Sotatercept for Pulmonary Arterial Hypertension

Evidence Report

November 14, 2023

Prepared for

AUTHORS:

Grace Lin, MD
Medical Director for Health Technology Assessment
Institute for Clinical and Economic Review

Melanie D. Whittington, PhD, MS
Senior Fellow
Center for the Evaluation of Value and Risk in Health (CEVR)
Tufts Medical Center

Dmitriy Nikitin, MSPH
Senior Research Lead
Institute for Clinical and Economic Review

Emily Nhan
Senior Research Assistant
Institute for Clinical and Economic Review

Marina Richardson, PhD, MSc
Senior Health Economist
Institute for Clinical and Economic Review

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review

David M. Rind, MD, MSc
Chief Medical Officer
Institute for Clinical and Economic Review

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Grace Lin served as the lead author for the report. Dmitriy Nikitin led the systematic review and authorship of the comparative clinical effectiveness section in collaboration with Emily Nhan. Melanie Whittington developed the cost-effectiveness model and authored the corresponding sections of the report with assistance from Marina Richardson. David M. Rind and Steven D. Pearson provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Yamaya Jean and Yasmine Kayali for their contributions to this report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at https://icer.org/.

The funding for this report comes from non-profit foundations, with the largest single funder being the Arnold Ventures. No funding for this work comes from health insurers, pharmacy benefit managers (PBMs), or life science companies. ICER receives approximately 22% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. Life science companies relevant to this review who participate in this program include: Merck & Co. For a complete list of funders and for more information on ICER's support, please visit https://icer.org/who-we-are/independent-funding/.

For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

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The Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. Midwest CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The Midwest CEPAC is an independent committee of medical evidence experts from across the Midwest, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Panel members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about Midwest CEPAC is available at https://icer.org/who-we-are/people/independent-appraisal-committees/midwest-comparative-effectiveness-public-advisory-council-m-cepac/.

The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

The economic models used in ICER reports are intended to compare the clinical outcomes, expected costs, and cost-effectiveness of different care pathways for broad groups of patients. Model results therefore represent average findings across patients and should not be presumed to represent the clinical or cost outcomes for any specific patient. In addition, data inputs to ICER models often come from clinical trials; patients in these trials may differ in real-world practice settings.

In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following experts provided input that helped guide the ICER team as we shaped our scope and report. It is possible that expert reviewers may not have had the opportunity to review all portions of this draft report. None of these individuals is responsible for the final contents of this report, nor should it be assumed that they support any part of it. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer.org/wp-content/uploads/2023/09/PAH_Stakeholder-List_For-Publication_09252023.pdf

Expert Reviewers

Murali Chakinala, MD
Professor of Medicine
Washington University
Dr. Chakinala has received manufacturer support in the area of pulmonary hypertension, such as through research funding or by serving as a Principle Investigator (PI) for the following health care companies: Merck (site PI), Janssen, United Therapeutics, Bayer, Liquidia, Gossamer, Medtronic, Altavant, Respira.

Doug Coyle, MA, MSc, PhD
Professor
University of Ottawa
Dr. Coyle has received consulting fees or honoraria in excess of $5,000 from TELUS Health.

Katie Kroner, MSW
Vice President, Advocacy and Patient Engagement
Pulmonary Hypertension Association
The Pulmonary Hypertension Association (PHA) receives greater than 25% of its funding from health care companies.

Marc Simon, MD, MS
Professor of Medicine
University of California at San Francisco
Dr. Simon has received consulting fees in excess of $5,000 from Merck Pharmaceuticals.

Table of Contents

List of Acronyms and Abbreviations Used in this Report

6MWD	6-Minute Walk Distance
AE	Adverse event
AESI	Adverse event of special interest
CI	Confidence Interval
cm	Centimeter
dyn	Dyne
ERA	Endothelin receptor antagonist
evLY	Equal value life year
FDA	Food and Drug Administration
hr	Hour
IV	Intravenous
m	Meter
mL	Milliliter
n	Number
N	Total Number
NR	Not reported
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
OLE	Open-label extension
PAH	Pulmonary arterial hypertension
PAH-SYMPACT	Pulmonary Arterial Hypertension-Symptoms and Impact
PDE5i	Phosphodiesterase-5 inhibitor
pg	Picogram
PHA	Pulmonary Hypertension Association
PVR	Pulmonary vascular resistance
REF	Reference
SC	Subcutaneous
SD	Standard deviation
sec	Second
sGCS	Soluble guanylate cyclase stimulators
WAC	Wholesale acquisition cost
WHO-FC	World Health Organization functional class
QALY	Quality-adjusted life year
US	United States

Executive Summary

Pulmonary arterial hypertension (PAH) is a rare, progressive disease that affects approximately 50,000 to 100,000 people in the US.[1] The disease is characterized by increased pressure in the pulmonary arteries, making it more difficult for the heart to pump blood to the lungs and leading to debilitating symptoms such as shortness of breath, fatigue, chest pain, dizziness, and syncope. PAH can be idiopathic, due to inherited genetic mutations or exposure to drugs or toxins, or associated with congenital heart disease or other systemic diseases such as connective tissue disease, liver disease, or HIV. Quality of life for persons with PAH is generally poor[2], and depression and anxiety are also common.[3] PAH can substantially shorten lifespan, with one-fifth of patients dying within three years of diagnosis.[4] People with PAH describe a large impact on their lives and the lives of their families both from symptoms and financially, with direct medical costs estimated at more than $100,000 per person per year.[5]

Current treatment for PAH includes medications that promote vasodilation with the goals of improving functional status and survival.[6] There are several classes of drugs available for treatment: those affecting the nitric oxide pathway, including phosphodiesterase-5 inhibitors (PDE5i, oral with an IV formulation available) and soluble guanylate cyclase stimulators (sGCS, oral); endothelin receptor antagonists (ERA, oral); and prostacyclin analogues (prostanoids; oral, inhaled, subcutaneous (SC), or intravenous (IV) as well as a prostacyclin receptor agonist (oral). Current clinical practice guidelines suggest that low and intermediate risk patients should be initiated on combination therapy with ERA and PDE5i agents; those with high-risk disease should be initiated on triple therapy with the addition of an IV or SC prostacyclin analogue.[6] Ultimately, lung or heart-lung transplantation may be necessary.

Sotatercept (Merck & Co., Inc) is a first-in-class activin signaling inhibitor and potentially disease-modifying drug which may improve pulmonary blood flow through inhibiting cellular proliferation, promoting cellular death, and decreasing inflammation in vessel walls.[7] It is administered as a subcutaneous injection every three weeks. A Biologics License Application for sotatercept has been filed with the US Food and Drug Administration (FDA), with a decision expected by March 26, 2024.

The pivotal trial for sotatercept was STELLAR, a Phase III randomized, placebo-controlled trial of 323 persons with World Health Organization functional class (WHO-FC) II and III PAH.[7] Participants were randomized to receive either sotatercept 0.7 mg/kg every 3 weeks added on to stable background double or triple therapy or continued background therapy. The primary outcome was change in 6-minute walk distance (6MWD) at 24 weeks; WHO-FC, quality of life, hemodynamic, and biomarker outcomes were also measured as secondary endpoints, as well as a multicomponent endpoint combining 6MWD, NT-proBNP level, and WHO-FC change.

Trial participants were mainly female and White, with a mean age of around 48 years and a mean of 8.8 years since diagnosis. Approximately 40% were on infused prostacyclin therapy at baseline.

The median difference in 6MWD was 40.8 meters, favoring the sotatercept group. Around twice as many participants in the sotatercept group had improvement in WHO-FC compared with placebo (29.4% vs. 13.8%). There was an 84% reduction in the risk of clinical worsening or death. Secondary outcomes were consistently in favor of sotatercept. Despite patient and provider reports of substantial improvements, overall measurements of quality of life using a PAH-specific scale did not improve with sotatercept although there were improvements in two of three. Open-label extension trials suggested that improvements in 6MWD, NT-proBNP, and WHO-FC are maintained up to 24 months.

Harms of sotatercept were relatively few, and there were more adverse events, severe adverse events, and discontinuations in the placebo group than in the sotatercept group. There were few deaths overall, but numerically fewer deaths in the sotatercept group. There were additional deaths during open-label extension. The most common adverse events included headache, diarrhea, epistaxis, telangiectasias, and dizziness. Adverse events of concern with sotatercept included a statistically significant higher rate of telangiectasias, increased hemoglobin levels, and bleeding events.

Based on the currently available data, treatment with sotatercept added to background therapy can improve clinical outcomes for patients with PAH, with relatively few harms. Additionally, the subcutaneous delivery system is less burdensome than many other PAH treatments, particularly inhaled and intravenous prostanoids. However, uncertainty remains about sotatercept's efficacy in sicker populations and in those with connective tissue disease, and about the durability of effect. In the absence of longer-term data, we necessarily have uncertainties about sotatercept's effects on mortality and as-yet-undetected adverse effects. Therefore, we have moderate certainty of a small to substantial net health benefit, with a high certainty of at least a small net health benefit, corresponding to an ICER Evidence Rating of **B+**.

Table ES1. Evidence Ratings

Treatment	Comparator	Evidence Rating
Adults with PAH classified in WHO-FC II and III		
Sotatercept	Background therapy	B+

We estimated the cost-effectiveness of sotatercept added to background therapy from a health care sector perspective using a de novo decision analytic model. Treatment with sotatercept resulted in longer time without symptoms at rest and more quality-adjusted life years (QALYs), life years, and equal value life years (evLYs). The health benefit price benchmark for sotatercept is $18,700 to $36,200 per year.

1. Background

Pulmonary arterial hypertension (PAH) is a rare, progressive disease characterized by thickening of the walls of the pulmonary arteries that carry blood from the right side of the heart to the lungs, leading to increased pulmonary vascular resistance. The increased pressure in the pulmonary arteries makes it more difficult for the heart to pump blood to the lungs and leads to debilitating symptoms such as shortness of breath, fatigue, chest pain and dizziness. Eventually, dysfunction of the right ventricle leads to premature death, with one-fifth of patients dying within three years of diagnosis.[4] The impact of PAH is significant, with medical costs estimated at greater than $100,000 per person per year.[5]

Approximately 50,000 to 100,000 people in the United States (US) have PAH[1], which is estimated to occur in 15 to 50 persons per million in the population.[4] The disease onset is generally between 30 and 60 years of age. PAH is more common in women than men; men, however, may have worse outcomes[8]. According to US registry data, more than 70% of people diagnosed with PAH are White, with Blacks and Asians constituting 12.7% and 4.6% of the PAH population, respectively; almost 11% report Hispanic or Latino ethnicity.[9] There are racial and ethnic differences in presentation. For example, some data suggest that Black people are at higher risk of developing PAH and are also more likely to be younger, female, and have an associated connective tissue disorder. PAH can be idiopathic, due to inherited genetic mutations or exposure to drugs or toxins (e.g., fenfluramine, methamphetamines), or associated with other conditions such as connective tissue disease, congenital heart disease, HIV, portal hypertension, and schistosomiasis.

The most common symptom of PAH is dyspnea on exertion, with more than 80% of patients reporting this symptom.[12] Fatigue, edema, chest pain, syncope, dizziness and lightheadedness are also frequent symptoms of PAH. As the disease progresses, shortness of breath may start to occur at rest; fatigue and edema may worsen as the right ventricle fails. Quality of life for people with PAH is generally poor, particularly in the physical function domains.[2] Severity of disease is mainly measured by WHO-FC, which ranges from WHO-FC I (no limitation in activity) to WHO-FC IV (severe limitation, any activity causes symptoms).

Delays in diagnosis of PAH are common since the symptoms can be mild and nonspecific at first and the diagnosis of PAH requires exclusion of other causes of pulmonary hypertension.[13] The mean time to diagnosis is 1.9 years;[12] younger age, history of obstructive lung disease, and history of obstructive sleep apnea are associated with delayed diagnosis.[14]

Treatment for PAH includes both medications and supportive care. Supportive care includes exercise training, oxygen supplementation, iron supplementation, referral for drug rehabilitation as needed,[15] and treatment for anxiety and depression,[16] which is common in persons with PAH. Currently available pharmacologic agents for PAH treatment promote vasodilation with the goals of

improving functional status and survival.[6] There are several classes of drugs available for treatment: those affecting the nitric oxide pathway, including phosphodiesterase-5 inhibitors (PDE5i, oral with an IV formulation available) and soluble guanylate cyclase stimulators (sGCS, oral); endothelin receptor antagonists (ERA, oral); and prostacyclin analogues (oral, inhaled, subcutaneous (SC), or intravenous (IV)) and prostatcyclin receptor agonists (oral). Intensity of therapy is based on whether a person has a low, intermediate, or high risk of death as calculated through various validated risk assessment tools that include prognostic indicators such as WHO-FC, 6MWD, and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels.[17] Current clinical practice guidelines suggest that low and intermediate risk patients should be initiated on combination therapy with ERA and PDE5i agents; the addition of other agents such as selexipag may be considered in some cases.[6] Those with high-risk disease are recommended to be initiated on triple therapy with the addition of an IV or SC prostacyclin analogue.[6] Ultimately, lung or heart-lung transplantation, which are considered the only cures for the disease, may be necessary. Treatment of PAH has been shown to improve pulmonary hemodynamics, exercise capacity and progression-free survival; however, even with treatment, 21% of patients die within 3 years of diagnosis.[18]

Sotatercept (Merck & Co., Inc) is a first-in-class activin signaling inhibitor which may improve pulmonary blood flow through inhibiting cellular proliferation, promoting cellular death, and decreasing inflammation in vessel walls.[7] Unlike current therapies, which work mainly via vasodilation, sotatercept's mechanism of action is distinct and is felt by some to potentially be disease-modifying. It has been studied as a subcutaneous injection every three weeks added on to stable background therapy. A Biologics License Application for sotatercept has been filed with the US FDA, with a decision expected by March 26, 2024.

Table 1.1. Interventions of Interest

Intervention	Mechanism of Action	Delivery Route	Prescribing Information
Sotatercept	Activin signaling inhibitor	Subcutaneous injection	0.3 mg/kg initial dose then 0.7 mg/kg every 3 weeks

2. Patient and Caregiver Perspectives

This section was developed with input from diverse stakeholders, including interviews with individuals living with PAH and patient groups, clinicians, researchers, and the manufacturer of sotatercept. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of treatments for PAH.

PAH has substantial impacts on quality of life, including physical, emotional, social, and financial burdens. The symptoms of PAH can be pervasive, including constant shortness of breath, fatigue and "brain fog", which can limit participation in activities or make them much harder to do. For example, people with PAH describe difficulty doing daily living tasks such as laundry, washing dishes, cooking, and having to stop participating in activities that they had once enjoyed due to their symptoms. The symptoms also fluctuate, and so persons with PAH described difficulty making firm plans because a "bad" day may mean that they are unable to do certain activities. Symptoms can also lead to substantial life changes including the need to leave the workforce, moving to a lower elevation, altering family planning, and a dependence on others (mainly partners and children) for daily life activities. Frequent symptoms and hospitalizations can also affect families, as partners and children may need to alter their daily lives to accommodate the limitations imposed on a person with PAH. People with PAH also described anxiety not only about the future and potentially not being able to be present for life milestones of their children but also the burden that their illness places upon their families.

Because symptoms can initially be generalized and nonspecific, there is often a delay both in seeking medical attention and in diagnosis, which can impact both survival and quality of life. Even after diagnosis, symptoms may be underreported or underrecognized by physicians; a survey of PAH patients and their physicians found that physicians reported fewer symptoms than patients, and patients reported fatigue as having the biggest impact on quality of life more frequently than their physicians (21% vs. 12%).[19] People with PAH describe currently available therapies as burdensome to manage in terms of administration and side effects, and also as creating financial strains. For example, oral and inhaled medications may need to be taken several times per day and intravenous medications require continuous infusions through a catheter. In addition to the burdens of having to have medication being infused 24 hours a day, having a catheter involves the need for meticulous care to avoid catheter-associated infections. People with PAH also mentioned that currently available treatments often have substantial side effects, including nausea, vomiting, diarrhea, flushing, dizziness, headache, and pain at the injection site, which can limit their use.

Access to therapies can be difficult. Treatments for PAH are expensive, with many patients meeting their annual insurance deductible very early in the benefit year. Those with high deductible health plans and copay accumulators reported particular difficulty affording their medications. Clinicians,

too, reported having to change drugs frequently due to patients being unable to afford medications without assistance. Patients reported that they sometimes depended on grants to afford their medications, but that grant money was not always available. Insurance coverage plays an important role in the lives of persons with PAH, with some people describing their partners having to turn down job opportunities if the insurance coverage was not sufficient. Furthermore, any change in insurance was stressful, as having to undertake a new prior authorization process could be long and might leave patients without necessary medication. Additionally, many medications are available only through specialty pharmacies; getting timely refills and deliveries can be challenging, with patients worried about being without medication due to delivery delays. These barriers had an impact on patients financially but also on their disease course; one patient reported that they had progression of symptoms when they had to change drugs from a stable regimen. Finally, people with PAH expressed hope that future treatments would have less complex regimens and less burdensome administration to allow for more freedom and flexibility in their lives, and were excited by the results of the sotatercept clinical trials.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Procedures for the systematic literature review assessing the evidence on sotatercept for the treatment of PAH are described in Supplement Section D1. A research protocol is published on Open Science Framework and registered with PROSPERO (CRD42023435218).

Scope of Review

We reviewed the clinical effectiveness of sotatercept as an add-on to stable background therapy versus stable background therapy alone for the treatment of PAH. We sought evidence on patient-important outcomes, including improvements in functional capacity, mortality, clinical worsening, health-related quality of life, and adverse events. The full scope of the review is described in Supplement Section D1.

