Annual National Student Pharmacist P&T COMPETITION EST. 2000

AMCP Foundation

Drug Monograph

Team 25123

Patients First Health Plan
Formulary Drug Monograph

Generic Name:	**Sotatercept**
Brand Name:	**WINREVAIR™**
Manufacturer:	**Merck & Co., Inc.**
Date of Review:	**January 2024**
Purpose:	**Individual drug review**
Indication:	**Treatment of pulmonary arterial hypertension (PAH) World Health Organization (WHO) Group 1, WHO Functional Class (FC) II or III**

Therapeutic Alternatives

AGENTS IN THE SAME PHARMACOLOGIC CLASS

Preferred/Formulary	Nonpreferred/Nonformulary
None	None

AGENTS IN A DIFFERENT PHARMACOLOGIC CLASS

Preferred/Formulary	Nonpreferred/Nonformulary
Tier 3 (Preferred): • Ambrisentan oral tablet • Bosentan oral tablet • Tadalafil oral tablet • TRACLEER™ (bosentan) oral tablet for suspension	Tier 4 (Non-preferred): • ADEMPAS™ (riociguat) oral tablet • ORENITRAM™ (treprostinil) oral tablet • Sildenafil oral tablet • TRACLEER™ (bosentan) oral tablet • TYVASO™ (treprostinil) inhalation cartridge with inhaler; inhalation solution for nebulizer • UPTRAVI™ (selexipag) oral tablet

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Abbreviations used in this monograph:			
ActRIIA	Activin receptor type II a	PCA	Prostacyclin analogue
AE	Adverse event	PCWP	Pulmonary capillary wedge pressure
CHD	Congenital heart defect	PDE-5i	Phosphodiesterase type 5 inhibitor
CI	Confidence interval	PH	Pulmonary hypertension
CTD	Connective tissue disease	PFHP	Patients First Health Plan
ERA	Endothelial receptor antagonist	PMPM	Per member per month
FC	Functional class	PPPM	Per patient per month
FDA	Food and Drug Administration	PVOD	Pulmonary veno-occlusive disease
HIV	Human Immunodeficiency Virus	PVR	Pulmonary vascular resistance
MAP	Mean arterial pressure	QALY	Quality adjusted life year
MCI	Multicomponent improvement	RHC	Right heart catheterization
MI	Myocardial infarction	RV	Right ventricle
NT-proBNP	N-terminal Pro-B-Type Natriuretic Peptide	SAE	Serious adverse event
PA	Prior authorization	sGCs	Soluble guanylate cyclase stimulator
PAH	Pulmonary arterial hypertension	SQ	Subcutaneous
PAH-SYMPACT	PAH-Symptoms and Impact	TGF-β	Transforming growth factor beta
		WHO	World Health Organization

Executive Summary

Efficacy in Clinical Trials: (Strength of Evidence: Moderate)

Sotatercept was studied in the STELLAR trial (NCT04576988), a phase 3, randomized, double-blinded placebo-controlled trial for patients aged ≥18 years diagnosed with pulmonary arterial hypertension (PAH) (World Health Organization [WHO] functional class II or III) with background PAH therapy, including endothelial receptor antagonists (ERA), prostacyclins, phosphodiesterase 5 (PDE5) inhibitors, and/or soluble guanylate stimulator (sGCS).[1] For the primary outcome of median change from baseline in 6-minute walking distance (6MWD) at 24 weeks, a moderate improvement of 34.4 m was observed in the sotatercept arm (95% confidence interval [CI], 33.0 to 35.5) in comparison to placebo (1.0 m, 95% CI, -0.3 to 3.5). For secondary outcomes, a greater proportion patients randomized to sotatercept saw multicomponent improvement (38.9% vs. 10.1% with placebo); however, there was no demonstrated improvement in quality of life.

Reason for evidence grade:

STELLAR demonstrated positive results for improvement in the primary outcome of 6MWD, with a minimal clinically important difference observed. STELLAR also provided evidence for improvement or maintenance of WHO FC and reduction of PVR. [1] However, baseline demographics and characteristics of participants enrolled in the trial, such as race, background therapy regimen, and etiology of PAH were not completely reflective of the real-world population. Additional evidence is needed only to assess efficacy and safety of sotatercept in these patients, but to also assess long-term clinical benefit and effect on mortality as the timeframe for STELLAR was only 24 weeks.

Safety in Clinical Trials: (Strength of Evidence: Moderate)

The most observed adverse event (AE) were bleeding events, which occurred in 21.5% of sotatercept patients enrolled in STELLAR. [1] Pre-specified adverse events of interest, which included telangiectasias, increased hemoglobin, and bleeding events occurred in 49.1% of the sotatercept group and 36.2% of the placebo group. Overall rates of adverse events and serious adverse events (SAEs) were lower in the sotatercept arm compared to placebo (84.7% vs. 87.5% and 8.0% vs. 13.1% respectively). Discontinuation due to AEs occurred at rates of 1.8% and 6.2% respectively in the sotatercept and placebo groups.

Reason for evidence grade:

In general, there were not many serious safety concerns associated with sotatercept and there were more adverse events, severe adverse events, and discontinuations in the placebo groups compared to the sotatercept group. Though rates of overall adverse events were high, many of these events were attributed to PAH and not sotatercept itself. Additional data will be needed to assess long-term safety as well as safety in certain patient populations.

Real World Comparative Effectiveness: (Strength of Evidence: Low)

At the time that this review was performed, there were no comparative effectiveness studies evaluating sotatercept with respect to current standard of care (combination therapy with PDE5i, ERA, and/or PCA). Studies utilizing indirect methods of comparison, such as network meta-analysis, were not identified during the literature search.

Reason for evidence grade: No evidence of real-world effectiveness was found.

Value Proposition: (Strength of Evidence: Low)

The ICER Final Evidence Report estimated the cost-effectiveness of sotatercept with background compared to background therapy alone and found it to be $2,380,000 per additional QALY gained, which is much greater than the generally accepted threshold of $150,000 per QALY. [2] An in-house estimation of the budget impact of sotatercept coverage of Patients First Health Plan (PFHP) projected an increase in $0.34 per member per month (PMPM) in the first year.

