

Sotatercept: A First-In-Class Activin Signaling Inhibitor for Pulmonary Arterial Hypertension

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Abstract

Objective: The objective of the study is to review the characteristics, efficacy, safety, and clinical relevance of sotatercept in pulmonary arterial hypertension (PAH). **Data Sources:** A literature search containing search terms related to sotatercept and PAH was conducted. Embase via Elsevier, MEDLINE via Ovid, the medRxiv preprint server, Cochrane Library CENTRAL trials registry, and ClinicalTrials.gov were searched from inception through October 31, 2024. The package insert was utilized to obtain drug information and additional data. **Study Selection and Data Extraction:** Phase II-III clinical trials investigating sotatercept for PAH were included. Articles written in English were extracted while animal studies and phase I clinical trials were excluded. **Data Synthesis:** In patients with WHO Group I, functional class II-III PAH, adding sotatercept to background therapy increased 6-minute walk distance in phase II-III trials. Pooled analysis from PULSAR (phase II) and STELLAR (phase III) showed improvements in pulmonary vascular resistance and NT-proBNP. Exploratory data from PULSAR revealed that BMPR2 genetic variant status was not associated with significant differences in treatment effects. SPECTRA (phase IIb) demonstrated improved right ventricular structure and function. Interim analysis from SOTERIA showed that treatment effects persist at 1 year. **Conclusions:** Sotatercept is a viable add-on therapy for patients with PAH Group I and functional class II-III. Additional data are needed to assess long-term outcomes among treatment-naïve patients and those with the most severe symptomatology.

Keywords

sotatercept, sotatercept-csrk, pulmonary arterial hypertension, activin signaling inhibitor, transforming growth factor-beta

Introduction

Pulmonary arterial hypertension (PAH) is a relatively rare yet complex disorder associated with impaired quality of life and increased mortality.^{1,2} Patients with PAH are subclassified by the World Health Organization (WHO) into 5 groups based on etiology.³ Patients in WHO Group 1 PAH are hemodynamically defined by a mean pulmonary artery pressure (mPAP) > 20 mmHg at rest, pulmonary arterial wedge pressure (PAWP) of ≤ 15 mmHg, and pulmonary vascular resistance (PVR) > 2 Wood units by right heart catheterization.^{3,4} Causes of the WHO Group 1 subtype include drug- or toxin-induced, heritable, or may be associated with other conditions.

In the past 20 years, several targeted therapies have been developed to manage PAH. The 3 major pathways targeted by current guideline-recommended agents are the endothelin, nitric oxide, and prostacyclin pathways (Figure 1). Medications that exert their effects within these pathways have vasodilatory and antiproliferative effects to help manage symptoms and improve quality of life. There have been

5 medication classes for the management of PAH: endothelin receptor antagonists (ERAs), phosphodiesterase-5 (PDE5) inhibitors, soluble guanylate cyclase stimulator, prostacyclin analogs, and prostacyclin (IP) receptor agonist. The 2019 CHEST Guideline on Therapy for Pulmonary Arterial Hypertension recommend first-line combination therapy with ambrisentan and tadalafil for treatment-naïve patients with WHO functional class (FC) II-III symptoms.^{5,6} The 2022 European Society of Cardiology and European