Evidence Base

The sotatercept clinical development portfolio currently consists of two completed trials.

STELLAR is the pivotal Phase III trial of sotatercept that compared the drug's efficacy and safety as an add-on to stable background therapy for the treatment of PAH.[7] The trial enrolled 323 adults with WHO-FC II (slight limitation, some symptoms with ordinary activities) or FC III (marked limitation, less than ordinary activity causes symptoms) PAH who were receiving stable background therapy (see Table 3.1 for an overview of baseline characteristics). Patients were randomly assigned to receive subcutaneous sotatercept or placebo every three weeks for 24 weeks. Sotatercept was administered at a starting dose of 0.3 mg/kg of bodyweight with a target dose of 0.7 mg/kg. Eligible PAH etiologies included idiopathic, heritable, drug or toxin-induced, connective tissue disease-associated, or corrected congenital shunts. Patients also met the screening criteria of having a 6MWD of between 150 and 500 meters as well as a pulmonary vascular resistance (PVR) measurement of ≥ 5 Wood units. See Supplement Tables D5 and D6 for additional study eligibility and baseline characteristics. The STELLAR trial provides the primary data on the clinical efficacy and safety of sotatercept presented in this report. All results discussed, unless otherwise noted, are derived from this trial.

PULSAR is an earlier Phase II randomized trial that evaluated 24 weeks of treatment with sotatercept (at 0.3 or 0.7 mg/kg subcutaneously every three weeks) or placebo in 106 patients with PAH already on stable background therapy.[20] The eligibility criteria for this trial were similar to those of the STELLAR trial (See Supplement Table D5). The PULSAR trial had an open-label extension (OLE) where patients either continued sotatercept treatment or crossed over from the

placebo arm for an additional 18 to 24 months.[21] 97 out of 106 participants (92%) from the initial period enrolled in the extension.

SOTERIA is an ongoing long-term (7-year) follow up study of participants who completed an initial trial from the sotatercept clinical development program, including STELLAR and PULSAR.[22] All patients enrolled in SOTERIA either continued sotatercept or, if originally in a placebo arm, were initiated on sotatercept. Evidence from the PULSAR OLE and interim analysis of the SOTERIA study was used to inform our understanding of the durability and long-term safety profile of sotatercept.

We did not conduct a meta-analysis of the available clinical evidence due to differences across trials in design factors, such as dosage (0.3 vs. 0.7mg/kg) and reporting of outcomes (mean vs. median).

Table 3.1. Overview of Key Trial of Sotatercept[7]

STELLAR				
Arm		**Sotatercept**	**Placebo**	**Total**
N		**163**	**160**	**323**
Female sex, n (%)		129 (79.1)	127 (79.4)	256 (79.3)
Age, mean years (SD)		47.6 (14.1)	48.3 (15.5)	47.9 (14.8)
North America region, n (%)		49 (30.1)	56 (35.0)	105 (32.5)
White race, n (%)		147 (90.2)	141 (88.1)	288 (89.2)
Time since PAH diagnosis, mean years (SD)		9.2 (7.3)	8.3 (6.7)	8.8 (7.0)
Classification of PAH, n (%)	**Idiopathic**	83 (50.9)	106 (66.2)	189 (58.5)
	Heritable	35 (21.5)	24 (15.0)	59 (18.3)
	Associated with connective-tissue disease	29 (17.8)	19 (11.9)	48 (14.9)
	Drug-induced or toxin-induced	7 (4.3)	4 (2.5)	11 (3.4)
	Associated with corrected congenital shunts	9 (5.5)	7 (4.4)	16 (5.0)
6-Minute walk distance, mean (SD), m		397.6 (84.3)	404.7 (80.6)	401.1 (82.4)
Pulmonary vascular resistance, mean, dyn·sec·cm−5		781.3 (398.5)	745.8 (313.5)	763.7 (358.8)
WHO-FC, n (%)	**II**	79 (48.5)	78 (48.8)	157 (48.6)
	III	84 (51.5)	82 (51.2)	166 (51.4)
Background therapy for PAH, n (%)*	**Prostacyclin infusion therapy†**	65 (39.9)	64 (40.0)	129 (39.9)
	Monotherapy	9 (5.5)	4 (2.5)	13 (4.0)
	Double therapy	56 (34.4)	56 (35.0)	112 (34.7)
	Triple therapy	98 (60.1)	100 (62.5)	198 (61.3)
	ERA+Prostacyclin+PDE5i combination therapy	79 (48.5)	85 (53.1)	164 (50.8)

cm: centimeter, dyn: dyne, ERA: endothelin receptor antagonist, m: meter, mL: milliliter, n: number, N: total number, PAH: pulmonary arterial hypertension, PDE5i: phosphodiesterase-5 inhibitor, sec: second, SD: standard deviation, WHO-FC: World Health Organization functional class

*Treatments included monotherapy, double therapy, or triple therapy with combinations of endothelin-receptor antagonists, phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators, prostacyclin analogues, and prostacyclin-receptor agonists.

†Prostacyclin infusion therapy includes intravenous epoprostenol and intravenous or subcutaneous treprostinil.

3.2. Results

Clinical Benefits

Key trial results of the pivotal trial, STELLAR, are outlined in Table 3.2.

Table 3.2. Key Trial Results of Sotatercept[7]

STELLAR			
Arm		**Sotatercept**	**Placebo**
N		**163**	**160**
Timepoint: 24 Weeks			
6-Minute walk distance, m	**Median change estimate from baseline**	34.4	1.0
	Hodges–Lehmann location shift from placebo estimate (95% CI)	40.8 (27.5 to 54.1)	
WHO-FC improvement, n/N (%)		48/163 (29.4)	22/159 (13.8)
Pulmonary vascular resistance, dyn·sec·cm−5	**Median change estimate from baseline**	-165.1	32.8
	Hodges–Lehmann location shift from placebo estimate (95% CI)	-234.6 (-288.4 to -180.8)	
NT-proBNP, pg/mL	**Median change estimate from baseline**	-230.3	58.6
	Hodges–Lehmann location shift from placebo estimate (95% CI)	-441.6 (-573.5 to -309.6)	
Multicomponent improvement (Patients who met all three criteria for 6MWD, NT-proBNP level, and WHO-FC), n/N (%)	**Overall**	63/162 (38.9)	16/159 (10.1)
	Improvement in WHO-FC or maintenance of WHO-FC II	115/163 (70.6)	82/159 (51.6)
	Improvement in NT-proBNP (decrease ≥30%) or maintenance/ achievement of NT-proBNP level <300 pg/mL	138/162 (85.2)	64/159 (40.3)
	Improvement in 6MWD ≥30 m	87/163 (53.4)	35/159 (22)
French low-risk score, n/N (%)*		64/162 (39.5)	29/159 (18.2)

6MWD: 6-Minute Walk Distance, cm: centimeter, dyn: dyne, hr: hour, m: meter, mL: milliliter, n: number, N: total number, NT-proBNP: N-terminal prohormone of brain natriuretic peptide, PAH: pulmonary arterial hypertension, pg: picogram, sec: second, WHO-FC: World Health Organization functional class

*The French low-risk score was defined by meeting the following three criteria for low risk: WHO-FC I or II, 6-minute walk distance of >440 m, and NT-proBNP level of <300 pg/mL.

Change in Functional Status

The primary endpoint of the STELLAR trial was the change from baseline in 6MWD at week 24. The 6MWD test is a measure of how far an individual can walk unassisted in 6 minutes. It is a validated assessment of change in exercise capacity in patients with PAH and is reported as an absolute difference in meters (m) or percentage.[23] See Supplement A1 for additional study outcome definitions.

In the STELLAR trial, the median change in 6MWD was 34.4 m in the sotatercept group compared to 1.0 m in the placebo group (P<0.001).[7] Although there is no consensus on what a minimal clinically important difference in the 6MWD is, a recent meta-analysis posited a value of approximately 33

meters.[24] Treatment with sotatercept resulted in a higher proportion of patients achieving a ≥30 m improvement in 6MWD compared to placebo (53.4 vs. 22 percent).

The median difference in 6MWD between the sotatercept and placebo groups at week 24 was also estimated using the Hodges-Lehmann approach, as requested by the FDA. This method allows for more accurate comparisons between treatment groups with different sample sizes or non-normal distributions, as it takes into account the variability within each group rather than just the overall mean.[25] The estimated median difference in 6MWD calculated using the Hodges-Lehmann approach was 40.8 meters, favoring the sotatercept-treated group. These results were consistent across several pre-specified and post-hoc sensitivity analyses which used different approaches to impute missing data due to death and non-fatal clinical worsening events.

The WHO-FC was assessed at baseline and at 24 weeks. Functional class ranges from I (no limitation to ordinary physical activity) to IV (severe limitation). The percentage of patients with improvement in WHO-FC from baseline to 24 weeks was greater in the sotatercept group (29.4%) compared to placebo (13.8%).[7] By end of Week 24, a smaller percentage of patients in the sotatercept arm progressed to WHO-FC IV as compared to placebo. See Supplement Table D7 for additional results on functional status.

Mortality and Clinical Worsening

Patients in the STELLAR trial were assessed on a composite endpoint of time to first occurrence of death or nonfatal clinical worsening event over a median follow-up of approximately 8 months. Clinical worsening events were adjudicated by an independent and blinded review committee and are listed in Table 3.3.

The composite endpoint of time to first clinical worsening event or death was improved with sotatercept compared to placebo. By end of trial follow-up, there was an 84% reduction in clinical worsening or death with sotatercept (HR 0.16; 95% CI 0.08-0.35).[7] This advantage in event-free survival was seen as early as 10 weeks in the Kaplan-Meier curves and was maintained throughout follow-up. Worsening of PAH, defined by both a worsened WHO-FC and a decrease in 6MWD by ≥15%, was the most frequent nonfatal clinical worsening event, occurring in 2.5% of sotatercept patients versus 9.4% of placebo patients.

Deaths occurred in 2 patients (1.2%) in the sotatercept group and 7 patients (4.4%) in the placebo group. However, the STELLAR trial was not statistically powered to assess the effects of sotatercept on mortality. Additionally, the trial did not use formal statistical comparisons between the two arms to assess mortality as a standalone measure separate from its inclusion in the composite endpoint. Therefore, no conclusions can be drawn about the effects of sotatercept on mortality from this trial. A list of ongoing trials evaluating sotatercept in patients with PAH are listed in

Supplement Table D10. These trials are anticipated to provide evidence on sotatercept's impact on overall survival.

Table 3.3. Mortality and Clinical Worsening Outcomes of Sotatercept[7]

STELLAR			
Arm		**Sotatercept**	**Placebo**
N		**163**	**160**
Timepoint: At Data-Cut-Off*			
Patients who died or had ≥1 clinical worsening event, n (%)		9 (5.5)	42 (26.2)
Time to first occurrence of death or nonfatal clinical worsening event, Hazard ratio (95% CI)		0.16 (95% CI 0.08-0.35, P<0.001)	
First occurrence of death or nonfatal clinical worsening event, n (%)	**Death as first event**	2 (1.2)	6 (3.8)
	Worsening-related listing for lung or heart–lung transplantation	1 (0.6)	1 (0.6)
	Initiation of rescue therapy or increase in dose of infusion prostacyclin by ≥10%	2 (1.2)	17 (10.6)
	Atrial septostomy	0	0
	PAH–related hospitalization for ≥24 hr	0	7 (4.4)
	Worsening of PAH	4 (2.5)	15 (9.4)

CI: confidence interval, n: number, N: total number, PAH: pulmonary arterial hypertension

*Outcomes were measured beyond week 24 through the data cut-off date of August 26, 2022.

†Worsening of PAH was defined by both of the following outcomes occurring at any time: Worsened WHO-FC and decrease in 6-minute walk distance by ≥ 15% (confirmed by two 6-minute walk tests ≥ 4 hours but no more than 1 week apart), as compared to their baseline values.

Quality of Life

Quality of life was assessed using the PAH-SYMPACT questionnaire, a PAH-specific patient-reported outcome measure (Supplement Table D7). The questionnaire has three domains: Physical Impacts, Cardiopulmonary Symptoms, and Cognitive/Emotional Impacts. Sotatercept improved patient-reported physical impacts and cardiopulmonary symptoms compared to placebo, suggesting benefits in disease-specific quality of life.[7] No difference was seen for cognitive/emotional impacts. The minimal clinically important differences for these domains have not yet been determined. Moreover, a high proportion (over 40%) of study participants had missing values for the PAH-SYMPACT questionnaire. As such, there is uncertainty around the clinical relevance and statistical validity of the improvements observed in this measure of quality of life.

Two other quality of life measures were administered to patients in the Phase II trial of sotatercept, the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) and Short Form Survey (SF-36). There was no statistically significant difference between the combined sotatercept arm (0.3 and 0.7mg/kg) and placebo in either measurement.

Durability of Treatment Effect

Among patients continuing sotatercept in the PULSAR open-label extension trial, improvements in pulmonary vascular resistance, 6MWD, and NT-proBNP were maintained over 18 to 24 months.[21] There was a statistically significant difference in the numeric WHO-FC from end of placebo-controlled treatment period to months 18–24, suggesting that there may be a continued improvement in functional status beyond 24 weeks of treatment. The percentage of sotatercept patients achieving WHO-FC I (no limitation to ordinary physical activity) increased from 7.5% at the end of the 24-week PULSAR trial to 20.6% by the end of the open-label extension follow-up.

In the SOTERIA open-label extension study, patients who completed previous sotatercept trials such as PULSAR and STELLAR are being followed for up to seven years. Interim one-year follow-up data suggested that there may be maintenance of benefit on the 6MWD, NT-proBNP, and WHO-FC compared with the study baseline (Table 3.4), although there was large variance around the mean for the 6MWD and NT-proBNP outcomes.[22] Very few patients (1.7%) experienced at least one clinical worsening event, including death, listing for transplant, PAH-related hospitalization, or deterioration in 6MWD and WHO-FC. Furthermore, while a few patients on prostacyclin therapy (10.7%) were able to decrease their dose or stop the prostacyclin, others (7.0%) required additional PAH therapy. For those on any other PAH therapies at baseline, 5.2% of patients had a decrease in dose, 4.7% required an increase in dose, and 9.4% of patients required additional PAH therapy.

Table 3.4. Long-Term Maintenance of Efficacy in SOTERIA

SOTERIA		
Efficacy Outcomes		
Timepoint	**24 Weeks from SOTERIA Baseline**	**1 Year from SOTERIA Baseline**
Change from baseline in 6-Minute walk distance, mean (SD), m	20.2 (66.5)*	10.9 (73.6)†
Change from baseline in NT-proBNP, mean (SD), pg/mL	-374.9 (1479.4)‡	-227.2 (1580.1)§
Improvement or maintenance of WHO FC II from baseline, n/N (%)	287/372 (77.2)	100/131 (76.3)
French low-risk score, n/N (%)#	113/375 (30.1)	49/131 (37.4)
Changes in background PAH therapy		
On any prostacyclin (N=272)¤		
Prostacyclin dose decreased, n (%)	29 (10.7)	
Needed additional PAH therapy, n (%)	19 (7.0)	
On infusion prostacyclin (IV/SC) (N=154)		
Prostacyclin dose decreased, n (%)	22 (14.3)	
Prostacyclin dose increased by ≥10%, n (%)	9 (5.8)	
Needed additional PAH therapy, n (%)	7 (4.5)	
On any other PAH therapy (N=406)		
Other PAH therapy dose decreased, n (%)	21 (5.2)	
Other PAH therapy dose increased, n (%)	19 (4.7)	
Needed additional PAH therapy, n (%)	38 (9.4)	

IV: intravenous, m: meter, mL: milliliter, n: number, N: total number, NT-proBNP: N-terminal prohormone of brain natriuretic peptide, PAH: pulmonary arterial hypertension, pg: picogram, SC: subcutaneous, SD: standard deviation, WHO-FC: World Health Organization functional class

*N=266.

†N=118.

‡N=318.

§N=98.

#The French low-risk score was defined by meeting the following three criteria for low risk: WHO-FC I or II, 6-minute walk distance of >440 m, and NT-proBNP level of <300 pg/mL.

¤As of data cutoff, April 20, 2023, 8 participants have discontinued a prostacyclin during SOTERIA.

Other Outcomes

Treatment with sotatercept led to significant improvements in pulmonary vascular resistance (PVR) and levels of NT-proBNP, which are important measures of disease severity and prognosis in PAH, compared to placebo. The Hodges-Lehmann estimate for median difference showed a greater reduction in PVR with sotatercept than placebo (-234.6 dyn·sec·cm-5; 95% CI -288.4 to -180.8). Multicomponent improvement was a key secondary endpoint assessing treatment effects on 6MWD, NT-proBNP, and WHO-FC together. At 24 weeks, 63/162 (38.9%) sotatercept patients met

all three criteria for multicomponent improvement, compared to only 16/159 (10.1%) placebo patients.[7]

There were six exploratory hemodynamic endpoints that were evaluated by right heart catheterization at week 24 in the intention-to-treat population. Sotatercept treatment showed improvement compared to placebo in three of the six measures: change in pulmonary artery pressure, right atrial pressure, and pulmonary arterial wedge pressure. There was no difference from baseline overall in cardiac output, cardiac index, and mixed venous oxygen saturation (See Supplement Table D7).

Harms

Table 3.5 provides an overview of the safety profile of sotatercept during 24 weeks of placebo-controlled treatment in the STELLAR trial. Treatment with sotatercept did not increase the risk of serious or severe adverse events and resulted in a lower rate of discontinuation related to treatment compared with placebo. Sotatercept was well tolerated at a dose 0.7 mg/kg for a majority of trial participants; 89% of participants on active treatment had no dose delays and no dose reductions.[7] The drug's tolerability was also demonstrated by the high proportion of patients (90.5%) in the Phase II PULSAR trial who continued sotatercept treatment (0.3 or 0.7mg/kg) beyond the trial's 24-week period and into the open-label extension.

