Health Technology Briefing
June 2022

Sotatercept for treating pulmonary arterial hypertension

Company/Developer	Merck Sharp & Dohme Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 25374	NICE ID: 11771	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Sotatercept is in clinical development for the treatment of pulmonary arterial hypertension (PAH). PAH is a rare condition causing high blood pressure in the lungs. 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. PAH can worsen over time and cause several problems including heart failure and blood clots. It often leads to limited physical activity and reduced life expectancy. Current treatments slow disease progression. However, the low survival rate highlights the need for therapies targeting alternative pathways.

Sotatercept is a novel protein that attaches to proteins in the body called activins and prevents them from activating a receptor (target) called ActRIIA. By activating ActRIIA, activins stimulate the growth of cells that make up the blood vessels. Sotatercept acts by preventing the activation of ActRIIA by activins, thus reducing the growth of new blood vessel cells, leading to reduced narrowing and thickening of the blood vessels, consequently improving the symptoms of PAH. Sotatercept is administered subcutaneously. If licensed, sotatercept will offer an additional treatment option for adult patients with PAH.

Proposed Indication

For the treatment of adults with pulmonary arterial hypertension (PAH).

Technology

Description

Sotatercept (ACE-011) is a first-in-class novel fusion protein composed of the extracellular domain of the human activin receptor type IIA fused to the Fc domain of human IgG1.[1] In the body, proteins called activins attach to a receptor (target) called ActRIIA to stimulate the growth of cells that make up the blood vessels. These receptors are thought to be over-active in patients with PAH. Sotatercept is a copy of ActRIIA, and because it also attaches to activins, it prevents them from activating the receptor. In this way, sotatercept is expected to reduce the growth of new blood vessel cells, leading to reduced narrowing and thickening of the blood vessels, thus improving the symptoms of the disease.[2]

Sotatercept is currently in phase III clinical development for the treatment of adult patients with PAH. In the phase III clinical trial (STELLAR, NCT04576988), sotatercept is administered subcutaneously at a starting dose of 0.3 mg/kg with a target dose of 0.7 mg/kg every 21 days plus background PAH therapy.[3]

Key Innovation

Sotatercept targets the imbalance between growth-promoting and growth-inhibiting signalling pathways exhibited in patients with PAH.[4] Sotatercept binds to ligands in the TGF-beta superfamily (growth differentiation factors 8 and 11, activin A and B), which are associated with promoting cell proliferation and differentiation. By binding to these ligands, sotatercept restores balance between the normally functioning growth-promoting cell pathway (ActRIIA) and the impaired growth-inhibiting pathway.[5]

In recent clinical trials, treatment with sotatercept in PAH patients resulted in a reduction in pulmonary vascular resistance in patients receiving background therapy for PAH.[1] Sotatercept is a potentially new treatment option for patients with PAH with a novel approach that may lead to pulmonary vascular wall remodelling.[5]

If licensed, sotatercept would offer an additional treatment option for adult patients with PAH.

Regulatory & Development Status

Sotatercept does not currently have Marketing Authorisation in the EU/UK for any indication.

Sotatercept is also in phase II clinical development for the combined post-capillary and pre-capillary pulmonary hypertension due to heart failure with preserved ejection fraction.[6]

Sotatercept has an orphan drug designation in the EU in 2020 for the treatment of PAH.[2]

Patient Group

Disease Area and Clinical Need

Pulmonary arterial hypertension (PAH) is a rare, progressive disorder characterised by hypertension in the arteries of the lungs (pulmonary arteries).[7] 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. 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.[8] 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. While pulmonary hypertension (PH) is relatively common, PAH is a rare subgroup. PH is classified into 5 groups depending on the underlying cause. PAH is Group 1 and includes idiopathic PAH (has no known cause), hereditary PAH (passed through genes), drug and toxin-induced PAH (caused by drugs or toxins, such as street drugs and some diet medicines), and PAH caused by several conditions (including HIV infection, connective tissue diseases, congenital heart disease, and liver disease).[9]

Symptoms of PAH 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.[7] 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, and bleeding into the lungs, all of which are potentially fatal.[10]

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.[11] In England in 2020-2021, there were 1,129 admissions and 1,504 finished consultant episodes for primary pulmonary hypertension (ICD10: I27.0), and 2,728 admissions and 4,007 finished consultant episodes for other secondary pulmonary hypertension (ICD10: I27.2).[12]