Reason for evidence grade:

There are many uncertainties affecting accuracy of the cost-effectiveness and budget impact models, such as pricing, the treatment eligible population, and trends in PAH medication utilization over the long term. With some of these variables accounted for, it was still found that sotatercept was highly unlikely to be cost-effective while having significant budget impact on the pharmacy benefit. Additional evidence, such as real-world data evaluating healthcare resource utilization with sotatercept, will be necessary to properly assess its value.

Target Patient Subgroups: (Strength of Evidence: Low)

Patients in STELLAR were stratified in a balance manner based on age, sex, baseline PVR, baseline WHO functional class, and current therapy being received for PAH. [1] Investigators looked at 6MWD, PVR, and NT-proBNP with respect to the subgroups with findings that were consistent with the primary analysis. However, due to small sample sizes, they were not statistically powered to be able to detect a subgroup treatment effect and were chiefly exploratory.

Reason for evidence grade:

STELLAR did not produce any evidence suggesting efficacy or safety in specific subgroups. Data such as those that will be found in the SOTAIRA open-label extension as well as real-world evidence data is necessary to draw conclusions regarding subgroup treatment effect.

Evidence Gaps

Population

In STELLAR, the patient demographics were broadly described as ≥ 18 years patients with symptomatic PAH that had been stabilized on background therapy. [1] There were no standardized eligibility criteria defining background therapy; most patients enrolled were receiving a triple agent background regimen (61.3%), suggesting that there is a greater level of uncertainty in interpretation of trial results for recently diagnosed patients, patients on monotherapy or double therapy. Additionally, patients with WHO-FC IV were excluded, making use of sotatercept in this population off-label. Demographically, participants skewed predominantly white (89.2%) and female (79.3%), which may not be reflective of what is observed in the PAH population. Some data suggests that Black patients may be at higher risk of developing PAH, though figures reported in the literature may be an underestimation due to underdiagnosis and other issues regarding healthcare access and equity; [3] Black patients made up 2.2% of the overall trial population. Alongside Asian (2.2%) participants, they were underrepresented in this trial, which may affect generalizability of overall results to these populations. Several PAH etiologies were underrepresented, such as connective tissue disease associated PAH; it is estimated that up to 35% of PAH is connective tissue disease associated, while only 15% of patients in the trial had this etiology. [1,4] PAH associated with HIV was also excluded from the trial, though there was no explicit rationale for this exclusion and baseline characteristics for HIV-associated PAH are largely similar to the general PAH population. [5]

Intervention

The intervention in STELLAR of a starting dose of sotatercept 0.3 mg/kg followed subsequently by a 0.7 mg/kg target dose was clearly described, and protocol for dose delay and modifications due to increases in hemoglobin or low platelet count were detailed. As most patients will already be on a background regimen of dual or triple therapy prior to initiating sotatercept, concerns of pill burden may be present as patients may struggle to manage multiple medications, especially as sotatercept is dosed every 21 days. Patient administration may also be a concern, as weight-based dosing for sotatercept necessitates the use of a vial requiring patients to draw up and administer each specific dose; careful teaching and instruction from a health care provider will be essential to ensure self-administration.

Comparator

As sotatercept is a first in-class medicine with a novel mechanism of action for the treatment of PAH, the use of placebo as a comparator in STELLAR is reasonable. However, there remains uncertainty regarding the efficacy and safety of sotatercept in comparison to other medication classes in treatment escalation, especially for patients on monotherapy or dual therapy. Though such a design in a clinical trial setting would not be feasible due to loss of blinding with different formulations, future retrospective analyses utilizing real-world evidence with sotatercept may provide some insight.

Outcome

One of the secondary endpoints described in the trial was PAH-SYMPACT, an evaluation of patient reported outcomes in PAH. [6] Though some improvement was shown in the domains of Physical Impacts and Cardiopulmonary Symptoms, no improvements were shown for Cognitive/Emotional Impacts, which is the domain associated with quality of life. While this may be a result of PAH-SYMPACT failing to capture relevant outcomes or an inadvertent bias in the PAH population leading to a diminished perception in change of quality of life, such measures should continue to be monitored in both clinical trial and real-world settings where possible, with incorporation of feedback from patient advocacy groups and clinicians for continual improvement of patient reported outcomes instruments.

Time Frame

In STELLAR, primary and secondary endpoints were assessed at 24 weeks, with an additional a composite endpoint of time to first occurrence of death or nonfatal clinical worsening event over a median follow-up of approximately eight months. While both timeframes are reasonable for detection of the selected endpoints, additional evidence is needed to evaluate long-term efficacy and safety, especially for mortality. In addition to long-term data from the phase 2 PULSAR extension trial (NCT03496207), an open-label follow-up study SOTERIA (NCT04796337) will provide additional long-term data. [7,8]

Important Questions That Remain Unanswered

1. What is the efficacy and safety of sotatercept in patients with WHO-FC IV?

2. What is the efficacy and safety of sotatercept in adolescent patients?

3. What is the efficacy and safety of sotatercept in comparison to current standard of care in treatment escalation from monotherapy or dual therapy in the real-world?