Patients in the PULSAR open-label extension experienced a new safety signal, telangiectasia[21], that was subsequently treated as an adverse event of special interest in the Phase III STELLAR trial. Its incidence was greater among participants receiving sotatercept than placebo. However, no case of telangiectasia was deemed to be serious or severe.

Bleeding events, mainly epistaxis, and dizziness were frequent and more commonly observed in patients treated with sotatercept versus placebo. See Supplement Table D9 for more detailed safety information. There were few deaths in either group, but more in the placebo group than in the sotatercept group (1.2% for sotatercept vs. 4.4% in the placebo group).[7] None of the deaths were judged to be due to the study drug.

Increased levels of hemoglobin, including cases of polycythemia, were more frequent with sotatercept treatment. However, these increases in hemoglobin did not lead to any treatment discontinuations and were manageable with alterations to the timing and dosage of the drug.

In the interim analysis of the SOTERIA open-label extension study, patients had a median exposure of 462 days to sotatercept.[22] Very few patients suffered serious treatment-related adverse events related to sotatercept treatment (0.7%) or discontinued treatment (1.2%). Likewise, the incidence of serious telangiectasia and thrombocytopenia events was low. There were four deaths due to adverse events reported in the trial; details of those deaths have not yet been reported by the manufacturer.

Table 3.5. Harms in Key Trial of Sotatercept[7]

STELLAR				
Arms		Sotatercept	Placebo	Between-Treatment Group Comparison Point Estimate (95% CI)
N		163	160	
Timepoint: Week 24				
AE, n (%)	Any	138 (84.7)	140 (87.5)	−2.8 (−10.5 to 4.8)
	Related to sotatercept or placebo	67 (41.1)	41 (25.6)	**15.5 (5.2 to 25.5)**
	Leading to discontinuation	3 (1.8)*	10 (6.2)	−4.4 (−9.5 to −0.1)
	Leading to withdrawal from trial	3 (1.8)	5 (3.1)	−1.3 (−5.5 to 2.5)
	Leading to death	0	6 (3.8)	**−3.8 (−7.9 to −1.4)**
Severe AE, n (%)		13 (8.0)	21 (13.1)	−5.1 (−12.2 to 1.6)
Serious AE, n (%)	Any	23 (14.1)	36 (22.5)	−8.4 (−16.9 to 0.1)
	Related to sotatercept or placebo	2 (1.2)	2 (1.2)	−0.0 (NR)
	Leading to discontinuation	1 (0.6)*	8 (5.0)	**−4.4 (−9.0 to −1.0)**
	Leading to withdrawal from trial	1 (0.6)	5 (3.1)	−2.5 (−6.6 to 0.6)
Death, n (%)†		2 (1.2)	7 (4.4)	NR
AESI – Telangiectasia, n (%)		17 (10.4)	5 (3.1)	**7.3 (2.0 to 13.3)**
AEs of interest, n (%)	Increased hemoglobin level: increased hematocrit or increased red-cell count	9 (5.5)	0	**5.5 (2.9 to 10.2)**
	Thrombocytopenia	10 (6.1)	4 (2.5)	3.6 (−0.9 to 8.8)
	Bleeding events	35 (21.5)	20 (12.5)	**9.0 (0.8 to 17.2)**
	Increased blood pressure	6 (3.7)	1 (0.6)	3.1 (−0.2 to 7.3)
AEs reported in ≥10% of patients in either group	Any	138 (84.7)	140 (87.5)	−2.8 (−10.5 to 4.8)
	Headache	33 (20.2)	24 (15.0)	5.2 (−3.1 to 13.6)
	Covid-19	24 (14.7)	21 (13.1)	1.6 (−6.1 to 9.3)
	Nausea	16 (9.8)	18 (11.2)	−1.4 (−8.4 to 5.4)
	Diarrhea	20 (12.3)	12 (7.5)	4.8 (−1.8 to 11.6)
	Fatigue	17 (10.4)	12 (7.5)	2.9 (−3.5 to 9.5)
	Epistaxis	20 (12.3)	3 (1.9)	**10.4 (5.2 to 16.6)**
	Telangiectasia	17 (10.4)	5 (3.1)	**7.3 (2.0 to 13.3)**
	Dizziness	17 (10.4)	3 (1.9)	**8.6 (3.6 to 14.4)**

AE: adverse event, AESI: adverse event of special interest, CI: confidence interval, n: number, N: total number, NR: not reported

*No discontinuation due to thrombocytopenia or increased hemoglobin levels.

†Outcome was measured beyond week 24 through the data cut-off date of August 26, 2022.

Subgroup Analyses and Heterogeneity

In the STELLAR trial, researchers explored potential subgroup treatment differences between sotatercept and placebo on improvements in 6MWD, PVR, and NT-proBNP at 24 weeks across seven subgroups.[7] The trial had six pre-specified patient subgroups based on baseline PAH medication use, baseline WHO-FC, baseline PVR, age, sex, and one post-hoc subgroup of geographic region. All analyses were conducted using the intention-to-treat population.

For each outcome and subgroup, the treatment effect was quantified using the Hodges-Lehmann location shift, which estimates the difference between the median values of sotatercept and placebo based on average imputed data. Results were reported as point estimates of the median difference with 95% confidence intervals (See Supplement Table D8).

Broadly, these findings were typically consistent with the overall study group for each of the three outcomes (6MWD, PVR, NT-proBNP).[7] In subgroups where the median difference between treatment groups was not statistically significant, the sample sizes were small (e.g., there were fewer than 15 participants in each trial arm who were on background monotherapy, were from the Asia/Pacific region, or had PAH associated with congenital heart disease).

However, definitive conclusions about subgroup treatment effects cannot be drawn from these exploratory analyses. Specifically, no between-group interaction p-values were reported, there were a large number of subgroups analyzed, and no adjustment was made for multiplicity. As such, authors of the STELLAR trial did not claim evidence of subgroup treatment effects.

Uncertainty and Controversies

Several populations were underrepresented in the STELLAR trial. Patients with connective tissue disease-associated PAH are an important population both with regard to efficacy and safety, since prior treatments for PAH have been shown to be less effective in this group.[27] Only around 15% of patients in STELLAR had connective tissue disease-associated PAH compared with up to 25-35% in registry data.[9] Additionally, bleeding events are of particular concern for this population, since patients with connective tissue disorders, particularly systemic sclerosis, commonly develop telangiectasias and bleeding as part of their disease.[28] More data are also needed in patients with congenital heart disease associated PAH, as some patients can have higher hemoglobin levels and thus may be more susceptible to adverse events from a medication that could further increase hemoglobin levels. Finally, drug or toxin-induced PAH is an increasingly important subpopulation, and less than 5% (11 patients) of the participants in STELLAR had this as the etiology of their PAH.

Effects of therapy on mortality are important in PAH and current data are insufficient to evaluate these effects for sotatercept. Additionally, long-term persistence of sotatercept's effect on clinical outcomes has yet to be established. Long-term data from the PULSAR and SOTERIA open-label

extension trials show promising results; however, we await additional long-term follow-up data, as there have been treatments that have shown promise in treating symptoms of disease but ultimately do not affect mortality or even cause harm (e.g., digoxin, rofecoxib).

Sotatercept's role in therapy has yet to be determined. Although it has the potential to be disease-modifying through modulation of the vascular remodeling process, clinical experts cautioned that the available data are not yet mature enough to conclusively determine its disease-modifying effects and whether sotatercept can be discontinued after a period of treatment. Additionally, patients enrolled in the trial were WHO-FC II or III, so it is unknown whether it has the same effects in the sicker population of WHO-FC IV (trials are ongoing in this population). Finally, patients in the STELLAR trial had longstanding disease and were on stable treatment regimens, so it is not clear whether sotatercept may have similar effects in newly diagnosed or less stable patients with PAH. Ongoing trials, as well as real world experience, will help answer these questions.

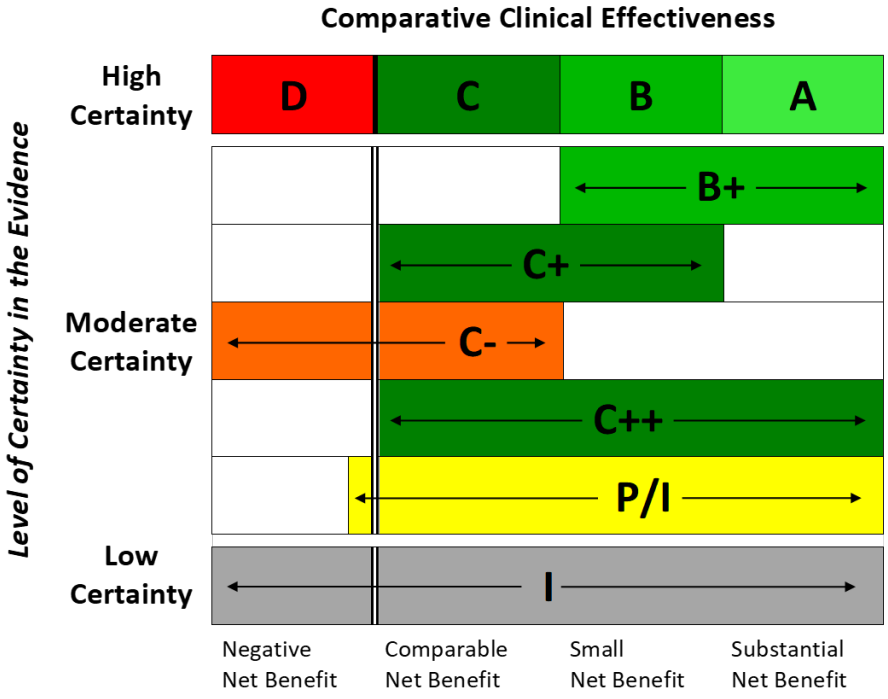
Sotatercept did not appear to significantly impact overall quality of life as measured by the PAH-SYMPACT score, although both the Physical Impacts and Cardiopulmonary Symptoms scores were lower in the sotatercept group. This may be a reflection of the limited measurement of some relevant domains such as activities of daily living and social functioning and/or a lack of responsiveness of the scale,[29] or the overall difficulty of measuring change in quality of life in this population. Nevertheless, patient-important outcomes are crucial outcomes and should continue to be incorporated into clinical trials.

Finally, recruiting a clinical trial population that reflects the racial and ethnic diversity of the patients with the condition is important for generalizability of the results. Black and Asian patients were underrepresented in the STELLAR trial compared with the general population of PAH patients; the number of Hispanic patients was not reported. Thus, any differences in efficacy and safety in these populations is currently unknown.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided here.

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable" *- High certainty of a comparable net health benefit*
D= "Negative" *- High certainty of an inferior net health benefit*
B+= "Incremental or Better" *– Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" *- Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" *– Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" *– Any situation in which the level of certainty in the evidence is low*

PAH can cause severe impairment in function and quality of life, and it ultimately shortens lifespan. Current treatments for PAH are effective, but are often burdensome, particularly for patients on infusion therapy. Additionally, none of the treatments are disease-modifying, and all come with substantial side effects, which further impact patient quality of life.

Based on the currently available data, treatment with sotatercept added to background therapy can improve clinical outcomes for patients with PAH, with relatively few harms. Additionally, the subcutaneous delivery system is less burdensome than many other PAH treatments, particularly

inhaled and intravenous prostanoids. However, uncertainty remains about sotatercept's efficacy in sicker populations and in those with connective tissue disease, and about the durability of effect. In the absence of longer-term data, we necessarily have uncertainties about sotatercept's effects on mortality and as-yet-undetected adverse effects.[30] Therefore, we have moderate certainty of a small to substantial net health benefit, with a high certainty of at least a small net health benefit, corresponding to an ICER Evidence Rating of **B+**.

Table 3.6. Evidence Ratings

Treatment	Comparator	Evidence Rating
Adult patients with WHO-FC II or III PAH		
Sotatercept	Stable background therapy	B+

PAH: pulmonary arterial hypertension, WHO-FC: World Health Organization functional class

4. Long-Term Cost Effectiveness

4.1. Methods Overview

In this analysis, we estimate the conventional cost-effectiveness of sotatercept added to background therapy as compared to background therapy alone. The base-case analysis took a health care sector perspective (i.e., focused on direct medical care costs only) and a lifetime time horizon. Productivity impacts and other indirect costs and effects were considered in a scenario analysis using a modified societal perspective. Costs and outcomes were discounted at 3% per year.

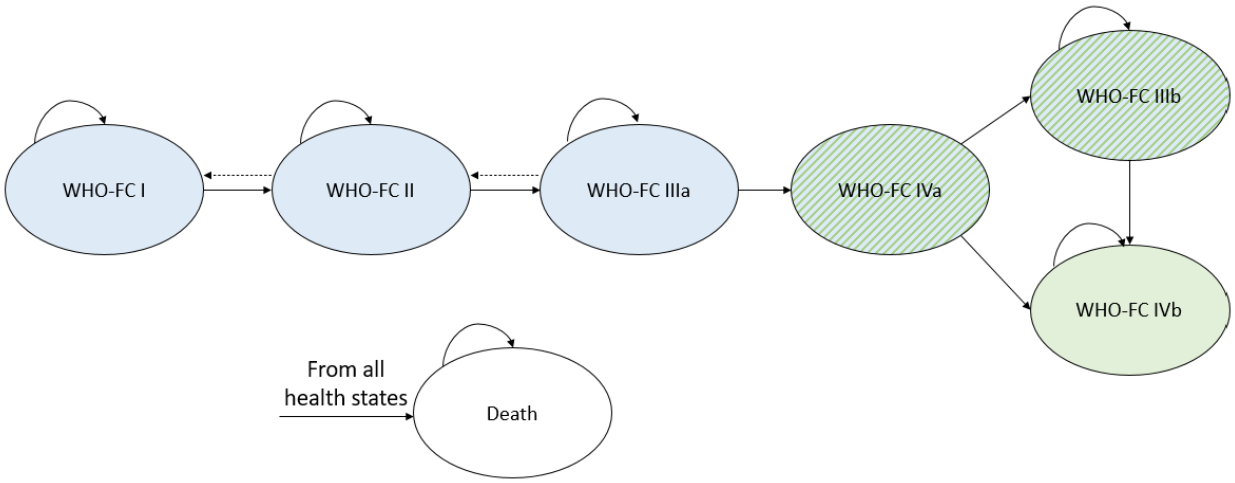
We developed a *de novo* decision analytic model for this evaluation, informed by key clinical trials and prior relevant economic models.[31-33] The model focused on an intention-to-treat analysis, with a hypothetical cohort of patients with PAH being treated with either sotatercept added on to background therapy or background therapy alone entering the model. The starting population consisted of adults with PAH in WHO-FC II or WHO-FC III who were on background therapy. Model cycle length was 12 weeks, based on the frequency at which the clinical data are assessed and on prior published economic models.

The model consisted of health states defined by WHO-FC and death (Figure 4.1). The cohort started in either WHO-FC II or WHO-FC III. The health of the hypothetical cohort could maintain (i.e., stay in the same functional class) or deteriorate (i.e., worsen in functional class) over the entire time horizon. For the first 24 weeks of the model, the health of the hypothetical cohort could also improve (i.e., improve in functional class). For example, if an individual was in WHO-FC II during the first cycle, they could stay in WHO-FC II, improve to WHO-FC I, or worsen to WHO-FC III in the next model cycle. After 24 weeks, members of the modeled cohort could only maintain or worsen in health. For example, if an individual was in WHO-FC II after 24 weeks on treatment, they could either stay in WHO-FC II or worsen to WHO-FC III in the next model cycle. This assumption that the health of the hypothetical cohort could only improve in functional class over the first 24 weeks of the model was tested through scenario analyses.

Once members of the hypothetical cohort reached WHO-FC IV, they initiated an infused prostacyclin. Within the first 12 weeks (i.e., one model cycle) after initiating the infused prostacyclin, members of the hypothetical cohort were able to again improve in functional class (i.e., transition to the WHO-FC III health state) at a rate observed in the clinical evidence for infused prostacyclins. After the first cycle on the infused prostacyclin, patients could only maintain or worsen in functional class. 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 after starting an infused prostacyclin, they discontinued sotatercept.

Members of the modeled cohort remained in the model until death and could transition to the death health state from any of the alive health states due to all-cause or disease-related mortality.

Figure 4.1. Model Structure



WHO-FC: World Health Organization functional class

The dashed arrows represent transitions that were only allowed in the first two model cycles (e.g., first 24 weeks). The blue ovals represent health states with patients receiving sotatercept (if applicable). The blue ovals with green diagonal lines represent health states with patients on sotatercept (if applicable) and an infused prostacyclin. The green oval represents a health state with patients on an infused prostacyclin (i.e., discontinue sotatercept). WHO-FC IVa represents the initial cycle in WHO-FC IV where an infused prostacyclin is added on to treatment to see if the patient can improve back to WHO-FC III (represented by WHO-FC IIIb). If after one cycle on sotatercept and an infused prostacyclin the patient does not improve to WHO-FC IIIb, that patient discontinues sotatercept treatment and stays in WHO-FC IV (represented by WHO-FC IVb).

4.2. Key Model Assumptions and Inputs

Table 4.1 presents several key model assumptions. A longer list of model assumptions can be found in the Supplement.