Recommended Treatment Options

There are various treatments for PAH. The treatment or combination of treatments a patient receives is dependent on a number of factors, including the cause of PAH and the severity of symptoms.[13]

Treatment for PAH can be broadly split into three categories:[7,13-15]

- Conventional (or background) therapy:
  - Oxygen therapy – inhalation of air which contains a higher concentration of oxygen than normal
  - Anticoagulant medication – warfarin
  - Diuretic medication – 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 – for example, epoprostenol, selexipag
- Soluble Guanylate Cyclase Stimulators – for example, 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)
  - Balloon pulmonary angioplasty

Clinical Trial Information

Trial	**PULSAR; NCT03496207; 2017-004738-27;** A Phase 2, Double-Blind, Placebo-Controlled, Randomized Study to Compare the Efficacy and Safety of Sotatercept (ACE-011) Versus Placebo When Added to Standard of Care for the Treatment of Pulmonary Arterial Hypertension (PAH) **Phase II** - Completed **Location(s):** 3 EU countries, UK, USA, and other countries **Study Completion date:** March 2022	**SOTERIA; NCT04796337;** An Open-Label Long-term Follow-up Study to Evaluate the Effects of Sotatercept When Added to Background Pulmonary Arterial Hypertension (PAH) Therapy for the Treatment of PAH **Phase III –** Recruiting **Location(s):** 3 EU countries, UK, USA and other countries **Primary completion date:** September 2027
Trial Design	Randomised, quadruple, parallel assignment, placebo-controlled	Open label, single group assignment
Population	N= 106 (actual); Subjects aged 18 and older with a confirmed diagnosis of PAH Group 1	N= 700 (estimated); Subjects aged 18 and older who have completed their current respective PAH sotatercept clinical study and its requirements and must not have discontinued early.
Intervention(s)	Sotatercept administered subcutaneously at either 0.3 mg/kg or 0.7 mg/kg every 21 days plus standard of care (SOC) for 24 weeks	Sotatercept at a starting dose of 0.3 mg/kg administered subcutaneously for visit 1 and a dose escalation to 0.7 mg/kg at visit 2 through the remainder of study. Participants rolling over from an unblinded parent study will continue sotatercept at their current dose and if at dose < 0.7 mg/kg SC can

		titrate up to 0.7 mg/kg SC for the remainder of the study.
Comparator(s)	Matched placebo plus SOC	No comparator
Outcome(s)	Change from baseline in Pulmonary Vascular Resistance (PVR) as measured by right heart catheterization [Time Frame: From initiation of treatment (Study Day 1) to end of placebo-controlled treatment period (Study Day 168)] See trial record for full list of other outcomes	Frequency of adverse events (AEs) [Time Frame: From date of first visit up to 200 weeks] See trial record for full list of other outcomes
Results (efficacy)	The least-squares mean difference between the sotatercept 0.3-mg group and the placebo group in the change from baseline to week 24 in pulmonary vascular resistance was −145.8 dyn·sec·cm−5 (95% confidence interval [CI], −241.0 to −50.6; P=0.003). The least-squares mean difference between the sotatercept 0.7-mg group and the placebo group was −239.5 dyn·sec·cm−5 (95% CI, −329.3 to −149.7; P<0.001). At 24 weeks, the least-squares mean difference between the sotatercept 0.3-mg group and the placebo group in the change from baseline in 6-minute walk distance was 29.4 m (95% CI, 3.8 to 55.0). The least-squares mean difference between the sotatercept 0.7-mg group and the placebo group was 21.4 m (95% CI, −2.8 to 45.7). Sotatercept was also associated with a decrease in N-terminal pro−B-type natriuretic peptide levels.[1]	-
Results (safety)	Thrombocytopenia and an increased haemoglobin level were the most common hematologic adverse events. One patient in the sotatercept 0.7-mg group died from cardiac arrest.[1]	-