4. What is the quality-of-life impact of sotatercept in comparison to current standard of care?

5. What is the long-term efficacy and safety of sotatercept, especially with respect to mortality?

Value Matrix

How much does this product improve over the current standard of care?	☐ Cure ☐ Substantial net health benefit ☒ Small/Incremental net health benefit ☐ Comparable net health benefit ☐ Negative net health benefit
Level of certainty in the evidence supporting net health benefit	☐ High certainty ☒ Moderate certainty ☐ Low certainty
ICER Evidence Rating *[ICER = Institute for Clinical and Economic Review]*	B+ (Moderate certainty of a small to substantial net health benefit, with a high certainty of at least a small net health benefit)
Risk of serious adverse effects	☐ Substantial ☐ Moderate ☒ Minimal ☐ Unknown
Incremental cost-effectiveness ratio	$2,380,000/QALY gained (compared to background therapy alone with placeholder annual cost of $400,000)
Potential Other Benefits	
Health benefits not captured by QALYs	No evidence to support.
Improves adherence	No evidence to support.
Reduces health disparities	No evidence to support.
Reduces caregiver burden	Reduce caregiver-related costs with lower WHO-FC; captured in ICER CEA with modified societal perspective
Work impact	Reduce absenteeism with lower WHO-FC; captured in ICER CEA with modified societal perspective
Other potential benefits	N/A

Recommendations to the P&T Committee

Formulary Placement	
Recommendation	☐ Must include *The medication is safe and effective for its indicated use and offers a clinical benefit not available by any other medication on the market.* ☒ May include *The medication is safe and effective for its indicated use, but other clinically equivalent alternatives are available.* ☐ Do not include (see "Rationale" below)
Formulary tier	☐ 1 ☐ 2 ☐ 3 ☒ 4 ☐ 5 ☐ NA
Preferred?	☐ Yes ☐ Maybe ☒ No
Budget Impact	
Projected spend:	$74,880,000 over 3 years
$ PMPM impact:	$1.96 PMPM at year 3
Utilization Management Considerations	
Prior authorization recommended?	☒ Yes ☐ Maybe ☐ No
Step therapy?	☐ 1st ☒ 2nd ☐ 3rd ☐ No
Quantity limit?	120 mg (2 x 60 mg vials) every 21 days
Other	Specialty Pharmacy/Limited Distribution

Rationale

Sotatercept is a first-in-class fusion protein biologic approved for the treatment of adults with pulmonary arterial hypertension with WHO functional class II or III. It was approved based on results from STELLAR, a phase III clinical trial which demonstrated a clinically meaningful and statistically significant improvement for its primary outcome of 6-minute walking distance. [1] Most secondary endpoints, which included a multicomponent improvement change in pulmonary vascular resistance, N-terminal pro–B-type natriuretic peptide level, and improvement in WHO functional class, also showed significant improvement. However, several important patient populations were either excluded or underrepresented in this trial, meaning results may not be as generalizable. Sotatercept demonstrated adequate safety during STELLAR, with lower adverse event and discontinuations rates compared to placebo. As primarily supported by the clinical trial evidence in comparison with placebo, we found sotatercept to have a moderate net health benefit as an add onto current background therapy with moderate certainty.

However, the cost-effectiveness analysis published by ICER found sotatercept in addition to background therapy to not be cost-effective in comparison to background therapy by itself, even when accounting for offsetting costs such as reduced hospitalization and improved productivity. [2] The Patients First Health Plan budget impact model found sotatercept to have a significant budget impact within the first three years of coverage. Both the ICER model and our budget impact model found that a significant price reduction from the reported list price would be necessary to improve cost-effectiveness and minimize budget impact. Though these models are limited by constraints such as unpredictability regarding pricing and extrapolation of clinical benefit from clinical trial timeframes, there remains a great deal of uncertainty regarding the value of sotatercept. This is due not only to its price, but also due to limited data supporting its long-term efficacy and safety. Because of these reasons, Patients First Health Plan has decided to include sotatercept as a non-preferred medication on our formulary with specific criteria for usage as detailed at the end of this monograph.

Clinical Evidence Evaluation

Efficacy

FDA approval of sotatercept was based upon results from STELLAR, a phase 3, randomized, double-blinded, placebo-controlled, multi-centered, parallel group clinical trial. [1] Efficacy and safety of sotatercept was compared to placebo when added to existing background PAH therapy. Participants were randomized at a 1:1 ratio to either sotatercept (n = 163) or placebo (n = 160) subcutaneously once every 21 days. Patients that were assigned to receive sotatercept were administered a starting dose of 0.3 mg/kg at their first visit and were then subsequently escalated to 0.7 mg/kg for the remainder of the trial. Enrolled patients had symptomatic PAH and were currently on stable background PAH therapy for ≥90 days. Exclusion criteria included PH Groups 2, 3,4, or 5, as well as PAH Group 1 associated with HIV, portal hypertension, schistosomiasis, and/or pulmonary veno-occlusive disease (PVOD). The mean participant age was 48 years, and the mean amount of time that patients had been diagnosed with PAH was 8.8 years.

The primary endpoint defined in STELLAR was change in baseline 6MWD at 24 weeks, which has been validated as an assessment of change in exercise capacity. Secondary end points included a multicomponent improvement, which was defined by investigators as patients meeting criteria for improvement in 6MWD as well as improvement or maintenance in N-terminal pro-B-type natriuretic peptide (NT-proBNP) level and WHO FC. Additional secondary end points included results for these individual components as well as change in pulmonary vascular resistance (PVR), change in time to death or clinical worsening, French risk score (stratification tool using WHO FC, 6MWD, and NT-proBNP), and changes in the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT) scores, which is an evaluation of patient reported outcomes in PAH.

For the primary end point, the median change in 6MWD in the sotatercept arm was 34.4 m compared to 1.0 m in the placebo group ($p < 0.001$), and the estimated difference between the two groups was found to be 40.8 m (95% CI, 27.5 to 54.1, $p < 0.001$) using a Hodges-Lehmann estimate. In addition, 53.2% of patients assigned to sotatercept had a ≥30 m improvement in 6MWD compared to 22% of those assigned to placebo. Sources in the literature have suggested a minimal clinically important difference in 6MWD as 33 m, suggesting moderate confidence for improvement in this measure with sotatercept.

For the secondary endpoints, 38.9% (95% CI, 31.3 to 46.9) of patients in the sotatercept group met criteria for multicomponent improvement in comparison to 10.1% (95% CI, 5.9 to 46.9) of patients in the placebo group. Significant improvements were observed similarly across most secondary endpoints except for PAH-SYMPACT scores, in which minimal differences were observed between both groups even where statistical significance was present.