Table 4.1. Key Model Assumptions

Assumption	Rationale
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.	Given the short duration of the majority of randomized controlled trials in PAH, evidence of further functional class improvement beyond a few months is lacking. Existing models in PAH primarily allow functional class improvement for only 12 weeks (i.e., the first model cycle). However, given evidence exists for sotatercept up to 24 weeks, we allowed for the potential for improvement in functional class for the first 24 weeks (i.e., the first and second model cycle). We tested this assumption through scenario analyses.
Members of the modeled cohort could only transition to adjacent functional classes between model cycles.	The 12-week cycle length was selected as it should be short enough to detect one increment changes in functional class. This is supported by transition probability evidence and other published economic models.
Sotatercept had no independent effect on functional class improvement after a patient progressed to WHO-FC 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.	Evidence on sotatercept's independent effect on improving from WHO-FC IV to WHO-FC III does not exist.
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.	Given members of the modeled cohort could not worsen from WHO-FC IV, sotatercept would only have an impact on cost. This structural assumption is supported by other published economic models. In clinical practice, treatment discontinuation with sotatercept in WHO-FC IV may be unlikely, and thus we modeled treatment continuation through WHO-FC IV in a scenario analysis.
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.	Trial evidence exists for approximately two model cycles after starting treatment with sotatercept. Clinical experts suggested that adverse events leading to discontinuation likely occur relatively soon after treatment initiation and thus it is reasonable to assume they occur over the trial follow-up period.

Table 4.2 presents several key model inputs. An exhaustive list of model inputs and their respective sources can be found in the Supplement.

Table 4.2. Key Model Inputs

Sotatercept-Specific Clinical Inputs		
Parameter	**Input**	**Source**
Effect on functional class worsening	RD1	Manufacturer data on file[35]
Adverse-event related discontinuation	1.8%	STELLAR[7]
Quality of Life Inputs		
Parameter	**Input**	**Source**
Utility, WHO-FC I	0.729	Keogh et al., 2007[36], Dufour et al., 2017[37], & Alsumali et al., 2021[38]
Utility, WHO-FC II	0.668	
Utility, WHO-FC III	0.598	
Utility, WHO-FC IV	0.515	
Cost Inputs		
Parameter	**Input**	**Source**
Annual cost of sotatercept	$400,000	Placeholder[39]
Annual cost of double therapy	$74,664	RED BOOK[40]
Annual cost of third therapy (oral or inhaled)	$169,004	RED BOOK[40] & SSR Health[41]
Annual cost of third therapy (infused)	$55,783	RED BOOK[40] & SSR Health[41]

WHO-FC: World Health Organization functional class

4.3. Results

Base-Case Results

Treatment with sotatercept results in greater time without symptoms at rest, greater QALYs, greater life years, and greater evLYs. Using a placeholder annual cost of $400,000 per year, treatment with sotatercept results in substantially more costs, due not only to the additional intervention costs but also additional non-intervention costs such as other pharmaceutical and medical costs. Table 4.3 reports the base-case model inputs for each arm of the model.

Table 4.3. Base-Case Model Outcomes for Sotatercept plus Background Therapy as Compared to Background Therapy Alone

Treatment	Intervention Cost	Non-Intervention Costs	Total Costs	Years without Symptoms at Rest†	QALYs	Life Years	evLYs
Sotatercept plus Background Therapy	$2,002,000*	$1,011,000	$3,013,000	5.02	3.41	5.46	3.69
Background Therapy Alone	$0	$880,000	$880,000	2.98	2.51	4.27	2.51

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 reports the base-case incremental cost-effectiveness ratios assuming a placeholder annual cost for sotatercept of $400,000 per year. At the assumed placeholder price for sotatercept, the incremental cost-effectiveness ratio for sotatercept plus background therapy as compared to background therapy alone is $1,805,000 per evLY gained and $2,380,000 per QALY gained.

Table 4.4. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Cost per Additional Year without Symptoms at Rest	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained
Sotatercept* plus Background Therapy	$1,046,000	$2,380,000	$1,792,000	$1,805,000

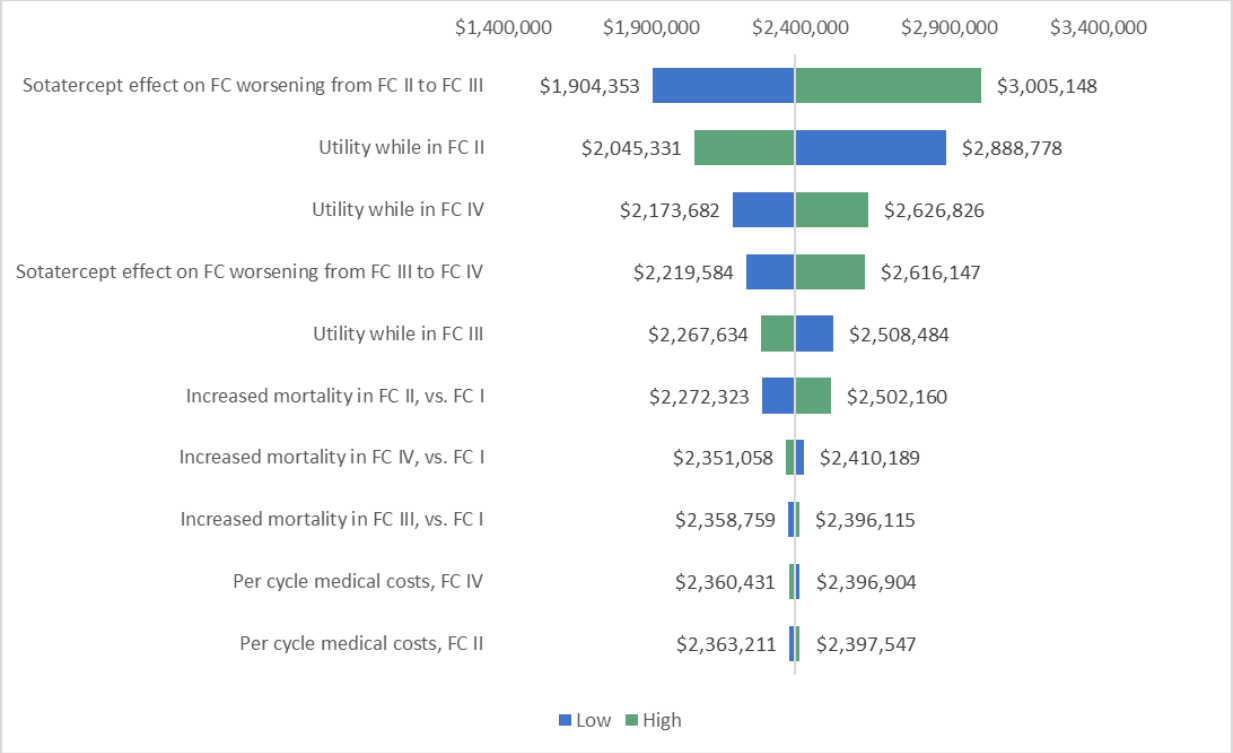
evLY: equal value life year, QALY: quality-adjusted life year

*Assuming a placeholder price of $400,000 per year.

Sensitivity Analyses

Figure 4.2 reports the inputs with the most influence on the incremental cost-effectiveness ratio. Notably, sotatercept's effect on functional class improvement was not able to be included in the tornado diagram as a single modifiable input because directly observed transition probabilities from the randomized controlled trial were used over the first 24 weeks of the model to capture functional class improvement.

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.

Tables 4.5 and 4.6 present the probability of sotatercept being cost-effective at common thresholds of $50,000, $100,000, $150,000, and $200,000 per QALY and evLY gained, respectively. At the assumed placeholder price for sotatercept, none of the 1,000 iterations within the probabilistic sensitivity analysis resulted in incremental cost-effectiveness ratios beneath these commonly used thresholds.

Table 4.5. Probabilistic Sensitivity Analysis Cost per QALY Gained Results: Sotatercept plus Background Therapy versus Background Therapy Alone

	Cost Effective at $50,000 per QALY Gained	Cost Effective at $100,000 per QALY Gained	Cost Effective at $150,000 per QALY Gained	Cost Effective at $200,000 per QALY Gained
Sotatercept* plus Background Therapy	0%	0%	0%	0%

*Assuming a placeholder price of $400,000 per year.

Table 4.6. Probabilistic Sensitivity Analysis Cost Per evLY Gained Results: Sotatercept plus Background Therapy versus Background Therapy Alone

	Cost Effective at $50,000 per evLY Gained	Cost Effective at $100,000 per evLY Gained	Cost Effective at $150,000 per evLY Gained	Cost Effective at $200,000 per evLY Gained
Sotatercept* plus Background Therapy	0%	0%	0%	0%

*Assuming a placeholder price of $400,000 per year.

Additional sensitivity analysis result tables can be found in the Supplement.

Scenario Analyses

Table 4.7 reports the incremental cost per evLY gained for the base-case and three scenario analyses assuming a placeholder price of $400,000 per year for sotatercept. Cost-effectiveness improved in the modified societal perspective scenario analysis, in the scenario analysis that assumed that sotatercept halted the functional class the patient was in at 24 weeks, and in the scenario analysis that allowed for functional class improvement over the entire lifetime. Cost-effectiveness worsened in the scenario analysis that assumed treatment would only be discontinued at death and thus would be continued through WHO-FC IV.

Table 4.7. Scenario Analysis Results

Treatment	Base-Case Results ($/evLY)	Modified Societal Perspective ($/evLY)	Treatment Discontinuation at Death Only ($/evLY)	Halt WHO-FC at 24 Weeks ($/evLY)	WHO-FC Improvement Over Lifetime ($/evLY)
Sotatercept*	$1,805,000	$1,761,000	$1,930,000	$1,199,000	$1,190,000

evLY: equal-value life year, WHO-FC: World Health Organization functional class

*Assuming a placeholder price of $400,000 per year.

Additional scenario analysis findings can be found in the Supplement.

Threshold Analyses

Tables 4.8 and 4.9 report the threshold prices at $50,000, $100,000, $150,000, and $200,000 per QALY and evLY gained, respectively. Due to sotatercept being added on to background therapy drugs that are costly, there was no positive price that could meet thresholds of $50,000 or $100,000 per QALY or evLY gained.

Table 4.8. QALY-Based Threshold Analysis Results

	Annual Price to Achieve $50,000 per QALY Gained	Annual Price to Achieve $100,000 per QALY Gained	Annual Price to Achieve $150,000 per QALY Gained	Annual Price to Achieve $200,000 per QALY Gained
Sotatercept	No positive price	No positive price	$700	$9,700

QALY: quality-adjusted life year

Table 4.9. evLY-Based Threshold Analysis Results

	Annual Price to Achieve $50,000 per evLY Gained	Annual Price to Achieve $100,000 per evLY Gained	Annual Price to Achieve $150,000 per evLY Gained	Annual Price to Achieve $200,000 per evLY Gained
Sotatercept	No positive price	No positive price	$9,300	$21,100

evLY: equal-value life year

In alignment with ICER's reference case for when no positive price can be found cost-effective, we also present the QALY-based and evLY-based threshold analysis results excluding all non-intervention costs (e.g., background therapy costs, health state medical costs) in Tables 4.10 and 4.11.

Table 4.10. QALY-Based Threshold Analysis Results, Excluding Non-Intervention Costs

	Annual Price to Achieve $50,000 per QALY Gained	Annual Price to Achieve $100,000 per QALY Gained	Annual Price to Achieve $150,000 per QALY Gained	Annual Price to Achieve $200,000 per QALY Gained
Sotatercept	$9,800	$18,700	$27,700	$36,600

QALY: quality-adjusted life year

Table 4.11. evLY-Based Threshold Analysis Results, Excluding Non-Intervention Costs

	Annual Price to Achieve $50,000 per evLY Gained	Annual Price to Achieve $100,000 per evLY Gained	Annual Price to Achieve $150,000 per evLY Gained	Annual Price to Achieve $200,000 per evLY Gained
Sotatercept	$12,600	$24,400	$36,200	$48,000

evLY: equal-value life year

Model Validation

We used several approaches to validate the model. First, we provided the preliminary model structure, methods and assumptions to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model, as needed. Second, we varied model input parameters to evaluate face validity of changes in results and performed model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we also shared the model with the manufacturer for external verification around the time of publishing this draft report. Finally, we compared results to

other cost-effectiveness models in this therapy area. The outputs from the model were also validated against the trial data and relevant observational data.

Uncertainty and Controversies

The long-term conventional cost-effectiveness of sotatercept is largely dependent on the long-term effect of sotatercept on improving functional class and slowing the worsening in functional class; however, controlled trial evidence for sotatercept is limited to 24 weeks. Long-term data are necessary to reduce the uncertainty in sotatercept's long-term effect on improving functional class and slowing the worsening in functional class. Scenario analyses were conducted to test the uncertainty around the long-term effectiveness assumptions. Even under the optimistic assumptions taken in these scenario analyses (e.g., sotatercept could entirely halt disease progression at 24 weeks or that sotatercept could be associated with improvements in WHO-FC over the entire lifetime), if priced at the placeholder price of $400,000 per year, sotatercept would far exceed typical thresholds.

Additionally, a published model with Merck co-authors predicted the long-term impact of sotatercept on morbidity and mortality and made the optimistic assumption that sotatercept has an independent effect on mortality (hazard ratio for all-cause mortality of 0.25).[42] Our model does not assume an independent effect of sotatercept on mortality at this time due to the small sample, short timeframe, double counting with mortality benefits downstream of functional class improvement, and the confidence interval on the hazard ratio for all-cause mortality was not statistically significant.

Our analyses suggested that sotatercept was associated with gains in life years, quality-adjusted life years, and equal-value life years. Patients treated with sotatercept added on to background therapy spent more time in WHO-FC I, WHO-FC II, and WHO-FC III than patients treated with background therapy alone. Each of these functional class health states are still associated with large increases in mortality risk and large reductions in quality of life.

Sotatercept is added on to background therapy, which consists of numerous costly medications. Although our analyses suggested that sotatercept would reduce some use of infused prostacyclins by way of less time spent in WHO-FC IV among sotatercept-treated patients, and thus would generate some cost offsets related to infused prostacyclins, the background therapies used in WHO-FC I, WHO-FC II, and WHO-FC III are also costly. We presented threshold analyses excluding all non-intervention costs to isolate the effects and costs of sotatercept alone.

4.4 Summary and Comment

Our analyses suggest that sotatercept produces improved clinical outcomes. At a placeholder price of $400,000 per year, the incremental cost-effectiveness ratios far exceed commonly used

thresholds. The conventional cost-effectiveness findings are primarily driven by the effectiveness of sotatercept on improving functional class and on slowing the worsening in functional class. Even under optimistic assumptions around sotatercept's effectiveness, sotatercept would far exceed commonly used thresholds at an annual price of $400,000 per year. Excluding all non-intervention costs, sotatercept would meet commonly used thresholds at an annual price of $18,700 to $36,200.

5. Contextual Considerations and Potential Other Benefits

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention(s) in this review.

Table 5.1. Contextual Considerations

Contextual Consideration	Relevant Information
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability	PAH has a substantial short-term risk of death with a median survival of around 5 years even with existing therapies. Patients are at high risk of becoming disabled even with current treatments.
Magnitude of the lifetime impact on individual patients of the condition being treated	Many patients develop PAH at a young age and, as such, experience the large burdens of PAH and its therapies for a substantial portion of their lives.
Other (as relevant)	N/A

Table 5.2. Potential Other Benefits or Disadvantages

Potential Other Benefit or Disadvantage	Relevant Information
Patients' ability to achieve major life goals related to education, work, or family life	Persons with PAH often need to leave the workforce due to their symptoms from PAH and/or side effects from their medications. A medication that prevents or slows disease progression and has minimal side effects may have a significant impact on patients' ability to achieve major life goals.
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	Persons with PAH describe a large impact on caregivers, as symptoms prevent them from performing activities of daily living and independent activities of daily living. Additionally, partners may need to alter their work schedules to care for patients and may be limited in the ability to pursue work opportunities due to the need for health insurance. A medication that allows for greater functioning would likely improve caregivers' ability to achieve major life goals.
Patients' ability to manage and sustain treatment given the complexity of regimen	Oral, inhaled, and infused treatments for PAH are highly burdensome, including the need for administration several times per day, significant side effects, and in the case of infused therapy, the need to manage the logistics of a 24-hour infusion. Sotatercept is a subcutaneous injection given once every 3 weeks, and may decrease regimen complexity, particularly if it prevents or delays the need for infused therapy.
Society's goal of reducing health inequities	Current therapies, particularly infused agents, may not be feasible or accessible for PAH patients due to age, limited social support, or socioeconomic status. This may contribute to disparities in outcomes for PAH patients. A treatment with a simpler regimen that is well-tolerated may decrease inequities in access and outcomes. We did not calculate the Health Improvement Distribution Index as the racial distribution of PAH in registry data is largely similar to the overall US population.[9]
Other (as relevant)	N/A

6. Health Benefit Price Benchmarks

Health Benefit Price Benchmarks (HBPBs) for the annual cost of treatment with sotatercept are presented in Table 6.1. The HBPB for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY or per evLY gained. Table 6.1 presents threshold prices for sotatercept from the health care sector perspective (with non-intervention costs excluded from the analysis). The HBPB for sotatercept is an annual price of $18,700 to $36,200.

Table 6.1. Annual Cost-Effectiveness Health Benefit Price Benchmarks for Sotatercept with Health State and Comparator Drug Costs Excluded from the Analysis (Health Care Sector Perspective)

	Annual Price to Achieve a Threshold of $100,000	Annual Price to Achieve a Threshold of $150,000
Per QALY Gained	$18,700	$27,700
Per evLY Gained	$24,400	$36,200

evLY: equal-value life year; QALY: quality-adjusted life year

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Results from the cost-effectiveness model (inclusive of all costs, including non-intervention costs) were used to estimate the total potential budget impact of sotatercept added to background therapy compared to background therapy alone for adult PAH patients. We used a placeholder annual price of $400,000 and threshold prices calculated with non-intervention costs excluded (at $50,000, $100,000, and $150,000 per QALY) in our estimates of the potential budget impact.