Trial	**SPECTRA; NCT03738150;** A Phase 2a Single-Arm, Open-Label, Multicenter Exploratory Study to Assess the Effects of Sotatercept (ACE-011) for the Treatment of Pulmonary Arterial Hypertension **Phase II –** Completed **Location(s):** USA **Study Completion date:** March 2022
Trial Design	Open label, single assignment
Population	N= 21 (actual); Subjects aged 18 and older with PAH Group 1
Intervention(s)	Sotatercept at a dose of 0.3 mg/kg for cycle 1 with a dose escalation to 0.7 mg/kg at cycle 2 administered subcutaneously with SOC. Dosing will be every three weeks during the 24 weeks treatment period and every three weeks during the 18 month extension period
Comparator(s)	No comparator
Outcome(s)	Change from baseline in peak oxygen uptake (VO2 max) [Time Frame: From initiation of treatment Cycle 1 Day 1 to the end of Cycle 9 (each cycle is 21 days)] See trial record for full list of other outcomes
Results (efficacy)	Improvements were seen in mean change from baseline to week-24 in VO2 max, ventilatory efficiency (VE/VCO2 slope), total workload, arteriovenous O2 content difference (Ca-vO2), and reductions were seen in mean change from baseline in mPAP, PAWP, and mRAP.[16]
Results (safety)	Nine patients reported at least one treatment-emergent adverse event, with 1 patient discontinuing. Two serious adverse events were reported, both considered not related to study drug.[16]

Trial	**HYPERION; NCT04811092;** A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate Sotatercept When Added to Background Pulmonary Arterial Hypertension (PAH) Therapy in Newly Diagnosed Intermediate- and High-risk PAH Patients **Phase III –** Recruiting **Location(s):** 4 EU countries, UK, USA and other countries **Primary completion date:** June 2028
Trial Design	Randomised, double blind, parallel assignment, placebo-controlled
Population	N= 662 (estimated); Subjects aged 18 and over with Group 1 PAH
Intervention(s)	Sotatercept at a starting dose of 0.3 mg/kg with a target dose of 0.7 mg/kg administered subcutaneously every 21 days plus background PAH therapy
Comparator(s)	Matched placebo plus background PAH therapy

Outcome(s)	Time to Clinical Worsening, defined as the first confirmed morbidity event or death. [Time Frame: From screening to the first clinical worsening event, up to 56 months.] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**STELLAR; NCT04576988;** A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Compare the Efficacy and Safety of Sotatercept Versus Placebo When Added to Background Pulmonary Arterial Hypertension (PAH) Therapy for the Treatment of PAH **Phase III –** Active, not recruiting **Location(s):** 7 EU countries, UK, USA, Canada and other countries **Primary completion date:** December 2022
Trial Design	Randomised, quadruple, parallel assignment, placebo-controlled
Population	N= 284 (estimated); Subjects aged 18 and older with a confirmed diagnosis of PAH Group 1
Intervention(s)	Sotatercept at a starting dose of 0.3 mg/kg with a target dose of 0.7 mg/kg administered subcutaneously every 21 days plus background PAH therapy
Comparator(s)	Matched placebo plus background PAH therapy
Outcome(s)	Change from baseline in 6MWD. [Time Frame: From initiation of treatment to Week 24] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**ZENITH; NCT04896008;** A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Sotatercept When Added to Maximum Tolerated Background Therapy in Participants With Pulmonary Arterial Hypertension (PAH) World Health Organization (WHO) Functional Class (FC) III or FC IV at High Risk of Mortality **Phase III –** Recruiting **Location(s):** USA **Primary completion date:** November 2025
Trial Design	Randomised, triple blind, parallel assignment, placebo-controlled
Population	N= 166 (estimated); Subjects aged 18 to 75 years with PAH Group 1

Intervention(s)	Sotatercept at a starting dose of 0.3 mg/kg, with a target dose of 0.7 mg/kg, administered subcutaneously every 21 days plus background PAH therapy
Comparator(s)	Matched placebo plus background PAH therapy
Outcome(s)	Time to first confirmed morbidity or mortality event. [Time Frame: From randomization to first event, up to approximately 46 months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of sotatercept is not yet known.

Relevant Guidance

NICE Guidance

- NICE interventional procedures guidance. Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension (IPG554). April 2016.

NHS England (Policy/Commissioning) Guidance

- 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.
- NHS England. 2013/14 NHS Standard Contract for Pulmonary Hypertension: Centres (Adult). A11/S/a.

Other Guidance

- European Society of Cardiology and European Respiratory Society. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. August 2015.[17]

Additional Information

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