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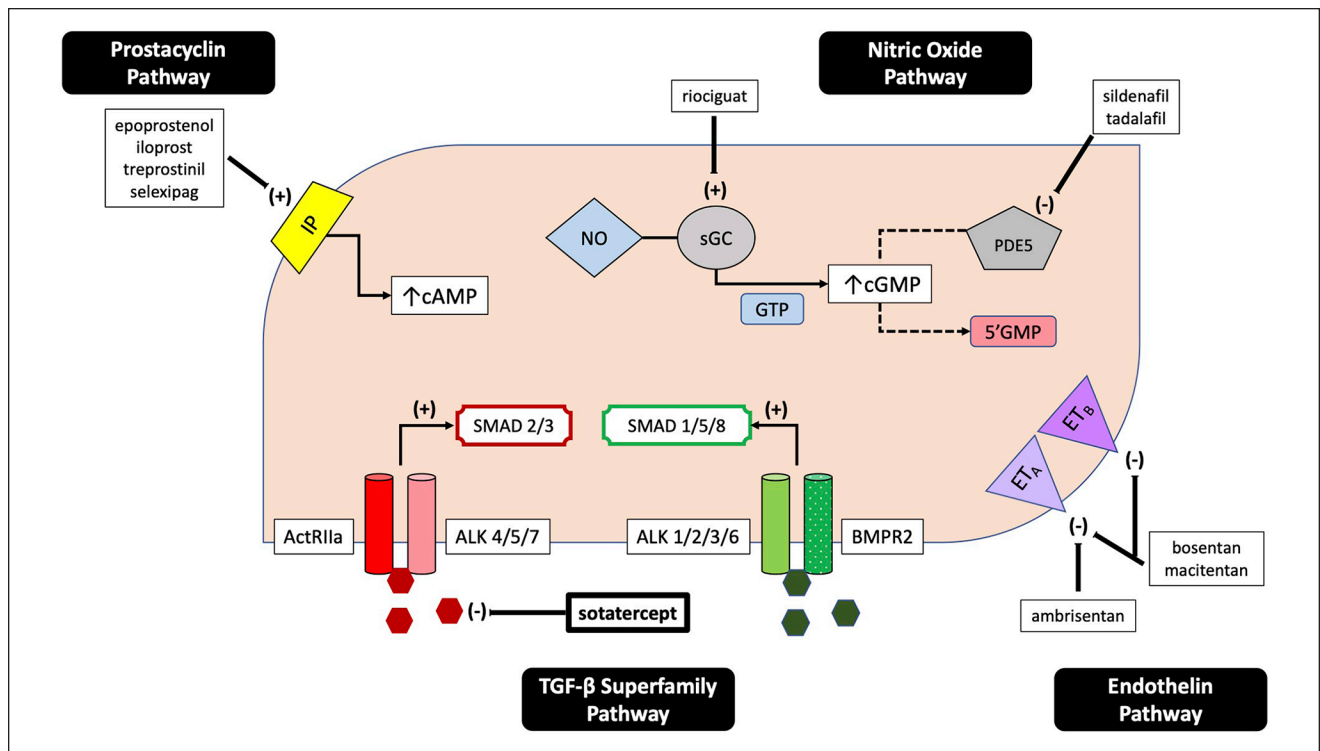


Figure 1. Mechanisms of action of FDA-approved PAH therapies. Prior to sotatercept approval, there were 3 major target pathways for PAH: (1) activation of the prostacyclin pathway using prostacyclin analogs or selexipag, (2) stimulation of the nitric oxide pathway by activating sGC with riociguat or using PDE5 inhibitors (sildenafil, tadalafil), and (3) blunting the effects of endothelin with endothelin receptor antagonists (ambrisentan, bosentan, macitentan). Sotatercept acts within the TGF-beta superfamily pathway, which is imbalanced in patients with PAH due to reduced antiproliferative BMPR2, ALK 1/2/3/6, and SMAD 1/5/8 signaling. Sotatercept acts as a “decoy” to the ActRIIa and ALK 4/5/7 receptor, binding to activin and other ligands to prevent the subsequent activation of proliferative pathways (SMAD 2/3).^{7,8}

Abbreviations: ActRIIa, activin receptor type IIa; ALK, activin receptor-like kinase; BMPR2, bone morphogenetic protein receptor type 2; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; ET, endothelin receptor type; GTP, guanosine triphosphate; IP, prostacyclin; NO, nitric oxide; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase type 5; sGC, soluble guanylate cyclase.

Respiratory Society guidelines also recommend combination therapy for the management of PAH without significant comorbidities, with the option of monotherapy with either ERA, PDE5 inhibitor, or riociguat in patients unable to tolerate initial combination therapy.⁴ For patients who are higher risk or in FC II-IV, triple combination therapy, including prostacyclin analogs are recommended. Prior to 2024, the last agent approved by the US Food and Drug Administration (FDA) for the treatment of PAH was selexipag in 2015. Sotatercept, first in its class, was granted a breakthrough therapy designation by the FDA and subsequently approved in March 2024. The purpose of this article is to provide an in-depth review of sotatercept, including pharmacology, pharmacokinetics, current safety and efficacy data, and its potential place in pharmacotherapy compared with other agents in PAH.

Data Selection

Published articles from inception through October 31, 2024, in Embase via Elsevier, MEDLINE via Ovid, the medRxiv

preprint server, and the Cochrane Library CENTRAL trials registry were identified. Search terms included Winrevair, sotatercept, sotatercept-csrk, MK-7962, ACE-01, activin receptor 2A immunoglobulin G1 Fc fragment fusion protein, and activin receptor IIA immunoglobulin G1 Fc fragment fusion protein. Phase II and III studies related to the treatment of PAH were included. Animal studies, phase I trials, and articles not written in English were excluded. ClinicalTrials.gov was used to identify pertinent ongoing studies while the package insert was utilized to obtain additional information on reported data and drug characteristics.