This potential budget impact analysis included the estimated number of individuals in the US who would be eligible for treatment. To estimate the size of the potential candidate populations for treatment, we used the mid-range of the estimated 50,000 to 100,000 individuals living with PAH in the US (75,000).[1] Based on PHA Registry estimates, we limited the potential eligible patient population to those with WHO-FC II and III (80.9%) and assumed that 100% of patients are on background therapy.[9] Applying these sources resulted in an estimated 60,675 eligible patients in the US. For the purposes of this analysis, we assumed that 20% of these patients would initiate treatment in each of the five years, or 12,135 patients per year.

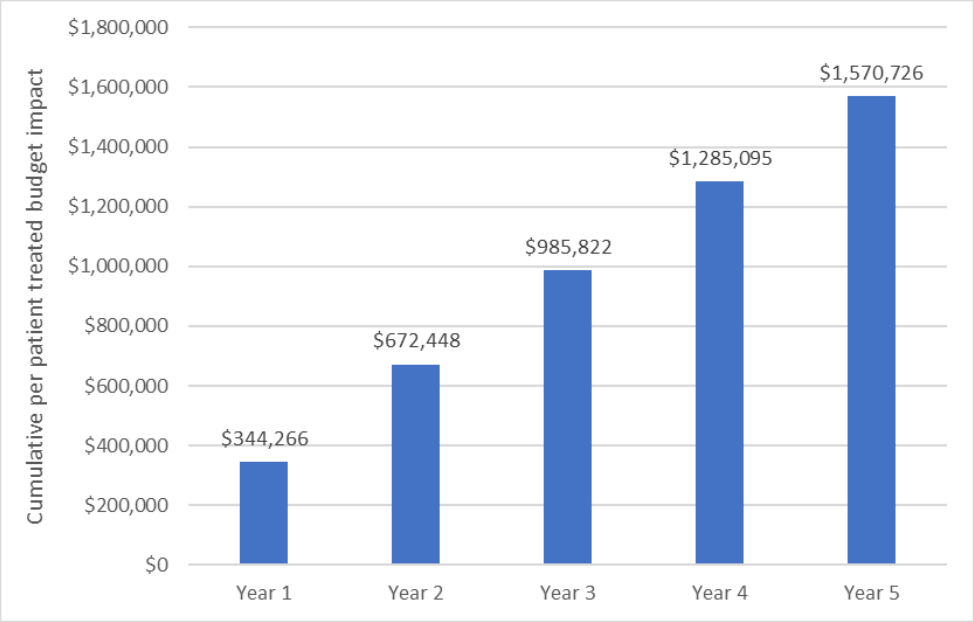
The aim of the potential budgetary impact analysis is to document the percentage of patients who could be treated at selected prices without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. The five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $777 million per year for new drugs. ICER's methods for estimating potential budget impact are described in detail in the Supplemental Section F.

7.2. Results

Results showed that at the placeholder price, 7% of patients could be treated with sotatercept without crossing the ICER potential budget impact threshold of $777 million per year. At prices to reach thresholds of $150,000, $100,000, and $50,000 per QALY, 100% of patients could be treated over five years without reaching the ICER potential budget impact threshold of $777 million per year.

Figure 7.1 illustrates the cumulative per patient potential budget impact for sotatercept added to background therapy compared to background therapy alone. At sotatercept's placeholder price, the average annual budget impact per patient was $344,000 in Year one with cumulative net annual costs increasing to $1.6 million in Year five.

Figure 7.1. Budgetary Impact of Sotatercept (using a placeholder price) in Patients with Pulmonary Arterial Hypertension



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Supplemental Material

A. Background: Supplemental Information

A1. Definitions

6 Minute Walking Distance[43]: The 6-minute walk distance (6MWD) is a measure of cardiopulmonary function, in which patients walk as far as possible for six minutes on flat ground. The 6MWD is used to assess response to exercise in individuals with chronic pulmonary and/or cardiac disease, such as PAH and chronic obstructive pulmonary disease (COPD).

Pulmonary Vascular Resistance (PVR) [44]**:** Pulmonary vascular resistance is defined as the quantitative value of resistance against blood flow by the blood vessels in the pulmonary circulation. A patient's PVR evaluates pulmonary circulation hemodynamics as well as overall health of the pulmonary vasculature.

NT-proBNP[45]**:** N-terminal pro B-type natriuretic peptide (NT-proBNP) is a prohormone produced by the heart, found usually at small levels in the bloodstream. NT-proBNP tests draw a blood sample to assess for raised levels of the protein, which may signal left ventricular dysfunction or heart failure in a patient.

WHO Functional Class: The World Health Organization Functional Class (WHO-FC) system is a scale used to characterize the severity of symptoms in a patient with pulmonary hypertension and assess impact on a patient's day-to-day functionality. The system ranges from functional class I to IV.

Table A1. WHO Functional Classification [46]

Class I	Patients with pulmonary hypertesion but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class IV	Patients with pulmonary hypertension 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. Discomfort is increased by any physical activity.

A2. Potential Cost-Saving Measures in PAH

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by therapies for PAH (e.g., need for heart/lung transplant), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of PAH beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with PAH that could be reduced, eliminated, or made more efficient. No suggestions were received.

B. Patient Perspectives: Supplemental Information

B1. Methods

As part of our review, we engaged with one patient advocacy group, seven patients with PAH, five physicians with expertise in treating PAH patients (cardiologists and pulmonologists), and two manufacturers in scoping calls. The patients were identified through the patient advocacy group and were interviewed in two groups. The patients included both men and women living with PAH, with varying stages of PAH, and on oral, inhaled, and infused therapy. One person participated in the sotatercept trial.

C. Clinical Guidelines

2022 European Society of Cardiology(ESC) and the European Respiratory Society (ERS) Guidelines for the diagnosis and treatment of pulmonary hypertension[6]

The 2022 clinical practice guidelines for pulmonary hypertension were jointly issued by the European Society of Cardiology and the European Respiratory Society. These guidelines encompass the epidemiology, screening, diagnosis, and treatment of all types of pulmonary hypertension, including PAH. Specifically for PAH, the guidelines recommend: 1) evaluation of disease severity with data derived from clinical assessment, exercise tests, biochemical markers, echocardiography, and hemodynamic evaluations; 2) a treatment goal of achieving and maintain a low-risk profile on medical therapy; 3) risk stratification into low, intermediate-low, intermediate-high and high risk based on WHO-FC, 6MWD, and B-type natriuretic peptide (BNP)/NT-proBNP. PAH therapy recommendations include: 1) physical activity and supervised rehabilitation; 2) Initial combination therapy with an endothelin receptor antagonists and a phosphodiesterase-5 inhibitor for PAH patients presenting at low or intermediate risk; 3) Initial triple-combination therapy including an intravenous/subcutaneous prostacyclin analogue and referral for consideration of lung transplantation should be considered in intermediate high or high risk of death. Treatment in special populations such as those with cardiopulmonary comorbidities, pregnancy, surgery, and specific PAH subsets (e.g., connective tissue disease, HIV, portal hypertension, congenital heart disease, etc.).

Therapy for Pulmonary Arterial Hypertension in Adults: 2019 Update of the CHEST Guideline and Expert Panel Report[47]

The American College of Chest Physicians published a Guideline and Expert Panel Report on Pharmacotherapy for PAH in 2019. The recommendations are based on a systematic review, and the committee developed recommendations and consensus-based statements using a modified Delphi technique to achieve consensus. Consensus recommendations included to evaluate the severity of disease in a systematic and consistent manner, using a combination of WHO-FC, exercise capacity, echocardiographic, laboratory and hemodynamic variables to help inform therapeutic decisions, and for patients to be evaluated at a center with expertise in treating PAH. The guidelines contained recommendations for treatment for WHO-FC I-IV, including: 1) For WHO-FC II and III, initial combination therapy with ambrisentan and tadalafil; 2) For WHO-FC III with rapid progression of disease, consider initial therapy with an infused prostanoid; 3) For WHO-FC III who have evidence of progression of disease and/or markers of poor clinical prognosis despite treatment with one or two oral agents, consider addition of inhaled or infused prostanoid. The guidelines also recommend incorporating palliative care in the management of PAH patients.

Finally, there were consensus-based statements for special situations such as pregnancy, travel, and surgery.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

The population for the review is adult patients with Pulmonary Arterial Hypertension WHO-FC II/III who are on standard of care treatment, defined as stable background therapy with agents from the following classes:

- endothelin receptor antagonists (ERA)
- phosphodiesterase 5 Inhibitors (PDE5i)
- soluble guanylate cyclase stimulators (sGC)
- prostacyclin receptor agonists
- prostacyclin analogues (prostanoids)

Data permitting, we sought to examine the evidence for subpopulations defined by:

- Age
- Sex (male, female)
- Race and Ethnicity (White, Black, Hispanic, Asian, other)
- PAH Diagnostic group (idiopathic, heritable, drug/toxin-induced, connective tissue disease, congenital heart disease with systemic to pulmonary shunt repair)
- Baseline background therapy
    - Double therapy
    - Triple therapy
- Baseline WHO-FC (II, III)
- Baseline pulmonary vascular resistance

Interventions

Our intervention of interest for this review is sotatercept (Merck & Co, Inc.) added to standard of care.

Comparators

Data permitting, we intended to compare sotatercept added to standard of care versus standard of care alone, as estimated by the placebo arm in clinical trials. We recognize that in some patients,

PAH treatment can include a third oral therapy such as an oral prostacyclin or prostacyclin receptor agonist before an infused or injectable prostacyclin is prescribed. However, based on input from clinical experts and our review of market analysis databases, these medications are variably used and thus we did not consider them to be separate comparators to sotatercept.

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Mortality
    - Improvements in exercise capacity (e.g., 6 Minute Walk Distance)
    - Health related quality of life (e.g., PAH-Symptoms and Impact questionnaire)
    - Risk of clinical worsening (e.g., French score, WHO-FC, hospitalizations, Registry to Evaluate Early and Long-Term PAH Disease Management [REVEAL] Risk Score)
    - Ability to maintain employment
    - Need for lung or heart-lung transplant
    - Need for additional symptomatic agents
    - Adverse events including
        - Treatment-related mortality
        - Serious adverse events
        - Treatment-related discontinuation
- Other Outcomes
    - Changes in cardiac related biomarkers (e.g., NT-proBNP levels)
    - Changes in hemodynamic endpoints (e.g., pulmonary vascular resistance, mean pulmonary artery pressure)

Timing

Evidence on intervention effectiveness and harms was derived from studies of at least three months duration.

Settings

All relevant settings were considered, including both inpatient and outpatient.

Study Design

Randomized controlled trials, non-randomized controlled trials, and observational studies with any sample size were considered.

Table D1. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item
TITLE		
Title	1	Identify the report as a systematic review.
ABSTRACT		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
METHODS		
Eligibility Criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information Sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search Strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.
Selection Process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data Collection Process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data Items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study Risk of Bias Assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect Measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.

Section and Topic	Item #	Checklist item
Synthesis Methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting Bias Assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty Assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
RESULTS		
Study Selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study Characteristics	17	Cite each included study and present its characteristics.
Risk of Bias in Studies	18	Present assessments of risk of bias for each included study.
Results of Individual Studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.
Results of Syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting Biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.

Certainty of Evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.

Section and Topic	Item #	Checklist item
DISCUSSION		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.
OTHER INFORMATION		
Registration and Protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing Interests	26	Declare any competing interests of review authors.
Availability of Data, Code, and Other Materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for PAH followed established best research methods. We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[50] The PRISMA guidelines include a checklist of 27 items (see Table D1).

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see the Policy on Inclusion of Grey Literature in Evidence Reviews. Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data).

Table D2. Search Strategy of EMBASE Search

#1	'pulmonary hypertension'/exp OR 'pulmonary hypertension'
#2	'pulmonary arterial hypertension':ti,ab
#3	#1 OR #2
#4	sotatercept/exp OR 'sotatercept'
#5	(ace011 OR 'ace 011'):ti,ab
#6	#4 OR #5
#7	#3 AND #6
#8	('case report'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#9	#7 NOT #8
#10	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
#11	#9 NOT #10
#12	#11 AND [English]/lim

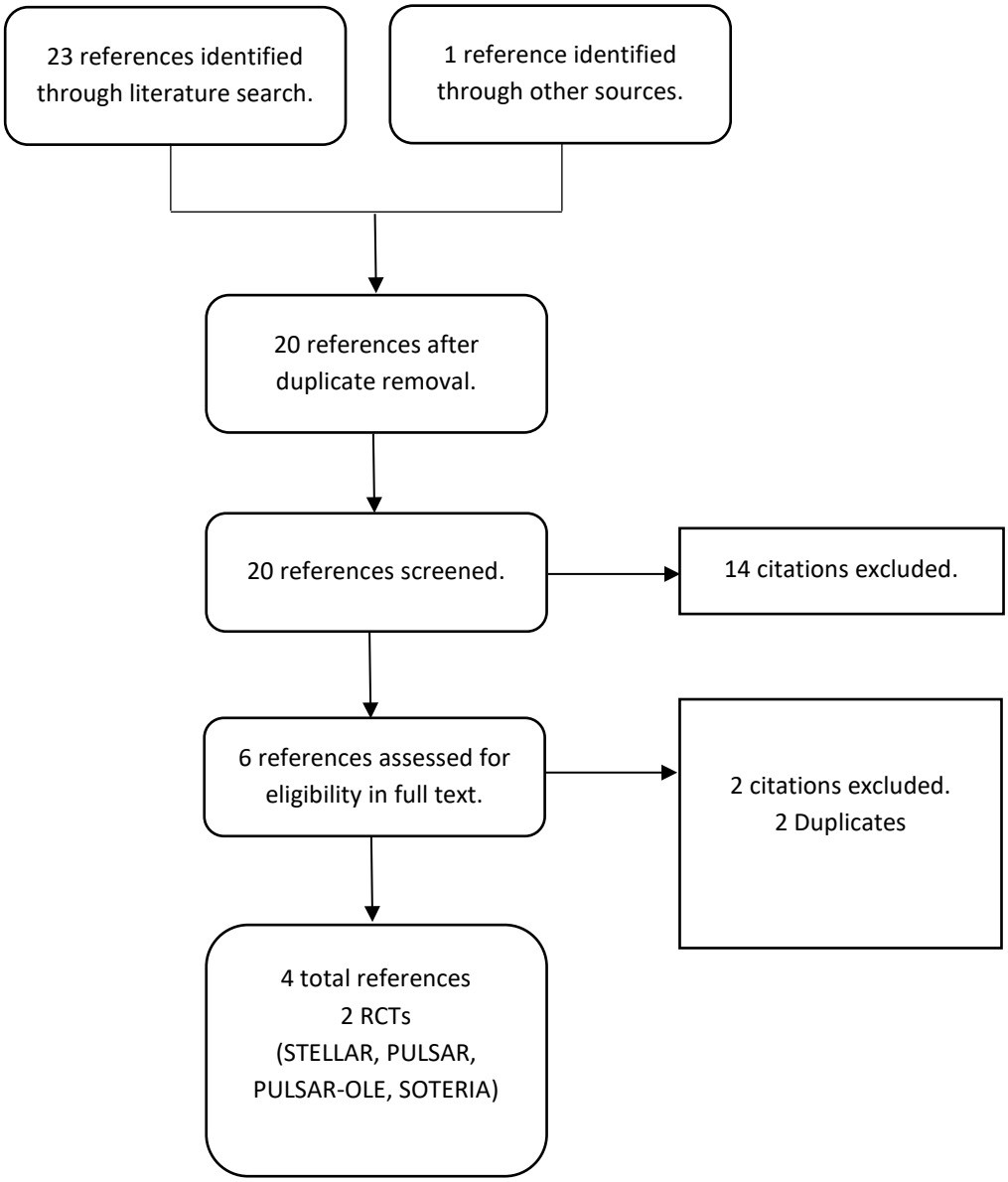
*Search last updated on October 19, 2023.

Table D3. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials

1	Exp pulmonary arterial hypertension/
2	(sotatercept or “ace 011”).ti,ab
3	1 AND 2
4	("address" or "autobiography" or "bibliography" or "biography" or "case reports" or "comment" or "congress" or "consensus development conference" or "duplicate publication" or "editorial" or "guideline" or "interview" or "lecture" or "legal case" or "legislation" or "letter" or "news" or "newspaper article" or "patient education handout" or "periodical index" or "personal narrative" or "portrait" or "practice guideline" or "review" or "video-audio media").pt.
5	3 NOT 4
6	(animals not (humans and animals)).sh.
7	5 NOT 6
8	Limit 7 to English language
9	Remove duplicates from 8

*Search last updated on October 19, 2023.

Figure D1. PRISMA Flow Chart Showing Results of Literature Search for Sotatercept for Pulmonary Arterial Hypertension



Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all titles and abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier using Nested Knowledge; a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study. All literature that did not undergo a formal peer review process is described separately.

Data Extraction

Data were extracted into Microsoft Excel. The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and risk of bias for each study. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.
2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

Risk of Bias Assessment

We examined the risk of bias for each randomized control trial in this review using criteria published in the Cochrane Risk of Bias Assessment Tool Version 2.[51,52] Risk of bias was assessed by study outcome for each of the following aspects of the trials: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. Two reviewers independently assessed these domains. Any disagreements were resolved through discussion or by consulting a third reviewer. We did not assess the risk of bias in trials where we only had access to conference abstracts/presentations.

