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INPLASY

# Sotatercept in Pulmonary Arterial Hypertension

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## ADMINISTRATIVE INFORMATION

**Support -** Nil.

**Review Stage at time of this submission -** The review has not yet started.

**Conflicts of interest -** None declared.

**INPLASY registration number:** INPLASY202420104

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 February 2024 and was last updated on 25 February 2024.

## INTRODUCTION

**Review question / Objective** To look at the efficacy, safety and tolerability of sotatercept in Pulmonary Arterial Hypertension.

**Rationale** Pulmonary Arterial Hypertension is currently treated with drugs which act on the nitric oxide, endothelin-1 and prostacyclin pathways. They predominantly work as pulmonary vasodilators there by providing symptomatic and in some cases survival benefit. Sotatercept is a first in class fusion protein made up of the extracellular domain of the activin receptor 2A and the Fc portion of the immunoglobulin G1. It acts as a ligand trap for activin and growth differentiation factors thereby inhibiting the pro-proliferative, anti-apoptotic SMAD2/3 signalling pathway. It is speculated to be a disease modifying drug capable of reverse remodelling of the pulmonary vasculature and thereby providing long term survival benefit.

**Condition being studied** Pulmonary arterial hypertension (PAH) in a rare, chronic, progressive, debilitating and life shortening condition which is characterised by pulmonary vasoconstriction, plexogenic lesions, in-stu thrombosis and pulmonary vascular remodelling due to increase in cellular proliferation in all the three layers of the pulmonary artery leading to increased pulmonary vascular resistance resulting in increased right ventricular after-load leading to right ventricular dysfunction, failure and ultimately death. PAH may result in worsening exercise capacity, symptoms and quality of life and may lead to psychological distress in a significant proportion of cases. The treatment options available for PAH are usually pulmonary vasodilators. Despite treatment the median life expectancy in PAH is only 7 years.

## METHODS

**Search strategy Sources:** MeSH terms: Sotatercept AND Pulmonary Arterial Hypertension.

Date restriction: from inception till 01/02/2024.

**Participant or population** Inclusion criteria: Adults (>18 years) patients with confirmed diagnosis of Pulmonary Hypertension at right heart catheterisation (RHC) at rest and diagnosed as Group 1 disease or Pulmonary Arterial Hypertension (PAH) who has a WHO functional class of 2 to 3 with a 6 minute walk distance of >150-500meters and pulmonary vascular resistance of >5 Wood Units and a pulmonary capillary wedge pressure of <15mmHg. The conditions within group 1 include Idiopathic PAH, Heritable PAH, Drug indued PAH, PAH associated with connective tissue disease. PAH associated with congenital heart disease (defects repaired more than 12 months ago) and are stable for more than 3 months on PH specific targeted therapy (1/2/3 medications). Exclusion Criteria: Group 2, 3., 4 and 5 PH and PAH due to Pulmonary Veno-occlusive disease, PAH associated with Shistosomiasis, PAH associated with HIV and PAH associated with portal hypertension. Forced vital capacity <60% or HRCT scan chest showing more than mild interstitial lung disease. left ventricular ejection fraction <45% and pregnancy.

**Intervention** Sotatercept 0.3mg/kg body weght or 0.7mg/kg body weight given subcutaneously every 3 weeks for the entire duration of the study as an add on therapy in patients with PAH.

**Comparator** Placebo (Saline) was given subcutaneously every 3 weeks for the entire period of the study in patients with PAHI.

**Study designs to be included** RCT, post hoc analysis, open label long term extensions, population health modelling and cost effectiveness data.

**Eligibility criteria** Inclusion criteria : Original research articles, short reports and conference abstracts.
Exclusion criteria: Editorials, view points, commentaries, case reports, reviews including narrative reviews, systematic reviews and meta analysis.

**Information sources Sources:** PubMed, Google Scholar, ClinicalTrials.gov, EU Clinical trials regsiter, Cochrane library and drug manufacturers (MSD) search.

**Main outcome(s)**
1.) 6 minute walk distance.
2.) Pulmonary Vascular Resistance.
3.) Safety (side effects).
4.) Tolerability.

**Additional outcome(s)**
1.) Pulmonary Haemodynamics (mean pulmonary arterial pressure, right atrial pressure, mixed venous oxygen saturations, cardiac output, pulmonary capillary wedge pressure and pulmonary arterial compliance).
2.) NT Pro BNP.
3.) WHO functional class.
4.) PAH risk stratification.
5.) Quality of life score (SF36, Sympact PAH and CAMPHOR).
6.) Arterial Blood gas (Partial pressure of oxygen and carbon dioxide) and oxygen saturations.
7.) Echo: Right ventricular functions including TAPSE/SPAP. RV FAC and Left ventricular ejection fraction.
8.) Pulmonary diffusion capacity.
9. Survival.
10.) Cost efficiency.

**Quality assessment / Risk of bias analysis** The two reviewers (RQ and NB) will review (search and screen) the data independently. If there are any differences it will be discussed with the rest of the collaborators and a consensus reached. We will use the risk of bias tool to assess the risk of bias in the RCTs included in our systematic review.

**Strategy of data synthesis** Systematic review.

**Subgroup analysis** Not applicable.

**Sensitivity analysis** Not applicable.

**Language restriction** English Only.

**Country(ies) involved** Ireland.

**Other relevant information** This is a systematic review of an investigational drug sotatercept which has met its primary end points in a phase 3 clinical trial and is about to be reviewed for licensing by the FDA in the USA.

**Keywords** Sotatercept, Pulmonary Arterial Hypertension.

**Dissemination plans**
Presentation in national and international conferences.
Publications in peer reviewed journals.

**Contributions of each author**
Author 1 - Dr Syed Rehan Quadery - Developed the idea, created the protocol, act as a reviewer of literature, analyse and interpret the data and will

co-draft the manuscript and take full responsibility for the accuracy of its contents..
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Author 2 - Dr Niamh Boyle - Act as a reviewer of the literature, analyse and interpret the data and will co-draft the manuscript and take full responsibility for the accuracy of its contents.
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Author 3 - Dr Ciara Mccormack - Act as collaborator. Analyse and interpret the data, critically appraise and edit the drafted manuscript and take full responsibility for the accuracy of its contents.
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