Clinical Pharmacology

Mechanism of Action

Imbalances within the transforming growth factor (TGF)-beta superfamily pathways have been found to play a key role in pathophysiology of PAH.^{8,9} There are several ligands involved, including TGF-beta, activin, growth differentiating factor (GDF), and bone morphogenetic protein (BMP).

Activins, GDF, and other TGF-beta ligands bind to human activin receptor type IIa (ActRIIa), which activates SMAD 2/3 signaling and downstream proliferation. Bone morphogenetic protein activates SMAD 1/5/8 through the BMP receptor type II (BMPRII), which has antiproliferative effects. In PAH, activin/SMAD 2/3 signaling is more pronounced than BMP/SMAD 1/5/8 signaling and BMPRII mutations have been implicated. BMPRII loss-of-function mutations are the most common cause of heritable PAH and are present in about 25% of idiopathic cases.^{8,10} Sotatercept is a homodimeric recombinant fusion protein that acts as an activin signaling inhibitor. Its structure consists of a modified extracellular human activin receptor type IIa linked to a human IgG1 Fc domain (ActRIIa-Fc). Sotatercept traps activin A and GDF ligands, thereby recalibrating TGF-beta proliferative and antiproliferative pathways, blunting vascular remodeling (Figure 1).^{7,11}

Pharmacokinetics

The absolute bioavailability of sotatercept after subcutaneous administration is 66%, with a peak concentration (C_{max}) of 9.7 µg/mL (0.7 mg/kg dosing) and median time to peak concentration (T_{max}) of 7 days (range: 2-8 days).⁷ A 0.7 mg/kg every-3-week dosing yields a steady state area under the curve concentration of 172 µg×d/mL after approximately 15 weeks. Sotatercept has a volume of distribution of approximately 5.3 L. It is metabolized by catabolic pathways into small peptides, with a clearance of 0.18 L/day and an elimination half-life of 24 days. In the STELLAR trial, 27% developed anti-drug antibodies. However, after 24 weeks, there were no clinically significant effects of these anti-drug antibodies on pharmacodynamics, pharmacokinetics, efficacy, or safety.⁷

Clinical Trials

Phase II

PULSAR was a randomized, double-blind, placebo-controlled trial assessing the efficacy and safety of sotatercept in FC II-III patients. One hundred six participants were randomized to receive either placebo, sotatercept at 0.3 mg/kg, or 0.7 mg/kg, with the ratio later adjusted to increase statistical power for the 0.7 mg/kg group. Sotatercept or placebo was administered subcutaneously every 21 days, and safety and efficacy were assessed at baseline and every 3 weeks for a total of 24 weeks. Baseline characteristics were similar across groups, with a mean age of 48.3 years, 87% women and 92% white. Notably, 56% of participants were on triple therapy and 37% were receiving prostacyclin infusions.¹²

Based on the intention-to-treat population, the primary endpoint of change from baseline to week 24 in pulmonary

vascular resistance (PVR) showed a decrease of 162.2 dyn • sec • cm⁻⁵ and 255.9 dyn • sec • cm⁻⁵ in the 0.3 mg/kg group and 0.7 mg/kg groups, compared with a decrease of 16.4 dyn•sec•cm⁻⁵ in the placebo group (Table 1). For secondary endpoints, changes in 6-minute walk distance (6MWD) were 58.1, 50.1, and 28.7 m in the sotatercept 0.3 mg/kg, 0.7 mg/kg, and placebo groups, respectively. NT pro-BNP decreased in the sotatercept groups, compared with an increase in the placebo group. Functional class improved by at least one class in 31% and 17% of patients in the sotatercept 0.3 mg/kg and 0.7 mg/kg groups, compared with 12% in the placebo arm. Clinical worsening occurred in 2 participants (6%) in the placebo group, 1 participant (2%) in the sotatercept 0.7 mg/kg group, and no participants in the sotatercept 0.3 mg/kg group.¹²

Ninety-seven participants from PULSAR transitioned to the open-label extension trial (PULSAR-OLE) from months 18 to 24.¹⁵ Participants in the placebo group were re-randomized in a 1:1 ratio to receive either sotatercept 0.3 mg/kg or sotatercept 0.7 mg/kg, forming the placebo-crossed group. The continued-sotatercept group included 31 and 36 participants continuing their sotatercept 0.3 mg/kg or 0.7 mg/kg dose. The placebo-crossed group showed a significant PVR improvement from baseline from months 18 to 24. Both placebo-crossed and sotatercept-continued groups demonstrated improvements in 6MWD, FC, and NT-proBNP levels.¹⁵ Serious treatment-emergent adverse events (TEAE) occurred in 30.8% of participants, with 4.8% deemed treatment-related. These included pyrexia, red blood cell increase, systemic lupus erythematosus, ischemic stroke, pleural effusion, and pulmonary hypertension. Telangiectasia was observed in 10.6% of patients, developing on average 1.5 years after sotatercept treatment.