Real World Comparative Effectiveness

At the time that this review was performed, there were no comparative effectiveness studies evaluating sotatercept with respect to current standard of care (combination therapy with PDE-5i, ERA, and/or PCA). Studies utilizing indirect methods of comparison, such as network meta-analysis, were not identified during the literature search.

Safety

Overall, sotatercept was well tolerated and the AE profile observed during the STELLAR trial was consistent with previous studies. [1,7] Though the overall AE rate for the sotatercept was high, it was lower than the rate observed in the placebo group (84.7% vs. 87.5%) and only 41.1% of AEs observed in the sotatercept arm

were attributed to the drug itself, suggesting that many AEs were a result of PAH itself. The most common adverse reactions included headache, epistaxis, and telangiectasia, and only 1.8% of patients randomized to sotatercept discontinued treatment due to adverse events. Precautions for use of sotatercept include erythrocytosis, thrombocytopenia, and serious bleeding, which may limit its use in patient populations with certain cardiovascular conditions. There is also a warning for fetal toxicity and impaired fertility. [9]

Serious Adverse Events

Adverse events (AEs) were classified as serious by investigators if they resulted in hospitalization, significant incapacity, or death. During STELLAR, serious adverse events (SAEs) were reported in 23 patients (14.1%) in the sotatercept arm, a rate lower than placebo (36 patients, 22.5%).[1] The majority of serious adverse events across both groups were cardiac disorders, gastrointestinal disorders, or infections and infestations. Investigators determined that many of these events were not study related; only 2 patients in each group experienced SAEs related to treatment according to the investigators (1.2%).

Other Adverse Events

The most frequently adverse event in the sotatercept was headache, though the difference in incidence rate compared to placebo was not significant (20.2% vs. 15.0%, 5.2% difference, -3.1 to 13.6). Common AEs occurring at a higher rate in the sotatercept arm compared to placebo included epistaxis (12.3% vs. 1.9%, 10.4% difference, 5.2 to 16.6), telangiectasia (10.4% vs. 3.1%, 7.3% difference, 2.0 to 13.3), and dizziness (10.4% vs. 1.9%, 8.6% difference, 3.6 to 14.4). Adverse events of special interest for sotatercept included any bleeding event (21.5%), thrombocytopenia (6.1%), telangiectasis (10.4%), and increased hemoglobin (5.5%); a significant difference in incidence between the two groups was only found for telangiectasia and increased hemoglobin.

Tolerability

Adverse events lead to discontinuation in 1.8% of sotatercept patients and 6.2% of placebo patients, suggesting satisfactory tolerability. 10.0% of patients assigned to sotatercept had a dose reduction or delay throughout the 24-week trial period, and adherence to trial regimen was 98.4% for sotatercept patients compared to 99.0% in placebo. [1]

Patient Subgroups

Prior to randomization, eligible patients were stratified based on age, sex, baseline PVR, baseline WHO functional class (Class II vs. III) and current therapy being received for PAH (monotherapy vs. combination therapy vs. triple therapy). [1] Distribution of patients for each variable were equal across the two groups; the number of patients in Class II and Class III for each arm were equivalent and most patients were receiving triple therapy prior to enrollment (61.3% for the entire study). Three outcomes were analyzed with respect to these subgroups - 6MWD, PVR, and NT-proBNP. Investigators found the results to be consistent with those for the overall study group; however, due to small sample sizes and the absence of statistical adjustment for the multiple variables, there was no clear evidence of any subgroup treatment effect.

Economic Evidence Evaluation

The only economic evidence included in this review was the January 2024 Institute of Clinical and Economic Review (I.C.E.R.) Final Evidence Report on treatment of PAH, which included a cost-effectiveness analysis and a budget impact model (BIM).[2] A BIM has not yet been submitted by the manufacturer; a simplified BIM derived from the ICER report was developed for PFHP and is described in this section.

Value Proposition

Summary of Product Value

The ICER cost-effectiveness analysis found sotatercept to be $2,380,000 per QALY gained based upon a placeholder annual cost of $400,000, and a budget impact model for a hypothetical national payer found that 7% of eligible patients could be treated at this.[2] A BIM was conducted by PFHP using a sotatercept list price of $240,000 annually and found a per member per month (PMPM) impact of $0.34 in the first year. As PAH is a rare disease, affecting an estimated 75,000 patients in the entire US, drug pricing is the primary lever affecting budgetary impact of coverage. There are no data suggesting that there may be specific subpopulations in which sotatercept's value may differ.

Incremental Cost-effectiveness

A model was developed by ICER to estimate the cost-effectiveness of sotatercept from a healthcare sector perspective.

Summary of incremental cost-effectiveness ratios found by studies included in this review.

A decision analytic model was developed by ICER to evaluate the cost-effectiveness of sotatercept added to background therapy in comparison to background therapy by itself.[2] A hypothetical population with PAH WHO FC II or III was followed over 12-week cycles in a lifetime time horizon, with clinical inputs informed by clinical trial data and quality of life inputs informed by sources in the literature. Notable assumptions included improvement in functional class only limited to the first 24 weeks of the model and no independent effect on functional class improvement for patients that had progressed to WHO-FC IV.

While investigators found that treatment with sotatercept with background therapy resulted in more years without symptoms at rest (5.02 vs. 2.98) and more quality-adjusted life years (QALYs) (3.41 vs. 2.51) in the base case, the cost per QALY gained was $2,380,000 for a placeholder annual cost of $400,000. This far exceeds the cost-effectiveness threshold of $150,000; the health benefit price benchmark was determined to fall around $17,900 to $35,400 annually.

Budget Impact Model

Using findings from their cost-effectiveness model, ICER was able to estimate the budgetary impact of sotatercept for the entire US population.[2] The treatment group was identified as US adults with PAH WHO-FC II and III on background therapy, and it was estimated 20% of patients would initiate sotatercept each year over a 5-year period. Under these parameters, it was determined that only 7% of eligible patients could be treated without crossing ICER's $777 million annual budget impact threshold using the placeholder annual cost of $400,000.