To assess the risk of bias in trials, we rated the categories as: “low risk of bias,” “some concerns,” or “high risk of bias.” Guidance for risk of bias ratings using these criteria is presented below:

***Low risk of bias**: The study is judged to be at low risk of bias for all domains for this result.*

***Some concerns**: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.*

***High risk of bias**: The study is judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.*

We examined the risk of bias for the outcome of the 6MWD (Table D4).

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias for sotatercept using ClinicalTrials.gov. Search terms included "sotatercept," "ace011," and "ace 011." We did not identify any studies for sotatercept that would have met our inclusion criteria for which no findings have been published within two years.

Data Synthesis and Statistical Analyses

Data on key outcomes of the main sotatercept studies were summarized in the Evidence Tables (see Section D2 below) and synthesized qualitatively and quantitatively in the body of the report. We assessed feasibility of quantitative synthesis and ultimately did not conduct any pairwise meta-analyses to compare sotatercept to standard of care due to differences in dosing and outcome measurements between sotatercept trials. We instead descriptively synthesized these data in the main report of the review.

D2. Evidence Tables

Table D4. Risk of Bias Assessment

Trial Name	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
Sotatercept						
STELLAR	Low risk	Low risk	Low risk	Low risk	Low risk	Low
PULSAR	Low risk	Low risk	Low risk	Low risk	Low Risk	Low

Table D5. Study Design

Trial (NCT)	Study Design & Follow-Up	Population, N	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Key Outcomes [Timepoint]
STELLAR[7] Hoeper 2023 NEJM NCT04576988	Phase III, DB, PC, RCT Follow-up: 24 Weeks following treatment initiation	Patients with PAH in WHO-FC II or III and on stable background therapy	SC Sotatercept + background PAH therapy every 21 days (starting dose: 0.3 mg/kg; target dose of 0.7 mg/kg) Placebo + background PAH therapy	**Inclusion Criteria:** -Age ≥ 18 years -WHO PAH Group 1 subtypes: Idiopathic PAH, Heritable PAH, Drug/toxin-induced PAH, connective tissue disease-associated PAH, PAH associated with simple, congenital systemic to pulmonary shunts ≥ 1 year following repair -Symptomatic PAH classified as WHO-FC II or III -PVR ≥ 5 WU and a PCWP or left ventricular end-diastolic pressure of ≤ 15 mmHg -On stable doses of background PAH therapy and diuretics -6MWD ≥150 and ≤500 m repeated twice, with both values within 15% of each other **Key Exclusion Criteria:** -Diagnosis of pulmonary hypertension WHO Groups 2, 3, 4, or 5 -Diagnosis of PAH Group 1 subtypes: HIV-associated PAH and PAH associated with portal hypertension -Uncontrolled systemic hypertension -Baseline SBP < 90 mmHg	**Primary Outcome:** Change from Baseline in 6MWD [Week 24]

Trial (NCT)	Study Design & Follow-Up	Population, N	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Key Outcomes [Timepoint]
				-LVEF<45% -History of untreated obstructive sleep apnea, portal hypertension, liver disease, restrictive cardiomyopathy, atrial septostomy, pneumonectomy, long QT syndrome or sudden cardiac death -Experienced symptomatic coronary disease events, cerebrovascular accident, heart failure, or mitral regurgitation or aortic regurgitation valvular disease	
PULSAR Humbert 2021 NEJM NCT03496207	Phase II, DB, PC, RCT Follow-up: 24 Weeks following treatment initiation	Patients with PAH in WHO-FC II or III and on stable background therapy	SC Sotatercept 0.3 mg/kg + background PAH therapy every 21 days SC Sotatercept 0.7 mg/kg + background PAH therapy every 21 days Placebo + background PAH therapy	**Inclusion Criteria:** -Age ≥18 years -WHO PAH Group 1 subtypes: Idiopathic; Heritable PAH; Drug- or toxin-induced PAH; connective tissue disease-associated PAH; PAH associated with simple, congenital systemic-to-pulmonary shunts at least 1 year following shunt repair -Symptomatic PAH classified as WHO-FC II or III -PVR of ≥400 dyn·sec/cm5 (5 Wood units) -6MWD ≥150 and ≤550 m repeated twice at Screening and both values within 15% of each other -PAH therapy at stable dose levels of SOC therapies **Exclusion Criteria:** -Received intravenous inotropes -History of atrial septostomy, untreated obstructive sleep apnea, portal hypertension or chronic liver disease, HIV-associated PAH, known pericardial constriction, long QTc syndrome, sudden cardiac death, cardiomyopathy, symptomatic coronary disease, opportunistic infection, allergy to investigational product, active malignancy -Experienced uncontrolled systemic hypertension, cerebrovascular accident, acutely decompensated heart failure, mitral regurgitation or aortic	**Primary Outcome:** Change from Baseline in Pulmonary Vascular Resistance (PVR) [Week 24]

Trial (NCT)	Study Design & Follow-Up	Population, N	Arms & Dosing Regimen	Inclusion / Exclusion Criteria	Key Outcomes [Timepoint]
				regurgitation valvular disease -Systolic BP <90 mmHg -LVEF <45%	
SOTERIA[22] NCT04796337	Phase III, open-label, long-term follow-up trial N~700 Locations: Global Timepoint: Up to 200 weeks	Adult patients with PAH who have completed prior Sotatercept studies	SC injection Sotatercept 0.7 mg/kg	**Inclusion Criteria:** -Must have completed respective PAH sotatercept clinical study and not have discontinued early **Exclusion Criteria:** -Not enrolled in a PAH parent study at the time of enrollment. -Missed more than the equivalent of 4 consecutive doses between the end of parent study and the start of this study. -Presence of an ongoing possibly sotatercept-related serious adverse event that occurred during a PAH sotatercept clinical study	**Primary Outcome [up to 200 Weeks]:** -AEs -ADAs -Abnormal hematology clinical chemistry lab results, or urinalysis results -Vital signs (body weight, BP, ECG for QTcF)

6MWD: 6-Minute Walk Distance, ADA: anti-drug antibody, AE: adverse event, BP: blood pressure, cm: centimeter, DB: double-blind, dyn: dyne, ECG: electrocardiogram, HIV: human immunodeficiency virus, kg: kilogram, LVEF: left ventricular ejection fraction, m: meter, mg: milligram, mmHg: millimeter of mercury, N: total number, NCT: National Clinical Trial, NEJM: New England Journal of Medicine, PAH: pulmonary arterial hypertension, PC: placebo-controlled, PCWP: pulmonary capillary wedge pressure, PVR: pulmonary vascular resistance, RCT: randomized controlled trial, SC: subcutaneous, sec: second, SOC: standard of care, WHO: World Health Organization, WHO-FC: World Health Organization functional class, WU: wood unit

Table D6. STELLAR: Baseline Characteristics[7]

STELLAR				
Arm		**Sotatercept**	**Placebo**	**Total**
N		**163**	**160**	**323**
Female sex, n (%)		129 (79.1)	127 (79.4)	256 (79.3)
Age, mean years (SD)		47.6 (14.1)	48.3 (15.5)	47.9 (14.8)
Geographic region, n (%)	**North America**	49 (30.1)	56 (35.0)	105 (32.5)
	South America	13 (8.0)	15 (9.4)	28 (8.7)

STELLAR				
Arm		**Sotatercept**	**Placebo**	**Total**
N		**163**	**160**	**323**
	Europe	91 (55.8)	77 (48.1)	168 (52.0)
	Asia-Pacific	10 (6.1)	12 (7.5)	22 (6.8)
Race, n (%)	**White**	147 (90.2)	141 (88.1)	288 (89.2)
	Black	2 (1.2)	5 (3.1)	7 (2.2)
	Asian	1 (0.6)	6 (3.8)	7 (2.2)
	American Indian/Alaska Native	0 (0)	1 (0.6)	1 (0.3)
	Native Hawaiian or Other Pacific Islander	0 (0)	1 (0.6)	1 (0.3)
	Other	5 (3.1)	4 (2.5)	9 (2.8)
	Missing	6 (3.7)	2 (1.3)	8 (2.5)
Ethnicity, n (%)	**Hispanic or Latino**	27 (16.6)	31 (19.4)	58 (18)
	Not Hispanic or Latino	132 (81)	124 (77.5)	256 (79.3)
	Not reported	4 (2.5)	5 (3.1)	9 (2.8)
Body-mass index, mean kg/m2 (SD)		26.1 (5.7)	26.6 (6.1)	26.4 (5.9)
Body-mass index ≥30 kg/m2, n (%)		36 (22.1)	38 (23.8)	74 (22.9)
Time since PAH diagnosis, mean years (SD)		9.2 (7.3)	8.3 (6.7)	8.8 (7.0)
Classification of PAH, n (%)	**Idiopathic**	83 (50.9)	106 (66.2)	189 (58.5)
	Heritable	35 (21.5)	24 (15.0)	59 (18.3)
	Associated with connective-tissue disease	29 (17.8)	19 (11.9)	48 (14.9)
	Drug-induced or toxin-induced	7 (4.3)	4 (2.5)	11 (3.4)
	Associated with corrected congenital shunts	9 (5.5)	7 (4.4)	16 (5.0)
WHO-FC, n (%)	**II**	79 (48.5)	78 (48.8)	157 (48.6)
	III	84 (51.5)	82 (51.2)	166 (51.4)
	Prostacyclin infusion therapy**	65 (39.9)	64 (40.0)	129 (39.9)

STELLAR				
Arm		**Sotatercept**	**Placebo**	**Total**
N		**163**	**160**	**323**
Background therapy for PAH, n (%)	**Monotherapy**	9 (5.5)	4 (2.5)	13 (4.0)
	Double therapy	56 (34.4)	56 (35.0)	112 (34.7)
	Triple therapy	98 (60.1)	100 (62.5)	198 (61.3)
	ERA+Prostacyclin+PDE5i combination therapy	79 (48.5)	85 (53.1)	164 (50.8)
Comorbidities, n (%)	**Coronary heart disease**	5 (3.1)	12 (7.5)	17 (5.3)
	Diabetes mellitus	10 (6.1)	10 (6.3)	20 (6.2)
	Hypertension	31 (19)	29 (18.1)	60 (18.6)
	Obesity	10 (6.1)	15 (9.4)	25 (7.7)
	Previous history of pulmonary embolism	6 (3.5)	8 (5)	14 (4.3)
Hemoglobin, mean (SD), g/dL		13.9 (1.7)	13.7 (1.6)	13.8 (1.6
6-Minute walk distance, mean (SD), m		397.6 (84.3)	404.7 (80.6)	401.1 (82.4)
NT-proBNP, mean (SD), pg/mL		1037.5 (2498.6)	1207.8 (2694.4)	1121.1 (2593.8)
Pulmonary vascular resistance, mean (SD), dyn·sec·cm−5		781.3 (398.5)	745.8 (313.5)	763.7 (358.8)
Cardiac output, mean (SD), liters/min		4.9 (1.3)	4.8 (1.2)	4.8 (1.2)
Cardiac index, mean (SD), liters/min/m2		2.7 (0.6)	2.7 (0.6)	2.7 (0.6)
Mean pulmonary artery pressure, mean (SD), mm Hg		53.0 (14.6)	52.2 (13.0)	52.6 (13.8)
Right atrial pressure, mean (SD), mm Hg		8.0 (4.3)	8.5 (4.5)	8.2 (4.4)
Pulmonary arterial wedge pressure, mean (SD), mm Hg		9.7 (3.2)	9.8 (3.1)	9.8 (3.1)

Cm: centimeter, dL: deciliter, dyn: dyne, ERA: endothelin receptor antagonist, g: gram, kg: kilogram, m: meter, mL: milliliter, mmHg: millimeter of mercury, n: number, N: total number, NT-proBNP: N-terminal prohormone of brain natriuretic peptide, PAH: pulmonary arterial hypertension, PDE5i: phosphodiesterase 5 inhibitor, pg: picogram, sec: second, SD: standard deviation, WHO-FC: World Health Organization functional class

*Treatments included monotherapy, double therapy, or triple therapy with combinations of endothelin-receptor antagonists, phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators, prostacyclin analogues, and prostacyclin-receptor agonists.

†Prostacyclin infusion therapy includes intravenous epoprostenol and intravenous or subcutaneous treprostinil.

Table D7. STELLAR: Efficacy[7]

STELLAR				
Arm		**Sotatercept**	**Placebo**	**Between-Group Comparison, LSM (95% CI)**
N		**163**	**160**	
Timepoint: Week 24				
6MWD, **m**	**Median change estimate (95% CI) from baseline**	34.4 (33.0 to 35.5)	1.0 (−0.3 to 3.5)	NR
	Hodges–Lehmann location shift from placebo estimate (95% CI)	40.8 (27.5 to 54.1)		NR
Multicomponent improvement (Patients who met all three criteria for 6MWD, NT-proBNP level, and WHO-FC), n/N (%)	**Overall**	63/162 (38.9) 95% CI: 31.3 to 46.9	16/159 (10.1) 95% CI: 5.9 to 15.8	NR
	Improvement in WHO-FC or maintenance of WHO-FC II	115/163 (70.6)	82/159 (51.6)	NR
	Improvement in NT-proBNP (decrease ≥30%) or maintenance of NT-proBNP <300 pg/mL	138/162 (85.2)	64/159 (40.3)	NR
	Improvement in 6MWD ≥30 m	87/163 (53.4)	35/159 (22)	NR
Pulmonary vascular resistance, dyn·sec·cm−5	**Median change estimate (95% CI) from baseline**	−165.1 (−176.0 to −152.0)	32.8 (26.5 to 40.0)	NR
	Hodges–Lehmann location shift from placebo estimate (95% CI)	−234.6 (−288.4 to −180.8)		NR
NT-proBNP, pg/mL	**Median change estimate (95% CI) from baseline**	−230.3 (−236.0 to −223.0)	58.6 (46.0 to 67.0)	NR
	Hodges–Lehmann location shift from placebo estimate (95% CI)	−441.6 (−573.5 to −309.6)		NR
WHO-FC improvement, n/N (%)		48/163 (29.4) 95% CI: 22.6 to 37.1	22/159 (13.8) 95% CI: 8.9 to 20.2	NR NR
WHO-FC distribution, n/N (%)	**I**	*9 (5.7)*†	*4 (2.7)*†	NR
	II	*106 (66.7)*†	*78 (53.1)*†	NR
	III	*42 (26.4)*†	*57 (38.8)*†	NR
	IV	*2 (1.3)*†	*8 (5.4)*†	NR

STELLAR					
Arm			**Sotatercept**	**Placebo**	**Between-Group Comparison, LSM (95% CI)**
N			**163**	**160**	
French low-risk score, n/N (%)*			64/162 (39.5) 95% CI: 31.9 to 47.5	29/159 (18.2) 95% CI: 12.6 to 25.1	NR
PAH-SYMPACT	**Physical Impacts domain‡**	**Median change estimate (95% CI) from baseline**	−0.13 (−0.15 to 0.00)	0.01 (0.00 to 0.13)	NR
		Hodges–Lehmann location shift from placebo estimate (95% CI)	−0.26 (−0.49 to −0.04)		NR
	Cardiopulmonary Symptoms domain‡	**Median change estimate (95% CI) from baseline**	−0.12 (−0.14 to −0.08)	−0.01 (−0.03 to 0.00)	NR
		Hodges–Lehmann location shift from placebo estimate (95% CI)	−0.13 (−0.26 to −0.01)		NR
	Cognitive/Emotional Impacts domain‡	**Median change estimate (95% CI) from baseline**	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	NR
		Hodges–Lehmann location shift from placebo estimate (95% CI)	−0.16 (−0.40 to 0.08)		NR
LSM change from baseline in pulmonary artery pressure (SE), mm Hg			-13.6 (0.8)	0.3 (0.8)	-13.9 (-16.03 to -11.80)
LSM change from baseline in right atrial pressure (SE), mm Hg			-2.4 (0.3)	0.3 (0.3)	-2.7 (-3.48 to -1.94)
LSM change from baseline in cardiac output (SE), liters/min			0.1 (0.1)	-0.2 (0.1)	0.1 (-0.16 to 0.29)
LSM change from baseline in cardiac index (SE), liters/min/m2			-0.1 (0.04)	-0.1 (0.1)	0.0 (-0.09 to 0.15)
LSM change from baseline in pulmonary arterial wedge pressure (SE), mm Hg			-0.7 (0.3)	0.3 (0.3)	-1.0 (-1.72 to -0.29)
LSM change from baseline in mixed venous oxygen saturation (SE), %			2.9 (0.6)	-1 (0.6)	3.8 (2.11 to 5.57)
Timepoint: At Data Cut-Off§					
Patients who died or had ≥1 clinical worsening event, n (%)			9 (5.5)	42 (26.2)	NR
Time to first occurrence of death or nonfatal clinical worsening event, Hazard ratio (95% CI)			0.16 (0.08 to 0.35)	NR	
First occurrence of death or nonfatal	**Death as first event**		2 (1.2)	6 (3.8)	NR
	Worsening-related listing for lung or heart–lung transplantation		1 (0.6)	1 (0.6)	NR
	Initiation of rescue therapy or increase in dose of infusion prostacyclin by ≥10%		2 (1.2)	17 (10.6)	NR

STELLAR				
Arm		**Sotatercept**	**Placebo**	**Between-Group Comparison, LSM (95% CI)**
N		**163**	**160**	
clinical worsening event, n (%)	**Atrial septostomy**	0	0	NR
	PAH–related hospitalization for ≥24 hr	0	7 (4.4)	NR
	Worsening of PAH	4 (2.5)	15 (9.4)	NR

6MWD: 6-Minute Walk Distance, CI: confidence interval, cm: centimeter, dyn: dyne, FC: Functional Class, hr: hour, m: meter, mL: milliliter, LSM: least squares mean, n: number, N: total number, NR: not reported, NT-proBNP: N-terminal prohormone of brain natriuretic peptide, PAH: pulmonary arterial hypertension, pg: picogram, sec: second, WHO: World Health Organization

*The French low-risk score was defined by meeting the following three criteria for low risk: WHO functional class I or II, 6-minute walk distance of >440 m, and NT-proBNP level of <300 pg/mL.

