NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
July 2022

Treprostinil diethanolamine for treating pulmonary arterial hypertension

Company/Developer	Ferrer International

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 34288	NICE ID: 11772	UKPS ID: 664929

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Treprostinil diethanolamine is in clinical development for treatment of pulmonary arterial hypertension (PAH). PAH is a rare blood vessel disorder of the lung in which the pressure in the pulmonary artery (the vessel that leads blood from the heart to the lungs) rises above normal levels. In PAH there appears to be an imbalance between vasoconstrictors (substances produced by certain cells that help to narrow the blood vessels) and vasodilators (substances produced by other cells that help to widen the blood vessels). This imbalance seems to be caused by the lack or reduction of the enzyme prostacyclin synthase, responsible for producing prostacyclin. Treprostinil diethanolamine is a substance similar to prostacyclin and is expected to act in a similar way on the pulmonary arteries in patients with PAH.

Treprostinil diethanolamine is an innovative salt form as it has been developed for oral delivery as a prolonged release (PR) osmotic tablet. Treprostinil has shown clinical effectiveness in reducing disease progression and is also licensed for the treatment of PAH when administered orally. If licensed, treprostinil diethanolamine will provide a novel oral treatment option for adults and adolescents 12 years and older with PAH.

Proposed Indication

Pulmonary Arterial Hypertension (PAH)[1-3]

Technology

Description

Treprostinil (treprostinil sodium) is a prostacyclin analogue. It exerts a direct vasodilation effect on the pulmonary and systemic arterial circulation and, inhibits platelet aggregation.[4] The primary mechanism of action of treprostinil is reduction in pulmonary artery pressure through direct vasodilation of the pulmonary and systemic arterial vascular beds, thereby improving systemic oxygen transport and increasing cardiac output with minimal alteration of the heart rate.[5] In addition to treprostinil's direct vasodilatory effects, it also inhibits inflammatory cytokine. As a synthetic analogue of prostacyclin, it binds to the prostacyclin receptor, which subsequently induces the aforementioned downstream effects.[6] Treprostinil diethanolamine (UT-15C, UT-15C SR) is an innovative salt form developed for oral delivery as a prolonged release (PR) osmotic tablet. Both treprostinil sodium and treprostinil diethanolamine disassociate in blood and exist as the ionized, bioactive form of treprostinil.[1,7]

In the phase III clinical trials (NCT01560624, NCT00325442, NCT00887978, NCT00325403) PAH patients are given 0.125, 0.25, 0.5, 1, 2.5 and 5mg oral tablets of treprostinil diethanolamine, which is administered orally every 12 hours.[1-3] If licensed, treprostinil diethanolamine will provide an oral treatment option for adults and adolescents 12 years and older with PAH.

Key Innovation

Treprostinil diethanolamine is an innovative salt form developed for oral delivery as a prolonged release (PR) osmotic tablet. As an orally available formulation, treprostinil diethanolamine SR avoids the need for infusion devices and the associated demands and risks associated with the intravenous or subcutaneous route of delivery.[7] Treprostinil diethanolamine (oral use) might be of potential significant benefit for the treatment of PAH. The FREEDOM-EV trial (NCT01560624) demonstrated that oral treprostinil administered as a monotherapy three times daily to participants with PAH reduced the likelihood of clinical worsening due to disease progression.[8]

Regulatory & Development Status

Treprostinil diethanolamine does not have MA in the UK/EU.

Treprostinil sodium has Marketing Authorization in the UK/EU for the following indications: [4,9]

- Idiopathic or heritable PAH to improve exercise tolerance and symptoms of the disease in patients classified as New York Heart Association (NYHA) functional class III.
- Treatment of adult patients with WHO Functional Class (FC) III or IV and: inoperable chronic thromboembolic pulmonary hypertension (CTEPH), or persistent or recurrent CTEPH after surgical treatment to improve exercise capacity.

Treprostinil sodium has the following regulatory awards/designations:[10]

- An orphan drug in the EU in 2004 for the treatment of PAH and chronic thromboembolic pulmonary hypertension