Using these findings, a simplified BIM with respect to PFHP's population can be designed. To estimate the treatment-eligible population, the estimated population from the ICER budget impact estimate can be applied to the PFHP member pool of 1,587,600. ICER estimated the population of individuals in the US with PAH to be 75,000, with 80.9% of these patients being eligible due to WHO-FC II and III classification and an assumption that they were all currently treated with background therapy. Scaling this to PFHP's population

would result in a treatment eligible population of 283 members. The primary deviation from the ICER model was an adaptation of a $240,000 list price that was reported following the ICER report's publication.

Table 1: PFHP Budget Impact Model Design Summary

Time Horizon	Three years
Perspective	Patients First Health Plan population with 1,587,600 adult members with 283 treatment-eligible members (WHO-FC II and III classification and currently treated on background therapy)
Sotatercept Price ($ USD)	Annual list price of $240,000, with ±25% to account for discounting, rebates, etc. ($180,000 to $300,000)
Discounting	N/A
Cost Included	Drug acquisition
Assumptions	• PFHP population is aligned with US population in terms of demographics, disease incidence, etc. • Addition of sotatercept does not affect utilization of other medications
Limitations	• Likely overestimation of sotatercept uptake • Unable to account for change in plan population • Does not account for discontinuation • Evaluation of pharmacy benefit only not allowing for cost offset (no evaluation of changes in resource utilization affecting medical benefit)

Table 2: PFHP Estimated PMPM Budget Impact

	Year 1	Year 2	Year 3
Total Population on Sotatercept	52	104	156
Estimated Annual Spend on Sotatercept	$12,480,000 ($9,360,000 to $15,600,000)	$24,960,000 ($18,720,00 to $31,200,000)	$37,440,000 ($28,080,000 to $46,800,000)
Estimated PMPM Spend on Sotatercept	$0.65 ($0.49 to $0.81)	$1.30 ($0.98 to $1.62)	$1.96 ($1.47 to $2.43)
Required Annual Price of Sotatercept for a $0.10 PMPM Increase	$36,637	$18,318	$12,212

Our model shows that with the addition of sotatercept to the PFHP formulary, there is a strong likelihood of significant budget impact, with a projected PMPM of $0.65 in the first year that far exceeds the general threshold of a $0.10 PMPM annual increase. An estimated price of $36,637, or a 84.7% reduction from the current list price, would be needed to meet this threshold in the first year.

This model has several limitations, as it adapted the ICER US population funnel to determine the treatment eligible population. Therefore, it does not account for changes in plan demographics and size due to a lack of available information; there may be significant differences between the general US population and the member population of PFHP leading to overestimation. Additionally, despite accounting for some variability in sotatercept pricing, the actual acquisition price may be highly variable.

Clinical Evidence Tables

Reference: STELLAR						
Study Design and Evidence Grade	**Drug Regimens**	**N**	**Time Horizon**	**Study Population**	**Endpoints**	
					Primary	**Secondary**
Phase 3, DB, MC, PC, RCT	1. Sotatercept administered subcutaneously every 21 days (starting dose of 0.3 mg/kg followed by 0.7 mg/kg for all subsequent doses) 2. Placebo administered every 21 days	N = 323 Sotatercept (n = 163) Placebo (n = 160)	24 weeks	**Inclusion:** Age ≥ 18 years; confirmation of WHO PAH Group 1 that is idiopathic, heritable, drug/toxin induced, associated with connective tissue disease AND symptomatic PAH classified as WHO FC II or III; baseline PVR of ≥ 5 Wood and a PCWP or left ventricular end-diastolic pressure of ≤ 15 mmHg; on stable background PAH therapy and diuretics for ≥ 90 days prior to screening; 6MWD tests of ≥ 150 and ≤ 500 m repeated twice at screening; use of contraception if sexually active **Exclusion:** WHO Groups 2, 3, 4, or 5; PAH Group 1 associated with HIV, portal hypertension, schistosomiasis, or pulmonary veno occlusive disease, hemoglobin above gender specific ULN; baseline platelet < 50k; systolic blood pressure > 160 or <90 mmHg; known history or portal hypertension or chronic liver disease; notable cardiac history including LVEF < 45% and symptomatic coronary disease events within 6 months	Change from baseline in 6-minute walk distance at week 24	Percentage of patients meeting all 3 criteria of multicomponent improvement at week 24 (increase in 6MWD of ≥30 m, decrease in NT-proBNP of ≥30% or maintenance of level <300 pg/mL, improvement in WHO functional class or maintenance of class II); change from baseline at week 24 in PVR; change from baseline at week 24 in NT-proBNP, improvement in WHO functional class from baseline at week 24, time to first occurrence of death or nonfatal clinical worsening event defined by death from any cause or specified nonfatal clinical worsening events; low French risk score; change from baseline in Physical Impacts, Cardiopulmonary Symptoms, and Cognitive/Emotional Impacts of PAH-SYMPACT questionnaire
Efficacy/Effectiveness					**Serious Adverse Events**	
					Serious adverse events (SAEs) were reported in 23 patients (14.1%) from the sotatercept group and 36 patients (22.5%) from the placebo group. 2 patients in each group experienced treatment-related SAEs (1.2%)	
					Weaknesses Impacting Internal/External Validity	

