Innovation Observatory

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EVIDENCE BRIEFING
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Beraprost modified release in addition to treprostinil for pulmonary arterial hypertension

NIHRIO ID	11537	**NICE ID**	9515
Developer/Company	Lung Biotechnology PBC and Toray Inc	**UKPS ID**	N/A

Licencing and market availability plans	Beraprost modified release in addition to treprostinil is currently in phase III trials for the treatment of peripheral arterial hypertension

SUMMARY

Beraprost modified release, in addition to treprostinil, is in clinical development for the oral treatment of pulmonary arterial hypertension (PAH), a rare condition causing high blood pressure in the lungs. PAH can worsen over time and cause several problems including heart failure and blood clots. In PAH, the arteries in the lungs become thickened and stiff meaning the arteries cannot stretch as well to allow blood to flow through. This makes it harder for the heart to bump blood through the arteries leading to high blood pressure and weakening of the heart.

Beraprost modified release works by mimicking a naturally available substance in the body called prostacyclin which relaxes and widens the blood vessels and prevents the formation of blood clots. It is expected that beraprost modified release will relax and widen the blood vessels in the lungs, lowering blood pressure and therefore improving symptoms of PAH. This formulation of beraprost releases the drug over several hours, which reduces the frequency of administration, making this treatment more convenient to take. If licensed, beraprost modified release will offer an additional treatment option for patients with PAH in addition to treprostinil targeted therapy.

PROPOSED INDICATION

Pulmonary arterial hypertension (PAH)[1]

TECHNOLOGY

DESCRIPTION

Beraprost modified release (Beraprost 314*d* modified release; BPS-314*d*-MR)[2, 3] is an oral chemically stable prostacyclin analog targeting the prostaglandin I2 (PGI2) receptor. PGI2 agonists are potent vasodilators and platelet aggregation inhibitors, and also help to relax smooth muscle cells through counteracting the effect of vasoconstrictive mediators. In PAH, the production of naturally occurring PGI2 is chronically impaired. This plays a crucial role in the excessive vasoconstriction, pulmonary vasculature remodeling, and thrombosis formation associated with the disease pathology. This formulation is a reformulated single isomer version of beraprost which has modified release, meaning fewer doses need to be administered.[4]

Treprostinil (Tyvaso)[5] is a potent oral antiplatelet agent. The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. 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 aforementioned downstream effects.[6]

Beraprost modified release, in addition to treprostinil, is in clinical development for the oral treatment of PAH.[3] In the phase III trial (BEAT; NCT01908699), patients already taking inhaled treprostinil (or for those who are not taking inhaled treprostinil, there is a run in period of 90 days before study enrolment where the patient takes treprostinil), are given 15µg beraprost tablets, 1 or 2 tablets four times daily.[1] Duration of treatment is not reported.

INNOVATION AND/OR ADVANTAGES

This modified formulation of beraprost is released over several hours, which reduces the frequency of administration to two oral doses per day (compared to four oral doses per day for the original beraprost formulation). This formulation of beraprost may provide benefit in relation to its mode of administration which is expected to make treatment more convenient for patients. However, this assumption will be confirmed at the time of Marketing Authorisation.[7, 4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Beraprost modified release and treprostinil do not currently have Marketing Authorisation in the EU for any indication.[8, 9]

Beraprost modified release was granted EU orphan drug status in May 2015 for the treatment of PAH.[7]

PATIENT GROUP

DISEASE BACKGROUND

PAH is a rare, progressive disorder characterised by hypertension in the arteries of the lungs (pulmonary arteries).[10] In PAH, changes to the cells which line the pulmonary arteries lead to the pulmonary arteries becoming thick and stiff, meaning they cannot expand as well to allow blood to flow through.[11, 12] This reduced blood flow makes it harder for the right side of the heart to pump blood through the arteries, resulting in gradual weakening of the right side of the heart. This can lead to heart failure.[11]

PAH can have many different causes, or be idiopathic in origin. Potential causes of primary PAH include: certain genetic mutations, certain drugs (e.g. diet drugs or methamphetamines), congenital heart disease and is associated with some other conditions (e.g. connective tissue disorders, HIV infection or chronic liver disease). PAH can also be secondary to other conditions including left sided heart disease or failure, lung disease (e.g. COPD, pulmonary fibrosis), pulmonary emboli, blood disorders, metabolic disorders or tumours pressing against pulmonary arteries.[12] Approximately 15-20% patients have heritable forms of PAH, identified causes of which include mutations in the BMPR2 gene.[10]

People with PAH may go years without diagnosis as symptoms can be mild, non-specific or only present during demanding exercise. In most cases the initial symptom is severe shortness of breath following exertion. Additional symptoms include excessive fatigue, weakness, chest pain, dizzy spells, fainting episodes, cough (sometimes with blood), enlarged heart and liver, hypotension, hoarseness and oedema of the face, ankles, abdomen and feet. People with advanced stage or severe PAH may also have cyanosis and right ventricle hypertrophy, which may lead to heart failure.[10]