The SPECTRA trial investigated the effects on sotatercept on change in peak oxygen uptake in FC III patients from baseline to week 24 using invasive cardiopulmonary exercise testing and right ventricular (RV) function using serial cardiac magnetic resonance (CMR) imaging.¹³ Twenty-one participants enrolled into the 24-week open label treatment period and received sotatercept 0.3 mg/kg every 3 weeks that was then escalated to a target dose of 0.7 mg/kg. Nineteen participants continued into the 18-month study extension period. Baseline characteristics showed a median age of 44 years and a primarily female (81%) population. Approximately half of the participants were on parenteral prostacyclin (57%), while 48% and 52% were on double and triple therapy, respectively. At 24 weeks, there was significant improvement from baseline in peak oxygen uptake that was maintained through 48 weeks. Sotatercept also demonstrated improvements in secondary endpoints and CMR imaging results. Improvement in RV structure and function indicate that sotatercept may be a disease modifying agent.

Table 1. Clinical Trial Endpoints for Sotatercept in PAH.

Trial	Phase/ Design/WHO Functional Class	Endpoints
PULSAR ¹²	Phase 2 RCT WHO FC II or III	<p>Primary Outcome</p> <ul style="list-style-type: none"> • Change in PVR from baseline to week 24: Improved PVR ($P < 0.001$) <p>Secondary Outcomes</p> <ul style="list-style-type: none"> • Change in 6MWD from baseline to 24 weeks: Improved 6MWD • Sotatercept 0.3 mg/kg, 0.7 mg/kg, and placebo groups, 58.1, 50.1, and 28.7 m, respectively • Sotatercept 0.3 mg/kg vs placebo, 29.4 m (95% CI, 3.8-55) • Sotatercept 0.7 mg/kg vs placebo, 21.4 m (95% CI, -2.8 to 45.7) • Change in NT-proBNP from baseline to 24 weeks: Improved NT-proBNP • Sotatercept 0.3 mg/kg, 0.7 mg/kg, and placebo groups, -621.1 ± 150.6, -340.6 ± 139.4, and $+310.4 \pm 151.3$ pg per milliliter, respectively <ul style="list-style-type: none"> ◦ Sotatercept 0.3 mg/kg vs placebo, -931.5 pg per milliliter (95% CI, -1353.2 to -509.7) ◦ Sotatercept 0.7 mg/kg vs placebo, -651 pg per milliliter (95% CI, -1043.3 to -258.7) • Tricuspid annular plane systolic excursion: No significant change • Improvement in WHO FC <ul style="list-style-type: none"> ◦ Sotatercept 0.3 mg/kg group: 10 patients (31%) ◦ Sotatercept 0.7 mg/kg group: 7 patients (17%) ◦ Placebo group: 4 patients (12%) • Clinical worsening <ul style="list-style-type: none"> ◦ Sotatercept 0.3 mg/kg group: 0 patients (0%) ◦ Sotatercept 0.7 mg/kg group: 1 patient (2%) ◦ Placebo group: 2 patients (6%)
PULSAR-OLE ¹³		<p>Primary Outcome</p> <ul style="list-style-type: none"> • Change from baseline to months 18 to 24 in PVR: Improved PVR <ul style="list-style-type: none"> ◦ Placebo-crossed group, -223 ± 58 dyn \cdot sec \cdot cm⁻⁵, $P < 0.0001$ ◦ Continued-sotatercept group, -213 ± 254 dyn \cdot sec \cdot cm⁻⁵, $P = 0.8745$ <p>Secondary Outcomes</p> <ul style="list-style-type: none"> • Change from baseline to months 18 to 24 months in 6MWD: Improved 6MWD <ul style="list-style-type: none"> ◦ Placebo-crossed group, 61 ± 13 m, $P < 0.0001$ ◦ Continued-sotatercept group, 60 ± 81 m, $P = 0.3987$ • Change from baseline to months 18 to 24 months in WHO FC: Improved FC <ul style="list-style-type: none"> ◦ Placebo-crossed group, -0.6 ± 0.7, $P < 0.0001$ ◦ Continued-sotatercept group, -0.4 ± 0.6, $P < 0.0001$ • Change from baseline to months 18 to 24 months in NT-proBNP: Improved NT-proBNP <ul style="list-style-type: none"> ◦ Placebo-crossed group, -506.2 ± 1190 pg/mL, $P = 0.0004$ ◦ Continued-sotatercept group, -470 ± 910.44 pg/mL, $P = 0.1384$

(continued)