End Point	Sotatercept (N=163)	Placebo (N=160)
Primary end point		
6-Minute walk distance — m		
Median change estimate (95% CI) from baseline at wk 24†	34.4 (33.0 to 35.5)	1.0 (−0.3 to 3.5)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	40.8 (27.5 to 54.1)§¶	
Secondary end points		
Multicomponent improvement		
Patients who met all three criteria for 6-min walk distance, NT-proBNP level, and WHO functional class — no./total no.	63/162‖	16/159‖
Percentage of patients (95% CI)	38.9 (31.3 to 46.9)¶**	10.1 (5.9 to 15.8)
Pulmonary vascular resistance — dyn·sec·cm^{-5}		
Median change estimate (95% CI) from baseline at wk 24†	−165.1 (−176.0 to −152.0)	32.8 (26.5 to 40.0)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	−234.6 (−288.4 to −180.8)§¶	
NT-proBNP — pg/ml		
Median change estimate (95% CI) from baseline at wk 24†	−230.3 (−236.0 to −223.0)	58.6 (46.0 to 67.0)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	−441.6 (−573.5 to −309.6)§¶	
WHO functional class		
Patients with improvement at wk 24 from baseline — no./total no.	48/163¶**	22/159‖
Percentage of patients (95% CI)	29.4 (22.6 to 37.1)	13.8 (8.9 to 20.2)
Time to first occurrence of death or nonfatal clinical worsening event		
Hazard ratio (95% CI)††	0.16 (0.08 to 0.35)¶‡‡	
French risk score§§		
Patients with a low-risk score with the use of the simplified French model at wk 24 — no./total no.	64/162‖	29/159‖
Percentage of patients (95% CI)	39.5 (31.9 to 47.5)¶**	18.2 (12.6 to 25.1)
PAH-SYMPACT Physical Impacts domain score¶¶		
Median change estimate (95% CI) from baseline at week 24†	−0.13 (−0.15 to 0.00)	0.01 (0.00 to 0.13)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	−0.26 (−0.49 to −0.04)¶‖‖	
PAH-SYMPACT Cardiopulmonary Symptoms domain score¶¶		
Median change estimate (95% CI) from baseline at week 24†	−0.12 (−0.14 to −0.08)	−0.01 (−0.03 to 0.00)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	−0.13 (−0.26 to −0.01)¶‖‖	
PAH-SYMPACT Cognitive/Emotional Impacts domain score¶¶		
Median change estimate (95% CI) from baseline at week 24†	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	−0.16 (−0.40 to 0.08)	

- Lack of active comparator drug
- Exclusion of patients with WHO-FC IV or PAH associated with HIV and/or portal hypertension (populations that may have poorer prognoses)
- Underrepresentation of patients with specific PAH etiologies (ex. Connective tissue disease associated, drug/toxin-induced)
- Underrepresentation of racial minorities (Asian, Black, Hispanic)
- Unknown effect on mortality due to study timeframe

Abbreviations used in this table: DB = double blind, PAH = pulmonary arterial hypertension, PC = placebo control, PCS = prospective cohort study, PG = parallel group, MA = meta-analysis MC = multicenter, RCS = retrospective cohort study, RCT = randomized controlled trial,

Cost-Effectiveness Evidence Summary

<table>
<tr><th>Ref. and Sponsor</th><th>QHES Score</th><th>Study Design and Treatments Compared</th><th>Time Horizon and Demographics</th><th>Model Inputs and Data Sources</th><th>Results:
Base Case, Sensitivity Analysis and Limitations</th></tr>
<tr>
<td>I.C.E.R.</td>
<td>88</td>
<td><u>Design:</u> Cost-effectiveness analysis of sotatercept using a decision analytic model

<u>Perspective:</u>
Health care sector, with modified societal perspective in scenario analysis

<u>Intervention/Comparators:</u>
• Weight-based sotatercept every 21 days with background therapy (intervention)
• Background therapy alone (comparator)

<u>Outputs:</u>
ICER, cost per LYG, cost per QALY gained

<u>Assumptions:</u>

Improvement in functional class occurred only over the first 24 weeks of the model. Subsequent functional class improvement could only occur during the cycle immediately after initiating an infused prostacyclin.

Members of the modeled cohort could only transition to adjacent functional classes between model cycles.

Sotatercept had no independent effect on functional class</td>
<td><u>Time horizon:</u>
Lifetime

<u>Discount rate:</u> 3%

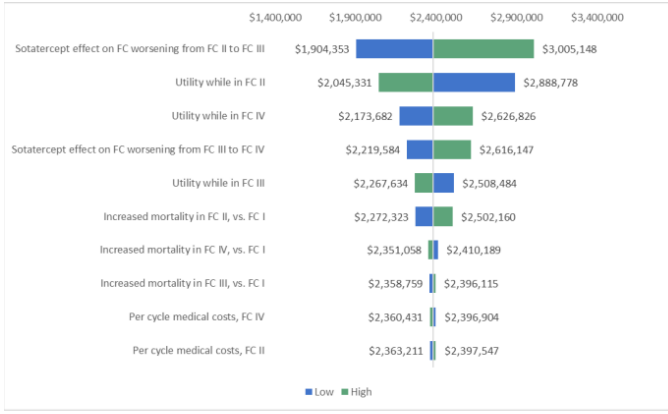
<u>Demographics:</u>
Hypothetical cohort of adult patients with WHO-FC II or WHO-FC III</td>
<td><u>Clinical inputs:</u>
• Effect on functional class worsening
• Adverse-event related discontinuation

<u>Quality of life inputs:</u>
• Utility of WHO-FC

<u>Cost inputs:</u>
• Annual cost of sotatercept, dual therapy, and triple therapy
• Medical costs associated with states and</td>
<td>Table 4.3. Base-Case Model Outcomes for Sotatercept plus Background Therapy as Compared to Background Therapy Alone
<table>
<tr><th>Treatment</th><th>Intervention Cost</th><th>Non-Intervention Costs</th><th>Total Costs</th><th>Years without Symptoms at Rest†</th><th>QALYs</th><th>Life Years</th><th>evLYs</th></tr>
<tr><td>Sotatercept plus Background Therapy</td><td>$2,002,000*</td><td>$1,011,000</td><td>$3,013,000</td><td>5.02</td><td>3.41</td><td>5.46</td><td>3.69</td></tr>
<tr><td>Background Therapy Alone</td><td>$0</td><td>$880,000</td><td>$880,000</td><td>2.98</td><td>2.51</td><td>4.27</td><td>2.51</td></tr>
</table>
evLY: equal value life year, QALY: quality-adjusted life year
*Assuming a placeholder price of $400,000 per year.
†Defined as years spent in WHO-FC I, WHO-FC II, and WHO-FC III.
Table 4.4. Incremental Cost-Effectiveness Ratios for the Base Case
<table>
<tr><th>Treatment</th><th>Cost per Additional Year without Symptoms at Rest</th><th>Cost per QALY Gained</th><th>Cost per Life Year Gained</th><th>Cost per evLY Gained</th></tr>
<tr><td>Sotatercept* plus Background Therapy</td><td>$1,046,000</td><td>$2,380,000</td><td>$1,792,000</td><td>$1,805,000</td></tr>
</table>
evLY: equal value life year, QALY: quality-adjusted life year
*Assuming a placeholder price of $400,000 per year.

