availability Plans

Currently in phase II/III clinical trials.

Summary

Pulmonary hypertension is a rare and serious condition that occurs when blood pressure within the lungs becomes abnormally high. It can be caused by thickening of the pulmonary artery walls, heart failure, lung disease and clots within the lungs' blood vessels. Symptoms of pulmonary hypertension include shortness of breath, tiredness, feeling faint or dizzy, chest pain, a racing heartbeat, and swelling in the legs, ankles, feet, or abdomen. The symptoms often get worse during exercise. Pulmonary hypertension related with interstitial lung disease is associated with reduced exercise capacity, greater need for supplemental oxygen, decreased quality of life, and earlier death. There are currently no approved therapies for people with pulmonary hypertension associated with interstitial lung disease.

Treprostinil is a synthetic compound designed to mimic prostacyclin, a hormone critical for regulating blood vessel dilation. Specifically, it exerts a direct widening of the blood vessels on both pulmonary and systemic arterial circulation. Treprostinil also plays a role in stopping blood cells from sticking together. Furthermore, it interferes with compounds involved in the body's inflammatory response. If licensed, treprostinil by inhalation could provide a treatment option for adults with pulmonary hypertension with interstitial lung disease including combined pulmonary fibrosis and emphysema.

Proposed Indication

Treating adult patients with pre-capillary pulmonary hypertension (PH) associated with interstitial lung disease (ILD) including combined pulmonary fibrosis and emphysema (CPFE).[1,2]

Technology

Description

Treprostinil is an analogue of prostacyclin that has a direct vasodilation effect on the pulmonary and systemic arterial circulation and inhibits aggregation of platelets.[3] Prostacyclins are hormones affecting blood vessel dilation; they are low in people with pulmonary hypertension.[4] In addition to direct vasodilatory effects, treprostinil also inhibits inflammatory cytokines. As a synthetic analogue of prostacyclin, it binds to the prostacyclin receptor, which subsequently induces the abovementioned downstream effects.[3]

Treprostinil is in currently in clinical development for the treatment of patients with PH associated with ILD (NCT02630316, NCT05564637). In a phase II/III clinical trial (NCT02630316), adults with PH and any form of ILD or CPFE were administered treprostinil by inhalation (0.6 mg/mL) four times daily by applying an ultrasonic nebuliser, which emits a dose of approximately 6 mcg per breath titrated up to a maximum of 12 breaths.[1] In a phase II clinical trial (NCT05564637), adults with pulmonary arterial hypertension due to ILD will be administered inhaled tresprostinil of 30 mcg (five breaths) for three months with gradual titration.[2]

Key Innovation

PH related with ILD is associated with reduced exercise capacity, greater need for supplemental oxygen, decreased quality of life, and earlier death. Despite the global prevalence and poor clinical course of PH due to ILD, there are currently no approved therapies for these patients.[5] It has been claimed that systemic vasodilators could worsen ventilation-perfusion mismatch in patients with PH with ILD, which could partially explain the reported adverse outcomes. As such, inhaled agents could offer more selective and effective vasodilatory effect.[6] Inhaled treprostinil has been shown to improve functional ability, exercise capacity and to delay clinical worsening in patients with PH associated with ILD.[5,7] If licenced, inhaled treprostinil could be a new treatment option for adults with PH associated with ILD, including CPFE.

Regulatory & Development Status

Treprostinil (by continuous intravenous/ subcutaneous infusion) currently has Marketing Authorisation in the UK for idiopathic or hereditary pulmonary arterial hypertension.[8] Treprostinil is also in phase II/III clinical trials for the following indications:[9]

- Pulmonary arterial hypertension
- Idiopathic pulmonary fibrosis
- Calcinosis in patients with systemic sclerosis
- Progressive pulmonary fibrosis
- Pediatric arterial hypertension
- Patients undergoing a lower limb endovascular procedure
- Reducing ischemia-reperfusion injury during kidney transplantation

Patient Group

Disease Area and Clinical Need

PH is a rare and serious condition that occurs due to high blood pressure in the blood vessels supplying the lungs. It can be caused by: conditions that cause problems with the smaller branches of the pulmonary arteries; conditions affecting the left side of the heart; lung diseases; a shortage of oxygen in the body (known as hypoxia); and blood clots that can narrow or block the pulmonary arteries.[10,11] Symptoms of PH include: shortness of breath; tiredness; feeling faint or dizzy; chest pain (known as angina); a racing heartbeat (known as palpitations); and swelling in the legs, ankles, feet, or abdomen. The symptoms can often get worse during exercise.[11] Certain risk factors make some people more likely to get PH, including: family history; obesity and obstructive sleep apnea; pregnancy; gender; living at a high altitude for years; and other diseases, including congenital heart disease, lung disease, liver disease. Certain drugs, such as methamphetamines, are also known to be a risk factor for PH.[12] PH due to lung diseases and/or hypoxia is the second most frequent type of PH. ILDs are a broad, heterogenous group of conditions with > 200 aetiologies, which are always accompanied by variable amounts of inflammation and/or fibrosis.[13,14] CPFE involves the existence of both interstitial lung fibrosis and emphysema in one individual, which is often accompanied by PH.[15]