†Data have been digitized.

‡A notable number of patients (at least 40%) were missing from each of these outcomes due to technical issues."

§Outcomes were measured beyond week 24 through the data cut-off date of August 26, 2022.

#Worsening of PAH was defined by both of the following outcomes occurring at any time: Worsened WHO functional class and Decrease in 6-minute walk distance by ≥ 15% (confirmed by two 6-minute walk tests ≥ 4 hours but no more than 1 week apart), as compared to their baseline values.

Table D8. STELLAR: Subgroup Efficacy Results[7]

Subgroup Category	**Subgroup**	**Arm**	**N**	6MWD**, median change, m**	**Pulmonary vascular resistance, median change, dyn·sec·cm-5**	**NT-proBNP, median change, pg/mL**
				Hodges-Lehmann location shift (95% CI)		
Sex	**Male**	**Sotatercept**	**34**	58.5 (20.3, 96.6)	-280.2 (-393.0, -167.4)	-518.8 (-880.1, -157.4)
		Placebo	**33**			
	Female	**Sotatercept**	**129**	37.2 (22.5, 51.9)	-215.6 (-275.7, -155.5)	-423.9 (-574.5, -273.4)
		Placebo	**127**			
PAH diagnostic subgroup	**iPAH**	**Sotatercept**	**83**	51.3 (32.2, 70.4)	-258 (-331.9, -184.2)	-467 (-654.1, -279.9)
		Placebo	**106**			
	hPAH	**Sotatercept**	**35**	25.6 (-1.3, 52.6)	-207.9 (-317.1, -98.6)	-290.3 (-505.4, -75.3)
		Placebo	**24**			

Subgroup Category	Subgroup	Arm	N	6MWD, median change, m	Pulmonary vascular resistance, median change, dyn·sec·cm-5	NT-proBNP, median change, pg/mL
				Hodges-Lehmann location shift (95% CI)		
	Drug/toxin-induced PAH	Sotatercept	7	18.4 (-14.5, 51.3)	-82 (-182, 102)	-282.6 (-481.8, -38)
		Placebo	4			
	Connective tissue disease	Sotatercept	29	8.7 (-26.6, 43.9)	-156.2 (-332.1, 19.7)	-561.4 (-1,131.9, 9)
		Placebo	19			
	Congenital heart disease with s/p shunt repair	Sotatercept	9	92.4 (-22.5, 207.3)	-344.4 (-886, 197.2)	-1,062.2 (-2,908.9, 784.6)
		Placebo	7			
Background therapy at baseline	Monotherapy	Sotatercept	9	6.3 (-564.5, 1530)	-359.4 (-10,303.7, 9,584.9)	-493.5 (-150,117.8, 49,848.3)
		Placebo	4			
	Double Therapy	Sotatercept	56	43.2 (21, 65.4)	-151.1 (-236.2, -66.1)	-449.9 (-706.1, -193.6)
		Placebo	56			
	Triple Therapy	Sotatercept	98	43.5 (26.5, 60.4)	-280.9 (350.4, -211.5)	-437.3 (-599.2, -275.5)
		Placebo	100			
Prostacyclin infusion therapy at baseline	Prostacyclin infusion therapy	Sotatercept	65	43.1 (22.6, 63.6)	-283.2 (-373.2, -193.2)	-493.8 (-732.4, -255.3)
		Placebo	64			
	No prostacyclin infusion therapy	Sotatercept	98	38.6 (21.2, 56)	-189.7 (-259.1, -120.4)	-428.4 (-579.2, -277.7)
		Placebo	96			
WHO-FC	WHO-FC II	Sotatercept	79	21.7 (6.6, 36.7)	-191.9 (-256, -127.9)	-251.8 (-343.1, -160.5)
		Placebo	78			
	WHO-FC III	Sotatercept	84	61.7 (40.9, 82.6)	-282.2 (-374.2, -190.1)	-724.3 (-1,011, -437.7)
		Placebo	82			
Baseline PVR	Baseline PVR ≤ 800	Sotatercept	108	30.8 (15.5, 46)	-170.4 (-217.6, -123.3)	-262 (-344.1, -179.9)
		Placebo	108			
	Baseline PVR > 800	Sotatercept	55	61.6 (35.2, 88.1)	-429.4 (-558.8, -300.1)	-987.9 (-1,328.8, -647)
		Placebo	52			
Region	North America	Sotatercept	49	38.4 (15.2, 61.5)	NR	NR
		Placebo	56			

Subgroup Category	Subgroup	Arm	N	6MWD, median change, m	Pulmonary vascular resistance, median change, dyn·sec·cm-5	NT-proBNP, median change, pg/mL
				Hodges-Lehmann location shift (95% CI)		
	South America	Sotatercept	13	78.8 (15.9, 141.7)	NR	NR
		Placebo	15			
	Europe	Sotatercept	91	28.6 (11.3, 46)	NR	NR
		Placebo	77			
	Asia/Pacific	Sotatercept	10	50.9 (-11.1, 113)	NR	NR
		Placebo	12			

6MWD: 6-Minute Walk Distance, CI: confidence interval, cm: centimeter, dyn: dyne, FC: Functional Class, hPAH: heritable pulmonary arterial hypertension, iPAH: idiopathic pulmonary arterial hypertension, m: meter, mL: milliliter, N: total number, NR: not reported, NT-proBNP: N-terminal prohormone of brain natriuretic peptide, PAH: pulmonary arterial hypertension, pg: picogram, PVR: pulmonary vascular resistance, sec: second, s/p: systemic-to-pulmonary, WHO-FC: World Health Organization functional class

Table D9. STELLAR: Safety Results[7]

STELLAR				
Arms		Sotatercept	Placebo	Difference, % (95% CI)
N		163	160	
Timepoint: Week 24				
AE, n (%)	Any	138 (84.7)	140 (87.5)	−2.8 (−10.5 to 4.8)
	Related to sotatercept or placebo	67 (41.1)	41 (25.6)	15.5 (5.2 to 25.5)
	Leading to discontinuation	3 (1.8)*	10 (6.2)	−4.4 (−9.5 to −0.1)
	Leading to withdrawal from trial	3 (1.8)	5 (3.1)	−1.3 (−5.5 to 2.5)
	Leading to death	0	6 (3.8)	−3.8 (−7.9 to −1.4)
Severe AE, n (%)		13 (8.0)	21 (13.1)	−5.1 (−12.2 to 1.6)
Serious AE, n (%)	Any	23 (14.1)	36 (22.5)	−8.4 (−16.9 to 0.1)
	Related to sotatercept or placebo	2 (1.2)	2 (1.2)	−0.0 (NR)
	Leading to discontinuation	1 (0.6)	8 (5.0)	−4.4 (−9.0 to −1.0)
	Leading to withdrawal from trial	1 (0.6)	5 (3.1)	−2.5 (−6.6 to 0.6)

STELLAR				
Arms		**Sotatercept**	**Placebo**	**Difference, % (95% CI)**
N		**163**	**160**	
Timepoint: Week 24				
Death, n (%)		2 (1.2)	7 (4.4)	NR
Change from baseline in hemoglobin, mean, g/dL		1.3	-0.1	NR
AESI –Telangiectasia (spider veins), n (%)		17 (10.4)	5 (3.1)	7.3 (2.0 to 13.3)
AEs of interest, n (%)	**Increased hemoglobin level: increased hematocrit or increased red-cell count**	9 (5.5)	0	5.5 (2.9 to 10.2)
	Thrombocytopenia	10 (6.1)	4 (2.5)	3.6 (−0.9 to 8.8)
	Bleeding events	35 (21.5)	20 (12.5)	9.0 (0.8 to 17.2)
	Increased blood pressure	6 (3.7)	1 (0.6)	3.1 (−0.2 to 7.3)
AEs reported in ≥10% of patients in either group	**Any**	138 (84.7)	140 (87.5)	−2.8 (−10.5 to 4.8)
	Headache	33 (20.2)	24 (15.0)	5.2 (−3.1 to 13.6)
	Covid-19	24 (14.7)	21 (13.1)	1.6 (−6.1 to 9.3)
	Nausea	16 (9.8)	18 (11.2)	−1.4 (−8.4 to 5.4)
	Diarrhea	20 (12.3)	12 (7.5)	4.8 (−1.8 to 11.6)
	Fatigue	17 (10.4)	12 (7.5)	2.9 (−3.5 to 9.5)
	Epistaxis (nose bleeds)	20 (12.3)	3 (1.9)	10.4 (5.2 to 16.6)
	Telangiectasia (spider veins)	17 (10.4)	5 (3.1)	7.3 (2.0 to 13.3)
	Dizziness	17 (10.4)	3 (1.9)	8.6 (3.6 to 14.4)

AE: adverse event, AESI: adverse event of special interest, CI: confidence interval, dL: deciliter, g: gram, n: number, N: total number, NR: not reported
*No discontinuation due to thrombocytopenia or increased hemoglobin levels.

D3. Ongoing Studies

D10. Ongoing Studies

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Estimated Completion Date
A Study of Sotatercept for the Treatment of Cpc-PH Due to HFpEF (MK-7962-007/A011-16) (CADENCE) NCT04945460	Phase II, double-blind, placebo-controlled RCT N~150 Locations: US and Europe Timepoint: 24 weeks (up to 114 weeks)	SC injection Sotatercept 0.3 mg/kg SC injection Sotatercept 0.7 mg/kg Placebo	Adult patients with Cpc-PH due to HFpEF	October 2024
A Study of Sotatercept in Japanese Pulmonary Arterial Hypertension (PAH) Participants (MK-7962-020) NCT05818137	Phase III, single-arm, open-label, nonrandomized trial N~35 Locations: Japan Timepoint: 24 weeks	SC injection Sotatercept 0.7 mg/kg	Adult Japanese patients with PAH	January 2025
A Study of Sotatercept in Participants With PAH WHO-FC III or FC IV at High Risk of Mortality (MK-7962-006/ZENITH) (ZENITH) NCT04896008	Phase III, double-blind, placebo-controlled RCT N~166 Locations: Global Timepoint: 24 weeks (up to 43 months)	SC injection Sotatercept 0.7 mg/kg Placebo	Adult patients with PAH in WHO FC III or IV at high risk of mortality	November 2025
A Long-term Follow-up Study of Sotatercept for PAH Treatment (MK-7962-004) (SOTERIA)	Phase III, open-label, long-term follow-up trial N~700	SC injection Sotatercept 0.7 mg/kg	Adult patients with PAH who have completed prior Sotatercept studies	September 2027

Title/Trial Sponsor	Study Design	Treatment Arms	Patient Population	Estimated Completion Date
NCT04796337	Locations: Global Timepoint: Up to 200 weeks			
Study of Sotatercept in Newly Diagnosed Intermediate- and High-Risk PAH Participants (MK-7962-005/A011-13) (HYPERION) NCT04811092	Phase III, double-blind, placebo-controlled RCT N~662 Locations: Global Timepoint: 24 weeks (up to 56 months)	SC injection Sotatercept 0.7 mg/kg Placebo	Adult patients newly diagnosed with intermediate- to high-risk PAH within 6 months of study screening	June 2028
Study to Evaluate Sotatercept (MK-7962) in Children With Pulmonary Arterial Hypertension (PAH) (MK-7962-008) (MOONBEAM) NCT05587712	Phase II, single-arm, open-label, nonrandomized trial N~42 Locations: US and Europe Timepoint: 24 weeks	SC injection Sotatercept 0.3 mg/kg Placebo	Children ≥1 to <18 years of age with PAH	September 2028

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Cpc-PH: combined post-capillary and pre-capillary pulmonary hypertension, HfpEF: heart failure with preserved ejection fraction, kg: kilogram, mg: milligram, N: total number, PAH: pulmonary arterial hypertension, RCT: randomized controlled trial, SC: subcutaneous, US: United States, WHO-FC: World Health Organization functional class

D4. Previous Systematic Reviews and Technology Assessments

NICE Assessment of Sotatercept[55]

The National Institute for Health and Care Excellence (NICE) in the United Kingdom is undertaking a health technology assessment of sotatercept for treating PAH. The assessment is ongoing and NICE recently released a draft scope that outlines the population, comparators, and outcomes the assessment will consider, the economic analysis, as well as a series of questions for consultation. The questions range from sotatercept's place in care to whether or not it would be a candidate for managed access.

Jaiswal et al., 2023[56]

The authors conducted a meta-analysis of the randomized, controlled trials to assess the efficacy of sotatercept for the treatment of PAH. Data from 429 patients from two trials, the Phase III STELLAR and Phase II PULSAR, were included in the analysis. The meta-analysis examined hemodynamic and biomarker outcomes. The results of the meta-analysis showed that treatment with sotatercept led to a statistically significant reduction in pulmonary vascular resistance, pulmonary arterial pressure, right atrial pressure, and NT-proBNP levels. Limitations of the study were that different dosages of sotatercept were used in the two studies but results were combined and also that no functional outcomes were included. Overall, the authors concluded that sotatercept is an effective treatment for PAH, improving both cardiac and pulmonary function.

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	X	X	
	Future related medical costs	X	X	
	Future unrelated medical costs	X	X	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	X	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	☐	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social Services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al[57]

Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.[58]
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps three and four.
6. The evLY for the comparator arm is equivalent to the QALY for each model cycle.
7. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

Target Population

The starting population consisted of adults with pulmonary arterial hypertension in WHO -FC II or III who are on background therapy. Baseline population characteristics are reported in Table E2.

Table E2. Baseline Population Characteristics

Characteristic	Overall	Source/Notes
Age at Baseline	47.9 years	STELLAR[7]
Percent Female	79.3%	STELLAR[7]
Mean Weight	80 kg	Average weight for US adult population, weighted by sex distribution in the trial from CDC National Center for Health Statistics[59]
WHO-FC at Baseline **Class II** **Class III**	 42% 58%	PHA Registry[9]

CDC: Centers for Disease Control and Prevention, PHA: Pulmonary Hypertension Association, WHO-FC: World Health Organization functional class

Treatment Strategies

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The intervention of interest for this review was sotatercept (Merck & Co, Inc.) added to background therapy. The primary comparator was background therapy alone as estimated by the placebo arm in the pivotal clinical trials.

E2. Model Inputs and Assumptions

Our model included several assumptions stated below in Table E3.

Table E3. Key Model Assumptions

Assumption	Rationale
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.	Given the short duration of the majority of randomized controlled trials in pulmonary arterial hypertension, evidence of further functional class improvement beyond a few months is lacking. Existing models in pulmonary arterial hypertension primarily allow functional class improvement for only 12 weeks (i.e., the first model cycle). However, given evidence exists for sotatercept up to 24 weeks, we allowed for the potential for improvement in functional class for the first 24 weeks (i.e., the first and second model cycle). This assumption was tested through scenario analyses.
Members of the modeled cohort could only transition to adjacent functional classes between model cycles.	The 12-week cycle length was selected as it should be short enough to detect one increment changes in functional class. This is supported by transition probability evidence and other published economic models.
Sotatercept had no independent effect on functional class improvement after a patient progressed to WHO-FC 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.	Evidence on sotatercept's independent effect on improving from WHO-FC IV to WHO-FC III does not exist.

Assumption	Rationale
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.	Given members of the modeled cohort could not worsen from WHO-FC IV, sotatercept would only have an impact on cost. This structural assumption is supported by other published economic models. In clinical practice, treatment discontinuation with sotatercept in WHO-FC IV may be unlikely, and thus we modeled treatment continuation through WHO-FC IV in a scenario analysis.
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.	Trial evidence exists for approximately two model cycles after starting treatment with sotatercept. Clinical experts suggested that adverse events leading to discontinuation likely occur relatively soon after treatment initiation and thus it is reasonable to assume they occur over the trial follow-up period.
The potential for transplantation was not included in the model structure.	The trial suggested no difference between sotatercept and background therapy in listing for lung or heart-lung transplantation. Evidence on the probability of transplantation was limited. The evidence we did find modeled transplantation as downstream of WHO-FC IV. Given sotatercept reduced time spent in WHO-FC IV in our model, it would subsequently reduce transplantation if that structural assumption was made, which would disadvantage the treatment. To not disadvantage the treatment and because no meaningful difference in transplantation was suggested by the trial, we did not include transplantation in our model.
Patients that discontinued sotatercept received the costs and consequences associated with background therapy.	Sotatercept is added to background therapy. If a patient discontinued sotatercept, they would continue to receive background therapy.

Model Inputs

Clinical Inputs

Key clinical inputs included evidence on health state transitions, treatment discontinuation, mortality, and adverse events.

Health State Transitions, First 24 Weeks

Transition probabilities for the placebo arm and the sotatercept arm of the STELLAR trial were provided by the manufacturer for the duration of the trial follow-up period (i.e., 24 weeks) which represented the first two model cycles. The transition probabilities from the placebo arm and the sotatercept arm provided by the manufacturer were used to inform the transitions between WHO-FC I, WHO-FC II, WHO-FC III, and to WHO-FC IV for the first two model cycles (i.e., 24 weeks). Small adjustments were made to limit the transitions to one increment changes in functional class per model cycle.