Table I. (continued)

Trial	Phase/ Design/WHO Functional Class	Endpoints
SPECTRA ¹³	Phase 2b Exploratory Trial WHO FC III	<p>Primary Outcome</p> <ul style="list-style-type: none"> Change in peak oxygen uptake from baseline to week 24: Improved; 102.74 mL/min, $P = 0.0097$ <p>Secondary Outcomes</p> <ul style="list-style-type: none"> Change from baseline to 24 weeks, at peak exercise in: <ul style="list-style-type: none"> Minute ventilation/carbon dioxide production slope (ventilatory efficiency): Improved, -6.84, $P = 0.0164$ Cardiac output: No change, -0.47 L/min, $P = 0.2242$ Cardiac index: No change, 0.34 L/min \cdot m², $P = 0.2414$ Mean pulmonary artery pressure (mPAP): Improved, -15.2 mmHg, $P < 0.0001$ Arteriovenous oxygen content difference (Ca-vO₂): No change, 0.78 mL/100 mL, $P = 0.1376$ Workload: Improved, 19.5 W, $P < 0.0001$ Mean right atrial pressure: Improved, -8.1 mmHg, $P < 0.0001$ Pulmonary arterial wedge pressure: Improved, -3.2 mmHg, $P = 0.0017$ <p>Change from baseline to 24 weeks in CMR imaging, at rest in:</p> <ul style="list-style-type: none"> RV SV: Reduced, -27.3 mL, $P = 0.0006$ RV end SV: Reduced, -39.2, $P < 0.0001$ RV end diastolic volume (RVEDV): Reduced, -66.5, $P < 0.0001$ RV ejection fraction (EF): No change, -1.3%, $P = 0.5222$ RV SV index: Reduced, -15.1, $P = 0.0007$ RV mass: Decreased, -6.2 g, $P = 0.0720$ <p>Additional endpoints from baseline to week 24, at rest in:</p> <ul style="list-style-type: none"> Changes in PVR: Improved, -227 dyn \cdot sec \cdot cm⁻⁵, $P = 0.0061$ Changes in 6MWD: Improved, 63 m, $P = 0.0019$ Changes in NT-proBNP: Improved, -540 pg/mL, $P < 0.0001$ <p>Changes in WHO FC: Improved</p>
STELLAR ¹⁴	Phase 3 RCT WHO FC II or III	<p>Primary Outcome</p> <ul style="list-style-type: none"> Change from baseline in 6MWD at week 24: Improved 6MWD <ul style="list-style-type: none"> Sotatercept group 40.1 m (95% CI, 29.9-50.2) vs placebo group -1.4 m (95% CI, -13.2 to 10.3) <p>Secondary Outcomes</p> <ul style="list-style-type: none"> Change from baseline to 24 weeks in: <ul style="list-style-type: none"> Percentage of participants achieving multicomponent improvement: 38.9% in sotatercept vs. 10.1% in placebo, $P < 0.0001$ PVR: Improved; -165.1 dyn \cdot sec \cdot cm⁻⁵ (95% CI, -176 to -152) vs placebo group 32.8 dyn \cdot sec \cdot cm⁻⁵ (95% CI, 26.5-40) NT-proBNP levels: Improved; -230.3 pg/mL (95% CI, -236 to -223) vs placebo group 58.6 pg/ml (95% CI, 46 to 67) Percentage of patients who improve in WHO FC: Improved; 29.4% (95% CI, 22.6-37.1) vs placebo group 13.8% (95% CI, 8.9-20.2) Percentage of participants who maintain or achieve a low-risk score using the Simplified French Risk Score Calculator: Improved; 39.5% (95% CI, 31.9-47.5) vs placebo group 18.2% (95% CI, 12.6-25.1) The Physical Impacts Domain Score of Pulmonary Arterial Hypertension—Symptoms and Impact (PAH-SYMPACT): Improved; -0.13 (95% CI, -0.15 to 0) vs placebo group 0.01 (95% CI, 0-0.13) The Cardiopulmonary Symptoms Domain Score of PAH-SYMPACT: Improved; -0.12 (95% CI, -0.14 to -0.08) vs placebo group -0.01 (95% CI, -0.03 to 0) The Cognitive/Emotional Impacts Domain Score of PAH-SYMPACT: No change

Abbreviations: 6MWD, 6-minute walk distance; ADA, anti-drug antibodies; AE, adverse events; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; CHAMPHOR, Cambridge Pulmonary Hypertension Outcome Review; CI, confidence interval; Cmax, peak concentration; ECG, electrocardiogram; FC, functional class; m, meters; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; PAH-SYMPACT, Pulmonary Arterial Hypertension—Symptoms and Impact; pg/ml, picograms per milliliter; PVR, peripheral vascular resistance; QTcF, QT corrected for heart rate by Fridericia's cube root formula; REVEAL, Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management; RBC, red blood cells; RCT, randomized control trial; RV, right ventricle; RVEDV, right ventricular end diastolic volume; SF-36, 36-item Short Form Health Survey; SV, stroke volume; WBC, white blood cells; WHO, World Health Organization.