<u>Scenario analysis results:</u>

Table 4.7. Scenario Analysis Results
<table>
<tr><th>Treatment</th><th>Base-Case Results ($/evLY)</th><th>Modified Societal Perspective ($/evLY)</th><th>Treatment Discontinuation at Death Only ($/evLY)</th><th>Halt WHO-FC at 24 Weeks ($/evLY)</th><th>WHO-FC Improvement Over Lifetime ($/evLY)</th></tr>
<tr><td>Sotatercept*</td><td>$1,805,000</td><td>$1,761,000</td><td>$1,930,000</td><td>$1,199,000</td><td>$1,190,000</td></tr>
</table>
evLY: equal-value life year, WHO-FC: World Health Organization functional class
*Assuming a placeholder price of $400,000 per year.
<u>Sensitivity analysis results:</u></td>
</tr>
</table>

Ref. and Sponsor	QHES Score	Study Design and Treatments Compared	Time Horizon and Demographics	Model Inputs and Data Sources	Results: Base Case, Sensitivity Analysis and Limitations
		improvement after a patient progressed to WHOFC IV and initiated an infused prostacyclin. Any improvement in functional class after adding an infused prostacyclin was equivalent to the effectiveness of the infused prostacyclin. If an individual had been on sotatercept and an infused prostacyclin for one model cycle and did not improve in functional class, or if they transitioned back to WHO-FC IV after initially improving to WHO-FC III once starting an infused prostacyclin, they discontinued sotatercept. Patients who discontinued sotatercept due to adverse events discontinued sotatercept after the second model cycle. No subsequent adverse event-related discontinuation was modeled after the second model cycle.			**Figure 4.2. Tornado Diagram for Sotatercept* plus Background Therapy as Compared to Background Therapy Alone**  FC: functional class *Assuming a placeholder price of $400,000 per year. <u>Limitations:</u> • Clinical trial efficacy and discontinuation rates were extrapolated based on STELLAR's 24 week time frame • No assumed independent effect of sotatercept on mortality
Abbreviations used in this table: evLY = equal value life year, ICER= incremental cost-effectiveness ratio, LYG = life-years gained, QALY = quality-adjusted life-year, QOL = quality of life, WHO-FC = World Health Organization Functional Class					

Ref. and Sponsor	QHES Score	Study Design and Treatments Compared	Time Horizon and Demographics	Model Inputs and Data Sources	Results: Base Case, Sensitivity Analysis and Limitations

Abbreviations used in this table: LYS = life-years saved, QALY = quality-adjusted life-year, QOL = quality of life.

Background

Disease Background

Pulmonary hypertension (PH) is a rare, rapidly progressing disease that is characterized by an increase in the lung's arterial blood pressure, which is quantified as a mean arterial pressure (MAP) of ≥20 mmHg at rest. It commonly presents with debilitating symptoms such as shortness of breath, fatigue, chest pain, and dizziness, which can lead to death; one-fifth of patients die within 3 years of a PH diagnosis. [10] The prevalence within the United States population is 50,000 to 100,000 people, or approximately 15 to 50 cases per million. [11] Onset of disease is typically during adulthood between the ages of 30 and 60. PH is more common in women compared to men; however, some evidence suggests that men may have comparatively worse outcomes. Risk factors for PH include family history, prior pulmonary embolism, a history of sleep apnea or chronic obstructive pulmonary disease (COPD), and sickle cell disease (SCD), though the ultimate cause is often idiopathic. The WHO classifies PH diagnoses into 5 groups as follows-

- Group I – Pulmonary arterial hypertension (PAH)
    - Idiopathic (most common)
    - Genetic disorder
    - Drug and toxin induced
    - Associated conditions (ex. HIV infection, portal hypertension, congenital heart diseae)
- Group II – PH caused by left heart disease
- Group III – PH due to chronic lung disease and/or hypoxemia
- Group IV – PH due to pulmonary artery obstructions
- Group V – PH due to unclear multifactorial mechanisms[12]

WHO functional classes (FCs) are a subgroup of symptoms present in patients in WHO Group I. The WHO FCs are as follows:

- Class I – Patients with PAH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea, fatigue, chest pain, and/or near syncope.
- Class II – Patients with PAH resulting in slight limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes dyspnea, fatigue, chest pain, and/or near syncope
- Class III – Patients with PAH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes dyspnea, fatigue, chest pain, and/or near syncope
- Class IV – Patients with PAH with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest, and discomfort is increased by any physical activity[12]

Sotatercept was approved for the treatment of PAH with WHO FC II and III, which is where most Group I patients fall. These classes are characterized by endothelial and smooth muscle cell proliferation and abnormal angiogenesis, resulting in a significant increase in pulmonary vascular resistance (PVR).

PAH is most commonly diagnosed in female and Caucasian patients, though healthcare disparities and social determinants of health may play in a role in the disease's underdiagnosis in other groups. Right heart catheterization (RHC) is the current standard diagnostic tool used for PAH. Risk factors for disease include type II bone morphogenic protein receptor mutation, connective tissue disease, portal hypertension, HIV, congenital heart disease, and schistosomiasis.