Patient Group

Disease Area and Clinical Need

PAH is a rare blood vessel disorder of the lung in which the pressure in the pulmonary artery (the vessel that leads blood from the heart to the lungs) rises above normal levels.[10] The pulmonary arteries are the blood vessels that carry blood from the right side of the heart through the lungs.[11] An increase of the number of smooth muscle cells in the walls of small lung arteries (a phenomenon called proliferation) that are remodelling the vessels, may lead to obstructions in the microcirculation, which will then lead to an increase in the blood pressure.[10] The World Health Organisation (WHO) functional class system defines the severity of an individual's symptoms and how they impact on day-to-day activities. WHO functional class II have pulmonary hypertension resulting in slight limitation of physical activity and experience PAH symptoms when carrying out ordinary physical activity. WHO functional class III results in marked limitation of physical activity, which can cause difficulty in carrying out general day-to-day activities, such as household chores.[12] Symptoms of PAH include shortness of breath (dyspnea) especially during exercise, chest pain, and fainting episodes. The exact cause of PAH is unknown and although treatable, there is no known cure for the disease. PAH usually affects women between the ages of 30-60 years. It is important to treat PAH because without treatment, high blood pressure in the lungs causes the right heart to work much harder, and over time, this heart muscle may weaken or fail.[11]

In England (2020-21), there were 1,504 finished consultant episodes (FCE) and 1,129 admissions for primary pulmonary hypertension (ICD-10 code I27.0) and 4,007 finished consultant episodes (FCE) and 2,728 admissions for other secondary pulmonary hypertension (ICD-10 code I27.2).[13] For patients with PAH in the United States, the 1-, 2-, and 3-year mortality rates are 8%, 16%, and 21%, respectively.[14]

Recommended Treatment Options

Treatment for PAH can be broadly split into three categories:[11,15]

- Conventional (or background) therapy:
  - Oxygen therapy – inhalation of air which contains a higher concentration of oxygen than normal
  - Anticoagulant medication – e.g. warfarin
  - Diuretic medication – e.g. furosemide, bumetanide, metolazone
- Targeted therapy: these therapies are used to slow disease progression and potentially reverse damage to the heart and lungs
  - Calcium channel blockers – nifedipine, diltiazem, nicardipine, amlodipine (used specifically for idiopathic PAH)
  - Endothelin receptor antagonists – ambrisentan, bosentan, macitentan
  - Phosphodiesterase 5 inhibitors – sildenafil, tadalafil
  - Prostaglandins – e.g. epoprostenol, selexipag
  - Soluble Guanylate Cyclase Stimulators – e.g. Riociguat (used for PAH generally and as the first targeted therapy for Chronic Thromboembolic Pulmonary Hypertension [CTEPH])
- Surgery
  - Pulmonary endarterectomy (removal of blood clots in the pulmonary artery)
  - Arterial septostomy (hole made between the left and right atria of the heart to reduce pressure in the right side of the heart, improving blood flow to the lungs)
  - Transplant surgery (of heart and lungs or lungs alone)

Clinical Trial Information

Trial	**FREEDOM-EV**, NCT01560624; A Phase III, International, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Clinical Worsening Study of UT-15C in Subjects With Pulmonary Arterial Hypertension Receiving Background Oral Monotherapy **Phase III**: Completed **Location(s)**: 9 EU countries, UK, US, Canada and other countries **Actual study completion date**: June 2018
Trial Design	Randomised, parallel assignment, quadruple masking
Population	N=690, adults ages 18 to 75 years, have a diagnosis of symptomatic idiopathic or heritable PAH, PAH associated with connective tissue disease (CTD), PAH associated with HIV infection, PAH associated with repaired congenital systemic-to-pulmonary shunt, or PAH associated with appetite suppressant or toxin use; are optimally treated with conventional pulmonary hypertension therapy with no additions, discontinuations, or dose changes for a minimum of 10 days prior to randomization; are receiving a PAH-approved oral monotherapy at a minimum dose that complies with the approved prescribing information for the product for at least 30 days prior to randomization and are receiving a stable dose for at least 10 days prior to randomization; a baseline 6MWD greater than or equal to 150 m in the absence of a concurrent injury, illness, or other confounding factor
Intervention(s)	Treprostinil diolamine extended-release tablets (oral) 0.125 to 12 mg TID
Comparator(s)	Matching placebo tablets (oral)
Outcome(s)	Primary outcome: - Time to first clinical worsening event [time frame: from randomization to approximately 4 years] See trial record for full list of records
Results (efficacy)	See trial record
Results (safety)	See trial record