Phase III

FDA approval of sotatercept is based on findings from the STELLAR trial in FC II-III patients.¹⁴ The double-blind, placebo-controlled trial occurred over 24 weeks. Participants were randomized to receive either sotatercept or placebo every 3 weeks in combination with stable background therapy.

Sotatercept was administered as a starting dose of 0.3 mg/kg and escalated to 0.7 mg/kg at day 21. Patients remained at the dose for the trial duration, unless there was a reason for dose reduction. A total of 323 patients at 91 sites in 21 countries were randomized to receive sotatercept or placebo. More than half of the enrolled patients were from Europe. The mean age for patients was 47.9 ± 14.8 years and the mean length of time since diagnosis was 8.8 years. For background therapy, 4% were on monotherapy, 34.7% on double, 61.3% on triple, and 39.9% were on prostacyclin infusion. The mean change from baseline in 6MWD at 24 weeks based on the intention-to-treat population was 34.4 m (95% confidence interval [CI]: 33.0-35.5) in the sotatercept group and 1.0 m (95% CI: -0.3 to 3.5) in the placebo group. Sotatercept was associated with an improvement in 8 of 9 secondary endpoints, except for the PAH-SYMPACT Cognitive/Emotional Impacts domain score ($P = 0.16$). Sotatercept showed an improvement in the first occurrence of death or nonfatal clinical worsening event. Any severe adverse event, discontinuation, or withdrawal rate was less common in the sotatercept group compared with placebo.

Ongoing Studies

There are 3 ongoing studies for sotatercept. SOTERIA (NCT04796337) is an open-label extension study evaluating the long-term safety, tolerability, and efficacy in patients who have completed previous sotatercept trials without early discontinuation.¹⁶ The primary objective is evaluating safety and tolerability. The secondary objectives are to determine continued efficacy through change in 6MWD, NT-proBNP levels, improvement in New York Heart Association (NYHA)/WHO functional status, PVR, overall survival, and simplified French risk score. Interim analysis from SOTERIA shows that the median duration of exposure to sotatercept was 336 days (range: 21-1072). At 1 year, improvements in 6MWD, NT-proBNP, FC, and French risk score were maintained.¹⁷ Seven participants had 6 clinical worsening events, which included 3 deaths and 3 PAH-related hospitalization. HYPERION (NCT04811092) is a phase III, randomized, placebo-controlled study to assess the addition of sotatercept to background therapy in newly diagnosed intermediate- or high-risk PAH.¹⁸ The objective is to evaluate the effects of sotatercept treatment on time to clinical worsening up to approximately 47 months, in

patients on double therapy for at least 90 days prior to screening. ZENITH (NCT04896008), a phase III double blinded randomized study, will evaluate the impact of sotatercept on time to first event of all cause death, lung transplantation, or PAH worsening related hospitalization of ≥ 24 hours among participants with FC III-IV, at high risk of mortality on maximally tolerated background therapy.¹⁹ Patients are currently being enrolled in both HYPERION and ZENITH.

Safety

Common adverse reactions include headache (24.5%), epistaxis (22.1%), rash (20.2%), telangiectasia (16.6%), diarrhea (15.3%), dizziness (14.7%), and erythema (13.5%). In the STELLAR trial, 8 (4.9%) patients in the sotatercept and 9 (5.6%) in the placebo group experienced an adverse event that led to study discontinuation.⁷

There are currently no contraindications listed for sotatercept. However, there is a risk for severe erythrocytosis, which can lead to hyperviscosity syndrome and thromboembolic events. These blood dyscrasias appeared to be dose-dependent. Severe thrombocytopenia may also occur.⁷ In PULSAR, 18% of patients on sotatercept experienced thrombocytopenia while there were no cases in the placebo group. In STELLAR, 6.1% of patients on sotatercept experienced thrombocytopenia compared with 2.5% in the placebo group, although this difference was not found to be statistically significant. In PULSAR, increased hemoglobin was not reported in the placebo group, but was observed in 2% and 17% of patients in the 0.3 mg/kg and 0.7 mg/kg groups, respectively. The mean increase was 1.2 g/dL in the 0.3 mg/kg group and 1.5 g/dL in the 0.7 mg/kg group.¹² In STELLAR, significantly more patients in the treatment arm experienced increased hemoglobin compared with placebo (difference: 5.5%, 95% CI: 2.9-10.2).¹³ Data from the 24-week placebo-controlled period and the long-term double-blind period showed 53% of patients treated with sotatercept had hemoglobin increase above normal and 25% experienced thrombocytopenia. Notably, sotatercept has been studied for the treatment of anemia in myelodysplastic syndromes, and its hematologic effects may be explained by the critical role that TGF-beta signaling plays in hematopoiesis.^{20,21}