Disease Burden

PAH is a rare, progressive disease that affects approximately 50,000 to 100,000 people in the United States, including patients and caregivers. Diagnosis tends to occur late into disease progression, as symptoms are present as generalized and non-specific. As a result, the 5-year mortality rate is approximately 43% with median survival ranging from 5 to 7 years after diagnosis. Worldwide prevalence is estimated at 15 million to 50 million, with 200,000 new cases diagnosed annually. Economic impact is also substantial; median medical costs per patient are estimated to exceed $100,000 annually. [13]

Patients with PAH are predisposed to heart failure, have reduced life expectancy, and limited ability to perform physical activity due to strain on the heart. This can result in an inability to perform daily living activities and subsequently impact quality of life. Patients describe fatigue as having the largest impact on quality of life, and report issues with currently available therapies such as the need for multiple administrations a day, use of an intravenous catheter for infused medications, and substantial side effects such as nausea, vomiting, and injection site reactions. [2]

Pathophysiology

The pathophysiology of PAH is characterized by the functional status of the right side of the heart. In a healthy heart, pulmonary circulation is highly compliant with a low resistance system, allowing blood flow to the right ventricle (RV). In PAH, higher PVR results in increased RV wall stress, leading to cardiac myocyte hypertrophy. As the disease progresses, the RV dilates, leading to inefficient contractility of the heart and ultimately right-sided heart failure (RHF).

Treatment Alternatives

Current treatment for PAH is centered around vasodilation with treatment goals being improved functional status and survival. [12] Their mechanism of action involves either nitric oxide or prostacyclin, two endogenous compounds which promote vasodilation. Drug classes currently used in the treatment of PAH include phosphodiesterase-5 inhibitors (PDE-5i), soluble guanylate cyclase stimulators (sGCS), endothelin receptor antagonists (ERA), and prostacyclin analogues (PCA), which includes prostanoids as well as prostacyclin receptor agonists. All listed classes have oral agent options; PCAs are also available as inhalation or injection.

Preferred Existing Therapy

In patients with low and intermediate risk PAH, combination therapy with an ERA and PDE5i should be initiated. Patients classified as high risk should be initiated on triple therapy, which consists of combination therapy with the addition of a PCA. [12]

Other Therapeutic Alternatives

For patients with end-stage pulmonary arterial hypertension, lung or heart-lung transplantation may be considered. [12]

Product Background

Pharmacology

Sotatercept is a first-in-class fusion protein biologic that is comprised of the Fc domain of human IgG linked to the extracellular domain of human activin receptor type II a (ActRIIA). [9] ActRIIA acts as a ligand trap for transforming growth factor beta (TGF-β), a cytokine that is implicated in pulmonary vascular remodeling in PAH. Inhibition of TGF-β is proposed to rebalance pulmonary vascular homeostasis toward growth-inhibiting and proapoptotic signaling. In animal models of pulmonary hypertension, sotatercept inhibited cell proliferation, promoted apoptosis, and alleviated inflammation in the vessel walls, leading to reverse remodeling and restoration of vessel patency. This suggest disease-modifying potential, though long-term data is needed to support this.

Pharmacokinetics[9]

Route of administration	Subcutaneous
Bioavailability	~66%
Time to peak	~7 days (range of 2 to 8 days)
Plasma half-life	20-32 days
Route(s) of elimination	Renal (minor)

Methodology

The methodology for our review was based on a literature search. which involved examining the associated phase 3clinical trial and economic evaluations for sotatercept. A articles were assessed for relevance and strength of evidence for use in our monograph.

Databases Searched

PubMed, Google Scholar, Clinicaltrials.gov, Cochrane Library

Secondary Sources

UptoDate,, Micromedex, FDA Label

Search Strategy

Sotatercept AND clinical trial OR RCT
Sotatercept AND cost-effectiveness OR economic OR budget impact OR value OR ICER OR QALY
Sotatercept AND meta-analysis OR comparative effectiveness

Inclusion Criteria

Completed phase 3 RCTs, cost effectiveness analyses, comparative efficacy and safety studies, meta-analyses with comparison to other therapies

Search Results

Study Type	N	Published	Unpublished
Randomized controlled trials (RCT)	3	3	
Cost-utility modeling studies	1	1	
Budget impact modeling studies	1	1	

Articles Excluded from Evidence Synthesis

Reason for Exclusion	N
Long-term extension of RCTs with only interim results	2

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11. Balasubramanian VP, Fares WH, Levine DJ, Sahay S, Test VJ. *Navigating PAH*. CHEST Foundation; 2018.

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Coverage Criteria: WINREVAIR™ (sotatercept)

Description and FDA-Approved Indication

Initial Approval Criteria

Winrevair™ (sotatercept) is an activin signaling inhibitor indicated for the treatment of adults with pulmonary arterial hypertension (PAH). Winrevair™ is used in combination with other background therapies for PAH such as phosphodiesterase-5 inhibitors (PDE5i), soluble guanylate cyclase stimulators (sGCS), endothelin receptor antagonists (ERA), and prostacyclin analogues (PCA).

Winrevair™ will be considered for coverage under the pharmacy benefit for the indication listed above when the following criteria are met.

- Diagnosis of PAH confirmed by right heart catheterization (RHC)
- WHO FC II or III
- ≥18 years of age
- Adequate trial and failure or contraindication to an ERA in combination with either a PDE-5i OR sGCS
- Continuation of current PAH background therapies unless not tolerated following the addition of Winrevair™
- Platelet count ≥ 50,000/mm^3
- Prescribed by or in consultation with a cardiologist or pulmonologist

Initial Approval Duration

6 months

Reauthorization Criteria

- Adherence to therapy as verified by prescriber or fill history with ≥80% proportion of days covered (PDC)
- Documentation verifying positive clinical response with no adverse effects, allergies, or hypersensitivities

Reauthorization Duration

1 year

Exclusions

- Any indication that is NOT for pulmonary arterial hypertension in an adult