Clinical Trial Information	
Trial	**FREEDOM-C2**, NCT00887978; A 16-Week, International, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of the Efficacy and Safety of Oral UT-15C Sustained Release Tablets in Subjects With Pulmonary Arterial Hypertension **Phase III**: Completed **Location(s)**: 8 EU countries, UK, US, Canada and other countries **Actual study completion date**: July 2011
Trial Design	Randomised, parallel assignment, double masking
Population	N=310, adults ages 18 to 75 years, body weight at least 40 kg (approximately 100 pounds), PAH that is either idiopathic/heritable; associated with appetite

	suppressant or toxin use; associated with collagen vascular disease; associated with repaired congenital shunts; associated with HIV, currently receiving an approved endothelin receptor antagonist and/or an approved phosphodiesterase-5 inhibitor for at least 90 days and on a stable dose for at least the last 30 days, baseline six-minute walk distance (6MWD) between 150-425 meters.
Intervention(s)	Doses were initiated at 0.25 mg twice a day (BID) and increased by 0.25 mg BID every three days (as clinically indicated based on tolerability and symptoms of PAH), to a max dose of 16 mg BID.
Comparator(s)	Identical placebo tablets to UT-15C, doses were titrated in the same manner
Outcome(s)	Primary outcome: - 6 minute walk distance (6MWD) [time frame: baseline and 16 Weeks] See trial record for full list of records
Results (efficacy)	See trial record
Results (safety)	See trial record

Clinical Trial Information	
Trial	**FREEDOM-M**, NCT00325403; A 12-Week, International, Multicenter, Double-Blind, Randomized, Placebo-Controlled Comparison of the Efficacy and Safety of Oral UT-15C Sustained Release Tablets in Subjects With Pulmonary Arterial Hypertension **Phase III**: Completed **Location(s)**: 6 EU countries, US, Canada and other countries **Actual study completion date**: April 2011
Trial Design	Randomised, parallel assignment, double masking
Population	N=349, adults and adolescents ages 12 to 75 years, body weight at least 40 kg Body Mass Index < 45, PAH that is either idiopathic/heritable; associated with repaired congenital systemic-to-pulmonary shunts (repaired ≥ 5 years); associated with collagen vascular disease; associated with HIV, baseline six-minute walk distance (6MWD) between 200-425 meters.
Intervention(s)	Subjects receive UT-15C (oral treprostinil) twice daily
Comparator(s)	Subjects receive placebo (sugar pill) twice daily
Outcome(s)	Primary outcome: - Six minute walk distance (6MWD) [time frame: baseline and 16 weeks] See trial record for full list of records
Results (efficacy)	See trial record
Results (safety)	See trial record

Clinical Trial Information

Trial	**FREEDOM-C**, NCT00325442; 16-Week, International, Multicenter, Double-Blind, Randomized, Placebo-Controlled Comparison of the Efficacy and Safety of Oral UT-15C Sustained Release Tablets in Combination With an Endothelin Receptor Antagonist and/or a Phosphodiesterase-5 Inhibitor in Subjects With Pulmonary Arterial Hypertension **Phase III**: Completed **Location(s)**: 9 EU countries, UK, US, Canada and other countries **Actual study completion date**: Dec 2010
Trial Design	Randomised, parallel assignment, quadruple masking
Population	N=354, adults and adolescents ages 12 to 70 years, body weight at least 45 kg (approximately 100 pounds), PAH that is either idiopathic/heritable (including PAH associated with appetite suppressant/toxin use), PAH associated with repaired congenital systemic-to-pulmonary shunts (repaired ≥ 5 years), PAH associated with collagen vascular disease, or PAH associated with HIV.
Intervention(s)	UT-15C 0.25, 0.5, 1, or 5 mg oral tablets by mouth every 12 hours
Comparator(s)	Placebo 0.25, 0.5, 1, or 5 mg oral tablets by mouth every 12 hours
Outcome(s)	Primary outcome: - Six minute walk distance (6MWD) [Time frame: baseline and 16 weeks] See trial record for full list of records
Results (efficacy)	See trial record
Results (safety)	See trial record

Estimated Cost

Treprostinil sodium is available from 20mg/20ml solution to 200mg/ml solution for infusion with the estimated cost ranging from £1,338.00 to £11,417.50.[16] The cost of the oral formulation is unknown.

Relevant Guidance

NICE Guidance

No relevant guidance identified.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Pulmonary Hypertension: Centers (Adult). A11/S/a.
- NHS England. 2013/14 NHS Standard Contract for Pulmonary Hypertension: Shared Care (Adult). A11/S/b.
- NHS England. Clinical Commissioning Policy: Selexipag for treating pulmonary arterial hypertension (all ages). NHS England 170065P. June 2018.

- NHS England. Clinical Commissioning Policy: Riociguat for pulmonary arterial hypertension. NHS England: 16055/P. February 2017.
- NHS England. Clinical Commissioning Policy: National policy for targeted therapies for the treatment of pulmonary hypertension in adults. NHS England/A11/P/b. May 2014.