PH has been reported to be prevalent in up to 86% of patients with ILDs.[16] Prognosis in PH associated with ILD is poor and worse than in other groups of PH.[17] By 2022, 8,267 individuals in the UK had pulmonary hypertension.[18] In England in 2022-23, there were 5,711 finished consultation episodes (FCE) and 4,411 admissions for other secondary pulmonary hypertension (ICD-10 code I27.2), 2,841 day cases and 11,187 FCE bed days recorded.[19]

Recommended Treatment Options

PH cannot be cured but treatments can reduce symptoms and help managing the condition. If PH is caused by another condition, such as a heart or lung problem, treatments will focus on the underlying condition.[11] Treatments for PH may include anticoagulant medicines, diuretics, oxygen therapy or an operation known as a pulmonary endarterectomy.[11,20]

Clinical Trial Information

Trial	NCT02630316; A Multicenter, Randomised, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects With Pulmonary Hypertension Due to Parenchymal Lung Disease **Phase II/III** - Completed **Locations:** United States and Puerto Rico **Primary completion date:** December 2019
Trial Design	Randomised, double-blind, quadruple blind
Population	N = 326 (actual); adults aged over 18 years with World Health Organization Group 3 PH and any form of ILD or CPFE
Intervention(s)	Inhaled treprostinil (6 mcg/breath) administered four times daily
Comparator(s)	Matching placebo administered four times daily
Outcome(s)	Primary outcome measures:

	• Change in 6-minute walk distance (6MWD) measured at peak exposure from baseline to week 16. See trial record for other outcomes
Results (efficacy)	At week 16, the least-squares mean difference between the treprostinil group and the placebo group in the change from baseline in the 6-minute walk distance was 31.12 m (95% confidence interval [CI], 16.85 to 45.39; P<0.001). There was a reduction of 15% in NT-proBNP levels from baseline with inhaled treprostinil as compared with an increase of 46% with placebo (treatment ratio, 0.58; 95% CI, 0.47 to 0.72; P<0.001). Clinical worsening occurred in 37 patients (22.7%) in the treprostinil group as compared with 54 patients (33.1%) in the placebo group (hazard ratio, 0.61; 95% CI, 0.40 to 0.92; P=0.04 by the log-rank test).[5]
Results (safety)	The most frequently reported adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhoea.[5]

Trial	NCT05564637; Comprehensive O2 Transfer Analysis From the Lung to Mitochondria of Inhaled Treprostinil in Interstitial Lung Disease Pulmonary Hypertension **Phase II** - Recruiting **Location:** United States **Primary completion date (estimated):** November 2023
Trial Design	Non-randomised, parallel assignment, open label
Population	N = 18 (estimated); adults aged 18 years and over with pulmonary arterial hypertension die to interstitial lung disease being considered for inhaled trepostinil
Intervention(s)	Inhaled treprostinil 30 mcg for three months with gradual titration
Comparator(s)	-
Outcome(s)	Primary outcome measures: • Change in cardiac output reserve (Qc) [Time frame: baseline, approximately 35 minutes] See trial record for other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of inhaled treprostinil is currently unknown.

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance in development. Sotatercept for treating pulmonary arterial hypertension (TA11103). Expected date of issue to be confirmed.
- Nice technology appraisal guidance in development. Treprostinil diethanolamine for treating pulmonary arterial hypertension (TA11123). Expected date of issue to be confirmed.
- NICE clinical guideline. Idiopathic pulmonary fibrosis in adults: diagnosis and management (CG163). June 2013
- NICE Interventional procedures guidance. Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension (IPG554). April 2016.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Pulmonary Hypertension centres (Adult). A11/S/a.
- NHS England. 2013/14 NHS Standard Contract for Pulmonary Hypertension: Shared Care (Adult). A11/S/b.
- NHS England. Commissioning Policy: Targeted Therapies for use in Pulmonary Hypertension in Adults. NHS England/A11/P/c. July 2015.
- NHS England. Clinical Commissioning Policy: Targeted Therapies for Pulmonary Hypertension Functional Class II A11/P/a. April 2013.

Other Guidance

- Pulmonary Fibrosis Foundation. Pulmonary Hypertension related to ILD (For Health Care Providers). 2023.[21]
- Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. 2022.[22]
- Rajagopal S, Ruetzler K, Ghadimi K, Horn EM, Kelava M, Kudelko KT, et al. Evaluation and Management of Pulmonary Hypertension in Noncardiac Surgery: A Scientific Statement from the American Heart Association. 2023.[23]

Additional Information

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