The progressive nature of PAH means that means that although people may start off with mild symptoms, they will eventually require treatment to maintain a reasonable quality of life.[10] PAH can also lead to a number of complications including: right sided heart enlargement and failure due to increased pulmonary pressure, increased risk of pulmonary blood clots (which are especially dangerous in those with narrowed or blocked arteries), arrhythmias from the upper and lower heart chambers causing palpitations, dizziness and fainting and bleeding into the lungs, all of which are potentially fatal.[12]

CLINICAL NEED AND BURDEN OF DISEASE

The estimated annual incidence of PAH in the UK general population ranges from 0.9 to 7.6 cases per 1,000,000 people and the estimated prevalence of PAH in the UK general population is between 6.6 and 26 per 1,000,000 people. These figures are thought to be underestimates due to misdiagnosis or underdiagnoses of PAH patients.[13]

In England in 2016-2017 there were 924 admissions and 1,170 finished consultant episodes for primary pulmonary hypertension (ICD10: I27.0) and 6,494 admissions and 7,786 finished consultant episodes for other secondary pulmonary hypertension (ICD10: I27.2).[14]

PAH survival varies according to cause. In a 2017 German study of 2,067 people with varying causes of PAH, one, three and five year survival rates were 88%, 72% and 53% respectively in patients with primary PAH and 80%, 59% and 38% respectively in patients with PAH secondary to lung disease.[15, 16]

PAH can result in premature mortality. A 2015 study of data on 1588 PAH patients across 9 European countries (including the UK) stratified by mortality risk (low [<5%], intermediate [5-10%] and high [>10%]) concluded that mortality risk 1 year after diagnosis was 2.8% in the low risk group (n=196), 9.9% in the intermediate risk group (n=1116) and 21.2% in the high risk cohort (n=276).[17]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

If PAH is secondary or caused by another condition, treatment will focus on the underlying condition (e.g. if PAH is caused by blood clots in the pulmonary articles, anticoagulant medication may be offered). Patients with PAH are referred to one of seven specialist centres for treatment in England (of which there are seven in England). There are many different treatments available for PAH and particular treatments or combination of treatments are offered according to cause and severity.[18] Many people with PAH are treated with both conventional and targeted therapies, and some people with PAH may require surgery. The aim of treatment for PAH is to reduce symptoms, thereby improving quality of life, slowing disease progression, and reversing damage to heart and lungs.[19, 20]

CURRENT TREATMENT OPTIONS

Treatment for PAH can be broadly split into three categories: [10, 19, 21]

- 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)

PLACE OF TECHNOLOGY

If licensed, beraprost modified release will offer an additional treatment option for patients with PAH in addition to treprostinil targeted therapy. The modified release formulation of beraprost provides an option for a prostaglandin drug treatment which is longer acting and requires less frequent dosing.[4]

CLINICAL TRIAL INFORMATION

Trial	BEAT, NCT01908699, BPS-314d-MR-PAH-302; beraprost modified release vs placebo; phase III
Sponsor	Lung Biotechnology PBC
Status	Ongoing
Source of Information	Trial registry[22]
Location	USA and Israel
Design	Randomised, placebo-controlled, parallel assignment, double-blind
Participants	n=240 (planned); aged 18-80 years; pulmonary arterial hypertension; WHO functional class III or IV and declining or unsatisfactory clinical response to current PAH therapy/inhaled treprostinil therapy
Schedule	Participants currently taking inhaled treprostinil are randomly allocated in a 1:1 ratio to one of two treatment arms: 1. 15 µg beraprost modified release tablets, 1 or 2 tablets taken orally four times daily 2. 1 or 2 placebo tablets taken orally four times daily
Follow-up	Up to 144 weeks
Primary Outcomes	• Time to clinical worsening defined as time from randomization to the first of any of the events described below. [Time Frame: Assessed every 4 weeks for first 12 weeks after randomization and assessed every 12 weeks up to 144 weeks] • Clinical worsening events include: death (all causes), hospitalization due to worsening PAH, initiation of a parenteral (infusion or sub-cutaneous) prostacyclin, directly related to worsening PAH, disease progression and unsatisfactory long-term clinical response
Secondary Outcomes	• 6 minutes walk distance [Time Frame: Assessed every 4 weeks for first 12 weeks after randomization and assessed every 12 weeks up to 144 weeks] • Borg Dyspnea Score [Time Frame: Assessed every 4 weeks for first 12 weeks after randomization and assessed every 12 weeks up to 144 weeks] • WHO Functional Class [Time Frame: Assessed every 4 weeks for first 12 weeks after randomization and assessed every 12 weeks up to 144 weeks] • NT-pro-BNP levels [Time Frame: Assessed every 4 weeks for first 12 weeks after randomization and assessed every 12 weeks up to 144 weeks] • Safety will be assessed by adverse events, physical examination, vital signs, clinical laboratory parameters, and electrocardiogram findings.

	[Time Frame: Assessed every 4 weeks for first 12 weeks after randomization and assessed every 12 weeks up to 144 weeks]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date reported as October 2018

ESTIMATED COST

The cost of beraprost modified release or treprostinil is not yet known.[8, 9]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Pulmonary arterial hypertension (adults) – drugs (ID12). Expected publication date TBC.
- NICE interventional proceedures 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: Centers (Adult). A11/S/a
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- 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 and European Respiratory Society. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. August 2015.[23]

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