Other Guidance

- European Society of Cardiology. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. 2015.[17]
- MJ Connolly and G Kovacs. Pulmonary hypertension: a guide for GPs. 2012.[18]

Additional Information

References

1 ClinicalTrials.gov. *Efficacy and Safety of Oral UT-15C Tablets to Treat Pulmonary Arterial Hypertension (FREEDOM-C2)*. *Trial ID: NCT00887978*. 2009. Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT00887978 [Accessed 30th May 2022].

2 ClinicalTrials.gov. *FREEDOM - M: Oral Treprostinil as Monotherapy for the Treatment of Pulmonary Arterial Hypertension (PAH)*. *Trial ID: NCT00325403*. 2006. Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT00325403 [Accessed 30th May 2022].

3 ClinicalTrials.gov. *FREEDOM-C: Oral Treprostinil in Combination With an Endothelin Receptor Antagonist (ERA) and/or a Phosphodiesterase-5 (PDE-5) Inhibitor for the Treatment of Pulmonary Arterial Hypertension (PAH)*. *Trial ID: NCT00325442*. 2006. Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/study/NCT00325442 [Accessed 30th May 2022].

4 Electronic Medicines Compendium (EMC). *Trepulmix 10 mg/ml solution for infusion*. 2022. Available from: https://www.medicines.org.uk/emc/product/12586/smpc#PHARMACODYNAMIC_PROPS [Accessed 30th May 2022].

5 Kumar P, Thudium E, Laliberte K, Zaccardelli D, Nelsen A. A Comprehensive Review of Treprostinil Pharmacokinetics via Four Routes of Administration. *Clinical Pharmacokinetics*. 2016;55(12):1495-505. Available from: https://doi.org/10.1007/s40262-016-0409-0.

6 The Human Metabolome Database. *Showing metabocard for Treprostinil (HMDB0014518)*. Available from: https://hmdb.ca/metabolites/HMDB0014518 [Accessed 30th May 2022].

7 Shah AA, Schiopu E, Hummers LK, Wade M, Phillips K, Anderson C, et al. Open label study of escalating doses of oral treprostinil diethanolamine in patients with systemic sclerosis and digital ischemia: pharmacokinetics and correlation with digital perfusion. *Arthritis Research & Therapy*. 2013;15(2):R54. Available from: https://doi.org/10.1186/ar4216.

8 White RJ, Jerjes-Sanchez C, Bohns Meyer GM, Pulido T, Sepulveda P, Wang KY, et al. Combination Therapy with Oral Treprostinil for Pulmonary Arterial Hypertension. A Double-Blind Placebo-controlled Clinical Trial. *Am J Respir Crit Care Med*. 2020;201(6):707-17. Available from: https://doi.org/10.1164/rccm.201908-1640OC.

9 Electronic Medicines Compendium (EMC). *Treprostinil Tillomed 10 mg/ml solution for infusion*. 2020. Available from:

https://www.medicines.org.uk/emc/product/11661/smpc#INDICATIONS [Accessed 30th May 2022].

10 European Medicines Agency (EMA). *EU/3/04/197: Orphan designation for the treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension*. 2004. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu304197 [Accessed 30th May 2022].

11 National Organization for Rare Disorders (NORD). *Pulmonary Arterial Hypertension*. 2021. Available from: https://rarediseases.org/rare-diseases/pulmonary-arterial-hypertension/.

12 Pulmonary Hypertension Association UK. *The WHO functional class*. Available from: https://www.phauk.org/resources/the-who-functional-class/ [Accessed 30th May 2022].

13 NHS Digital. *Hospital Admitted Patient Care Activity 2020-21*. 2021. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21.

14 Chang KY, Duval S, Badesch DB, Bull TM, Chakinala MM, Marco TD, et al. Mortality in Pulmonary Arterial Hypertension in the Modern Era: Early Insights From the Pulmonary Hypertension Association Registry. *Journal of the American Heart Association*. 2022;11(9):e024969. https://www.ahajournals.org/doi/abs/10.1161/JAHA.121.024969.

15 Pulmonary Hypertension Association (UK). *Treatment for Pulmonary Hypertension*. Available from: https://www.phauk.org/treatment-for-pulmonary-hypertension/.

16 National Institute for Health and Care Excellence (NICE). *Treprostinil - Medicinal forms*. Available from: https://bnf.nice.org.uk/drugs/treprostinil/medicinal-forms/ [Accessed 30th May 2022].

17 Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *European Heart Journal*. 2015;37(1):67-119. Available from: https://doi.org/10.1093/eurheartj/ehv317.

18 Connolly MJ, Kovacs G. Pulmonary hypertension: a guide for GPs. *British Journal of General Practice*. 2012;62(604):e795. Available from: https://doi.org/10.3399/bjgp12X658467.

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.