Sotatercept should not be given if serious bleeding is present.⁷ In STELLAR, 21.5% patients on sotatercept experienced a bleeding event, compared with 12.5% in the placebo group (difference: 9.0%, 95% CI: 0.8-17.2).¹⁴ Serious bleeding has been reported in 4% of patients receiving sotatercept compared with 1% on placebo.⁷ Therefore, concomitant use of prostacyclin analogs or antithrombotic agents should be undertaken with caution due to potentially increased bleeding risk.

Special Populations

No significant differences in pharmacokinetics were observed with sotatercept in renal impairment and it is not dialyzable.⁷ It is also not well-studied in hepatic impairment. Sotatercept has not been adequately investigated in pregnant women but demonstrated risk for fetal harm in animal reproduction studies. Women of reproductive potential should be advised of risks and use effective contraception while on treatment and for at least 4 months after the last dose. The presence of sotatercept in breast milk is unknown. Nonetheless, breastfeeding should be avoided during treatment and for at least 4 months after the last dose.⁷

The safety and efficacy of sotatercept have not been well-studied in the pediatric population. The ongoing MOONBEAM trial (NCT05587712) will provide more insight.²² The geriatric population has been historically underrepresented in landmark trials for PAH therapies.^{4,6,23} Similarly, the median age was about 49 and 47 years among patients in the PULSAR and STELLAR trials.^{12,14} There were no differences in efficacy observed among patients 65 years or older nor in adverse events between the <65-year-old and ≥65-year-old subgroups, except for overall bleeding.⁷ Although there were more bleeding events observed in patients ≥ 65 years of age, there were no significant imbalances between different age groups with regard to types of bleeding events.⁷ Clinicians should still consider the impact of advanced age and other factors on overall bleeding risk when assessing risks and benefits.

Dosing and Administration

Sotatercept should be initiated at a weight-based dose of 0.3 mg/kg administered subcutaneously every 3 weeks.⁷ Hemoglobin and platelets should be monitored before administration during the first 5 doses. If there is no evidence of erythrocytosis or thrombocytopenia, sotatercept can be increased to target 0.7 mg/kg every 3 weeks. Dyscrasias can be managed by either reducing or delaying the dose. Sotatercept should be held for at least 3 weeks if platelets decrease to less than 500 000/mm³ or if hemoglobin increases more than 4 g/dL from baseline, more than 2 g/dL above upper limit of normal (ULN), or by greater than 2 g/dL from the previous dose and is above the ULN. Hemoglobin and platelet counts should be monitored and normalized before restarting therapy. If treatment is interrupted for more than 9 weeks, patients must be restarted at the 0.3 mg/kg dose and titrated up to target dose based on hemoglobin and platelet levels. Patients or caregivers may administer the medication after proper training. Sotatercept is available as a lyophilized powder in 45 or 60 mg vial kits that should be stored in the refrigerator (36°F-46°F), and requires reconstitution to a final concentration of 50 mg/mL.⁷

Place in Therapy

Sotatercept, when added to background therapy, demonstrated consistent benefit in 6MWD with a mean improvement of 34.4 m in STELLAR, which is considered to be clinically meaningful.²⁴ Agents such as the PDE5 inhibitors, ERAs, or intravenous prostacyclin analogs have shown a mean 6MWD improvement of 48, 25, and 91 m, respectively.^{1,24-26} A pooled analysis of the STELLAR and PULSAR showed improvements in 6MWD, PVR, and NT-proBNP regardless of cardiac index.²⁷ Exploratory data from PULSAR have also suggested genetic BMPR2 variants have no difference in treatment effect on PVR, 6MWD, nor incidence of TEAEs.²⁸

Based on the trial safety data, there is a need to monitor hemoglobin and platelets, which are already part of routine care. Consideration should be taken for those on antithrombotic agents due to the potential risk of thrombocytopenia and bleeding. Other guideline-recommended agents do have associated safety concerns that were not observed with sotatercept. Notably, the ERAs (ambrisentan, bosentan, and macitentan) must be used through Risk Evaluation and Mitigation Strategies (REMS) programs. Prostacyclin analogs have off-target effects, such as flushing, hypotension, and jaw pain, and parenteral and inhaled administration can be a barrier to use. An advantage of sotatercept is its unique every 3-week dosing that may be preferable to patients over a continuous prostacyclin infusion. Table 2 provides comparisons between sotatercept and other PAH therapies.

There are uncertainties and limitations to consider when weighing the benefits of sotatercept. Existing data are primarily for patients on background therapy rather than treatment-naïve patients. In addition, when to add sotatercept for combination therapy is not entirely clear, as approximately 60% of patients in the trials were on triple therapy. Data from PULSAR-OLE have shown that patients continued on sotatercept showed further gains in 6MWD from the end of PULSAR to months 18 to 24.¹⁵ Sotatercept is a disease modifying agent, so it is unknown whether there is significant improvement or impact beyond 24 weeks, although interim data from SOTERIA have shown treatment effects persisting at 1 year.¹⁶ It is also unknown whether treatment can be discontinued without a worsening of symptoms and/or FC. Based on data using a population health model to compare clinical outcomes of sotatercept with background therapy to standard therapy alone from STELLAR, adding sotatercept to background therapy may be associated with an increased life expectancy by roughly 3-fold while reducing utilization of infused prostacyclin, hospitalizations, and lung/dual heart-lung transplantations.³⁰ Another model evaluating long-term cost effectiveness found that sotatercept with background therapy produced greater time without

Table 2. Comparison of FDA-Approved Therapies for PAH.^{4,7,29}

Drug class	Agent(s)	Year FDA approved	WHO group and FC	Adverse reactions	Route(s) of administration	Clinical pearls
Activin signaling inhibitor	Sotatercept	2024	Group I FC II-III	Headaches, epistaxis, rash, telangiectasia, diarrhea, dizziness, erythema	Subcutaneous	Avoid in pregnancy; monitor Hgb and PLT; hold for severe bleeding
Endothelin-1 receptor antagonist	Ambrisentan Bosentan Macitentan	2007 2001 2013	Group I FC II-IV	Peripheral edema, headaches	Oral	Avoid in pregnancy, REMS; hepatotoxicity (variable within class); Significant DDI
PDE5 inhibitor	Sildenafil Tadalafil	2005 2009	Group I FC II-IV	Hypo-tension	Oral; intravenous (sildenafil)	CI with nitrates and riociguat; bosentan can decrease concentrations by 50%
Soluble guanylate cyclase stimulator	Riociguat	2013	Group I FC II-IV/ Group 4	Hypo-tension	Multiple-daily oral dosing	Avoid in pregnancy; smoking reduces concentrations by 50%-60%
Prostacyclin analogs	Epoprostenol Iloprost Treprostinil ^a	1995 2004 2002	Group I FC III-IV / Group 3 ^a	Hypo-tension, peripheral edema, headache, flushing, jaw pain, musculoskeletal pain, diarrhea	Multiple-daily oral dosing; Continuous intravenous or subcutaneous infusion; Continuous nebulization	Short elimination half-lives; ease of use and infection risk are concerns with continuous infusion pumps
Prostacyclin receptor agonist	Selexipag	2015	Group I FC II-III		Oral; intravenous	Contraindicated with strong CYP2C8 inhibitors

Abbreviations: CI, contraindication; DDI, drug-drug interactions; FC, functional class; FDA, Food and Drug Administration; Hgb, hemoglobin; PDE5, phosphodiesterase type 5; PLT, platelets; REMS, Risk Evaluation and Mitigation Strategies; SC, subcutaneous; WHO, World Health Organization.

^aTreprostinil is approved for WHO Group 3.

symptoms at rest, quality-adjusted life-years, life-years, and equal-value life-years, but resulted in higher total costs.³¹ This benefit is primarily driven by the effectiveness of sotatercept on improving and slowing the worsening in FC. Key unknowns related to sotatercept include long-term efficacy and safety, potential harm to the fetus and effects of fertility, and currently, its impact on mortality in PAH.³²

Conclusion

Sotatercept, a subcutaneous injection and fusion protein, targets a new pathway to reduce endothelial proliferation, thus adding a new pharmacotherapeutic option while improving clinical outcomes in addition to existing therapies. Based on available evidence, sotatercept may be a reasonable therapeutic addition in the management of WHO Group 1 FC II-III patients to further improve symptoms, particularly in those on background triple therapy. Presently, there is no evidence to support sotatercept as a first-line agent or monotherapy. In addition, clinicians should be aware of the potential for increased hemoglobin and thrombocytopenia, which may necessitate dose adjustments or

discontinuation. Ongoing trials will provide insight on the long-term safety and efficacy of sotatercept.

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