The transition probabilities provided by the manufacturer were supplemented with published literature on transitions from WHO-FC IV given the small number of transitions out of WHO-FC IV observed in the STELLAR trial due to the short time horizon, the trial participants starting in WHO-FC II or III, and because of the structural assumption we made in our model that patients would start an infused prostacyclin once in WHO-FC IV. The published literature used to inform the probability of improving functional class (from WHO-FC IV to WHO-FC III) for those initiating an infused prostacyclin was a study by Roman and colleagues.[33]

Table E4 reports the background therapy transition probabilities and Table E5 reports the sotatercept transition probabilities, with the transition probabilities provided by the manufacturer as academic in confidence at this time. Transitions marked as N/A are not applicable transitions as they represent more than one increment in functional class (either improvement or worsening). Given these transitions occur within the first 24 weeks on treatment, improvements in functional class are modeled. The rows represent the starting functional class health states, and the columns represent the ending functional class health states. The probabilities are conditioned on if the individual is alive. Mortality was factored in separately based on all-cause and disease-specific mortality that varied by functional class. Therefore, each row in Table E4 and Table E5 sums to 100%.

Table E4. Background Therapy Alone Transition Probabilities, First 24 Weeks

Cycle 1 Week 1-Week 12	To			
From	**Functional Class I**	**Functional Class II**	**Functional Class III**	**Functional Class IV**
WHO-FC I			N/A	N/A
WHO-FC II				N/A
WHO-FC III	N/A			
WHO-FC IV	N/A	N/A	29%*[33]	71%*[33]
Cycle 2 Week 13-Week 24	**To**			
From	**Functional Class I**	**Functional Class II**	**Functional Class III**	**Functional Class IV**
WHO-FC I			N/A	N/A
WHO-FC II				N/A
WHO-FC III	N/A			
WHO-FC IV	N/A	N/A	29%*[33]	71%*[33]

N/A: not applicable transition, WHO-FC: World Health Organization functional class

*Improvements from WHO-FC IV to WHO-FC III only occur for the first cycle immediately after initiating treatment with an infused prostacyclin.

Table E5. Sotatercept plus Background Therapy Transition Probabilities, First 24 Weeks

Cycle 1 Week 1-Week 12	To			
From	**Functional Class I**	**Functional Class II**	**Functional Class III**	**Functional Class IV**
WHO-FC I			N/A	N/A
WHO-FC II				N/A
WHO-FC III	N/A			
WHO-FC IV	N/A	N/A	29%*[33]	71%*[33]
Cycle 2 Week 13-Week 24	**To**			
From	**Functional Class I**	**Functional Class II**	**Functional Class III**	**Functional Class IV**
WHO-FC I			N/A	N/A
WHO-FC II				N/A
WHO-FC III	N/A			
WHO-FC IV	N/A	N/A	29%*[33]	71%*[33]

N/A: not applicable transition, WHO-FC: World Health Organization functional class

*Improvements from Functional Class IV to Functional Class III only occur for the first cycle immediately after initiating treatment with an infused prostacyclin.

Health State Transitions, After 24 Weeks

After 24 weeks (i.e., model cycles three and onward), the week 13 through week 24 background therapy transition probabilities provided by the manufacturer were recalculated to remove any improvement in functional class by adding the transition probability for improvement to the probability of maintaining functional class. Those recalculated background therapy transition probabilities were used to model health state transitions for background therapy after 24 weeks and are reported in Table E6.

Transitions marked as N/A are not applicable transitions as they represent more than one increment in functional class or are transitions to an improved functional class. Given these transitions occur after the first 24 weeks on treatment, improvements in functional class were not modeled. The rows represent the starting functional class health states, and the columns represent the ending functional class health states. The probabilities are conditioned on if the individual is alive. Mortality was factored in separately based on all-cause and disease-specific mortality that varied by functional class. Therefore, each row in Table E6 sums to 100%.

Table E6. Background Therapy Alone Transition Probabilities, After 24 Weeks

Cycles 3+	To			
From	**WHO-FC I**	**WHO-FC II**	**WHO-FC III**	**WHO-FC IV**
WHO-FC I			N/A	N/A
WHO-FC II				N/A
WHO-FC III	N/A			
WHO-FC IV	N/A	N/A	29%*[33]	71%*[33]

N/A: not applicable transition, WHO-FC: World Health Organization functional class

*Improvements from WHO-FC IV to WHO-FC III only occur for the first cycle immediately after initiating treatment with an infused prostacyclin.

To estimate sotatercept's health state transition probabilities after 24 weeks on treatment, we applied sotatercept's effect on slowing the worsening in functional class (provided as academic in confidence at this time) to the background therapy transition probabilities reported in Table E6. Table E7 reports sotatercept's health state transition probabilities after 24 weeks on treatment.

Transitions marked as N/A are not applicable transitions as they represent more than one increment in functional class or are transitions to an improved functional class. Given these transitions occur after the first 24 weeks on treatment, improvements in functional class were not modeled. The rows represent the starting functional class health states, and the columns represent the ending functional class health states. The probabilities are conditioned on if the individual is alive. Mortality was factored in separately based on all-cause and disease-specific mortality that varied by functional class. Therefore, each row in Table E7 sums to 100%.

Table E7. Sotatercept plus Background Therapy Transition Probabilities, After 24 Weeks

Cycles 3+	To			
From	**WHO-FC I**	**WHO-FC II**	**WHO-FC III**	**WHO-FC IV**
WHO-FC I			N/A	N/A
WHO-FC II				N/A
WHO-FC III	N/A			
WHO-FC IV	N/A	N/A	29%*[33]	71%*[33]

N/A: not applicable transition, WHO-FC: World Health Organization functional class

*Improvements from WHO-FC IV to WHO-FC III only occur for the first cycle immediately after initiating treatment with an infused prostacyclin.

We assumed sotatercept would have no independent effect on functional class improvement after a patient progressed to WHO-FC 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. Sotatercept's effect on functional class worsening was applied to the transitions from WHO-FC IIIb to WHO-FC IVb.

Sotatercept Discontinuation

Patients could discontinue treatment with sotatercept for three reasons, including 1) adverse event-related discontinuation, 2) being in WHO-FC IV for more than 12 weeks, 3) dying.

Patients who discontinued sotatercept due to adverse events discontinued sotatercept 24 weeks after initiating treatment. The STELLAR trial reported that 1.8% of patients treated with sotatercept discontinued due to adverse event by week 24, and thus the model assumed that 1.8% of sotatercept-treated patients discontinued sotatercept after week 24 (i.e., the second model cycle). The 1.8% of patients in the sotatercept model arm who discontinued sotatercept at week 24 received the costs and consequences associated with background therapy over the remaining model time horizon that they are alive.

Patients also discontinued sotatercept if they had been on sotatercept and an infused prostacyclin for one model cycle (i.e., 12 weeks) 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. This structural assumption is supported by other published economic models. Given members of the modeled cohort could not worsen from WHO-FC IV and trial evidence for sotatercept does not suggest an effect on listing a patient for transplantation,[7] sotatercept would only have an impact on cost once a patient was in WHO-FC IV. In clinical practice, treatment discontinuation with sotatercept while a patient is in WHO-FC IV may be unlikely, and thus we modeled treatment continuation through WHO-FC IV in a scenario analysis.

Mortality

To estimate mortality by functional class, we used estimates based on a 2015 publication by Farber and colleagues[60] that provided 5-year survival data, stratified by functional class, for previously diagnosed PAH patients. The manufacturer provided ICER the distribution parameters for the survival curve for WHO-FC I, as well as standardized mortality ratios versus WHO-FC I for WHO-FC II, WHO-FC III, and WHO-FC IV. Table E8 reports these mortality parameters.

Table E8. Mortality Inputs

Health State	Mortality Estimate	Source
WHO-FC I	Distribution Form: [redacted] Shape: [redacted] Scale: [redacted]	Merck analysis of survival curves in Farber et al., 2015[60]
WHO-FC II, vs. WHO-FC I	[redacted]	
Functional Class III, vs. WHO-FC I		
WHO-FC IV, vs. WHO-FC I		

WHO-FC: World Health Organization functional class

Adverse Events

Adverse events related to sotatercept affected the model by way of discontinuation only. The STELLAR trial reported that 1.8% of patients treated with sotatercept discontinued due to adverse events by week 24, and thus the model assumed that 1.8% of sotatercept-treated patients discontinued sotatercept after week 24 (i.e., the second model cycle). The 1.8% of patients in the sotatercept model arm that discontinued sotatercept at week 24 received the costs and consequences associated with background therapy over the remaining model time horizon that they were alive. There was no additional disutility or cost associated with any adverse event that emerged from treatment with sotatercept.

Utility Inputs

Health state utilities were derived from publicly available literature and applied to health states (Table E9). We used consistent health state utility values across each intervention evaluated in the model. Health state utility values for the functional class health states were derived from a published analysis of Australian patients with PAH using the Short Form-36.[36] We then adjusted the utility values from the published analysis of Australian patients to include an additional disutility decrement to account for additional disutilities experienced while hospitalized that may not be captured in the utility estimates from the published study. The per day disutility of hospitalization was -0.077 which equated to the utility decrement due to a heart failure hospitalization reported by Alsumali and colleagues.[38] The number of hospitalization days by functional class was retrieved from a study by Dufour and colleagues.[37]

Table E9. Health State Utilities

Health State	Utility Value	Source
Functional Class I	0.729	Keogh et al., 2007[36] & Coyle et al., 2016[32]
Functional Class II	0.668	
Functional Class III	0.598	
Functional Class IV	0.515	

The manufacturer provided ICER utility estimates as academic-in-confidence based on the patients in STELLAR. Those estimates were not used in the model because they likely have a very small sample size for patients in WHO-FC I and WHO-FC IV. Results from Vizza et al., 2023 were not used to inform the utilities in the model because only the visual analogue scale findings from the EQ-5D-5L were presented, rather than the utility values from the EQ-5D-5L.[61]

Drug Utilization Inputs

Background therapy consists of numerous different treatment regimens. We assumed 100% of the modeled cohort in any of the alive health states, in both the comparator and intervention arms, would be on a double therapy market basket. Table E10 lists the common double therapy regimens. Using utilization estimates reported in the PHA registry,[9] we estimated the market basket percent for each regimen.

Table E10. Double Therapy Market Basket

Drug 1	Drug 1 Regimen	Drug 2	Drug 2 Regimen	Market Basket Percent
Ambrisentan	5 mg po daily	Tadalafil	40 mg po daily	24.3%
Ambrisentan	5 mg po daily	Sildenafil	20 mg po TID	21.4%
Ambrisentan	5 mg po daily	Riociguat	1 mg po TID	3.6%
Bosentan	125 mg po BID	Tadalafil	40 mg po daily	0.9%
Bosentan	125 mg po BID	Sildenafil	20 mg po TID	0.8%
Bosentan	125 mg po BID	Riociguat	1 mg po TID	0.1%
Macitentan	10 mg po daily	Tadalafil	40 mg po daily	24.1%
Macitentan	10 mg po daily	Sildenafil	20 mg po TID	21.3%
Macitentan	10 mg po daily	Riociguat	1 mg po TID	3.5%

BID: twice a day, PO: by mouth, TID: three times a day

In addition to being on double therapy, some patients in WHO-FC II, WHO-FC III, and WHO-FC IV were assumed to also be on a third therapy. For patients not on an infused prostacyclin, this third therapy was a market basket of selexipag, oral treprostinil diolamine, iloprost, and inhaled treprostinil. We assumed 20.2% of patients in WHO-FC II and WHO-FC III were also on this third therapy market basket so long as they were not on an infused prostacyclin. The 20.2% was based on the percent of patients in STELLAR who were on a triple therapy that wasn't an infused prostacyclin.[7] When patients started an infused prostacyclin upon entrance into the WHO-FC IV health state, they discontinued this third oral/inhaled therapy market basket and started a market basket of infused prostacyclins in addition to the double therapy market basket. We assumed 100% of patients in the WHO-FC IV health state, and the patients that transitioned from WHO-FC IV to WHO-FC III after initiating an infused prostacyclin, were on this infused prostacyclin market basket. We assumed 0% of patients in WHO-FC I were on a third therapy. Table E11 reports the treatments and relative weight of each treatment in the market baskets for this third therapy.

Table E11. Triple Therapy Market Basket

Third Oral/Inhaled Therapy Market Basket*		
Drug	**Share of Market Basket**	**Source**
Selexipag (oral)	59.6%	PHA Registry[9]
Treprostinil diolamine (oral)	10.6%	
Iloprost (inhaled)	1.0%	
Treprostinil (inhaled)	28.8%	
Infused Prostacyclin Market Basket†		
Drug	**Share of Market Basket**	**Source**
Epoprostenol sodium (intravenous)	72%	PHA Registry[9]
Treprostinil (intravenous)	28%	

*Patients discontinued this market basket upon starting an infused prostacyclin or dying.

†Patients started this market basket upon initial entrance to the Functional Class IV health state and stayed on it until death. They stayed on this market basket even if they transitioned back to Functional Class III upon initiating this market basket.

The inputs in Table E12 will be used to model sotatercept utilization and associated costs.

Table E12. Sotatercept Recommended Regimen

Dose per Administration	0.3 mg per kg at time 0, escalated to 0.7 mg per kg thereafter
Frequency of Administration	Every three weeks
Manufacturer	Merck & Co, Inc.
Route of Administration	Subcutaneous injection
Monitoring Schedule	TBD

KG: kilogram, MG: milligram, TBD: to be determined

Cost Inputs

All costs used in the model were updated to 2022 US dollars.

Drug Costs

Given sotatercept is still undergoing FDA review, a price is not yet known and thus a placeholder price was used in the economic model. IPD Analytics estimates an annual price between $300,000 and $500,000 per year based on other branded drugs in PAH, population size, and positive results from the phase III trial.[39] Therefore, we used an annual price of $400,000 per year as a placeholder price in our economic model. This price will be updated when and if the price becomes known or if the manufacturer suggests otherwise.

For approved drugs with generic equivalents available, we used the lowest cost generic wholesale acquisition cost (WAC) as the estimate of the net price in alignment with ICER's reference case. For approved drugs without a generic equivalent available, we used RED BOOK to identify the average

WAC and we then applied an average discount from WAC to estimate the net price for each drug without a generic equivalent available. The net price was used in the economic model. The average discount from WAC was obtained from SSR Health, LLC, which combines data on unit sales with publicly-disclosed US sales figures that are net of discounts, rebates, patient assistance programs, and concessions to wholesalers and distributors. We compared the most recent four-quarter averages of both net prices and wholesale acquisition cost (WAC) per unit reported in the SSR Health, LLC data to arrive at a mean discount from WAC for the drug. The mean discount from WAC calculated from the SSR Health, LLC data was applied to the average WAC from RED BOOK. If the net prices and WAC per unit were not reported in SSR Health, LLC, we assumed a similar WAC to net price discount as a similar drug with a similar route of administration that is available in SSR Health, LLC. Table E13 reports the modeled dose, route of administration, WAC per dose, net price per dose, and net price per year.

Table E13. Drug Costs

Drug	Dose / Route of Administration	WAC per Dose	Net Price per Dose	Net Price per Year
Drugs Used in Double Therapy				
Ambrisentan	5 mg / oral	$29.75	$29.75	$10,859
Bosentan	125 mg / oral	$19.39	$19.39	$14,155
Macitentan	10 mg / oral	$402.65	$332.99[†]	$121,542
Tadalafil	40 mg / oral	$0.66	$0.66	$241
Sildenafil	20 mg / oral	$0.10	$0.10	$109.5
Riociguat	1 mg / oral	$145.01	$119.92[‡]	$131,316
Drugs Used in Triple Therapy				
Selexipag	200 mcg / oral	$237.74	$175.69[§]	$128,254
Treprostinil diolamine	4 mg / oral	$211.83	$179.21[#]	$196,244
Iloprost	10 mcg / inhaled	$141.44	$118.81[¤]	$260,193
Treprostinil	64 mcg / inhaled	$195.81	$164.48**	$240,141
Epoprostenol sodium	20 ng/kg/min / infused	$58.25*	$58.25*	$21,259
Treprostinil	60 ng/kg/min / infused	$396.05*	$396.05*	$144,560

WAC: wholesale acquisition cost
*Price per dose reported is per day.
[†]Assuming a 17.3% WAC to net price discount as suggested by SSR Health, LLC for macitentan.
[‡]Assuming an equivalent WAC to net price discount as what was suggested by SSR Health, LLC for macitentan.
[§]Assuming a 26.1% WAC to net price discount as suggested by SSR Health, LLC for selexipag.
[#]Assuming a 15.4% WAC to net price discount as suggested by SSR Health, LLC for Orenitram ER.
[¤]Assuming an equivalent WAC to net price discount as what was suggested by SSR Health, LLC for Tyvaso.
**Assuming a 16.0% WAC to net price discount as suggested by SSR Health, LLC for Tyvaso.

Non-Drug Costs

Administration Costs

Drugs that were administered orally or inhaled had no associated administration costs. Drugs that were infused included administration costs. The infused drugs (e.g., epoprostenol sodium and infused treprostinil) were assumed to be administered via a permanent intravenous catheter and an infusion pump and thus they were associated with a one-time insertion cost of $672.22 (HCPCS code: 36260) at the start of treatment.[62]

Monitoring Costs

No monitoring costs were included for any of the drugs included in the economic model with the rationale being that these patients are already closely monitored and frequently encounter the health care system, and thus any drug-specific monitoring that may occur would be captured in the health care costs noted below.

Non-Drug Health Care Costs

Non-drug health care costs were included in the model and varied by health state. Table E14 reports the health state specific non-drug health care costs for each model cycle. The estimates reported in Table E14 have been inflated from their original source to 2022 US dollars following the approach outlined in ICER's Reference Case and have been updated to reflect the 12-week model cycle.

The non-drug health care costs for the functional class health states were retrieved from a source by Dufour and colleagues that reported the mean medical costs for PAH patients stratified by functional class.[37] The mean annual cost for WHO-FC II was adjusted from what was reported in the original source. The original source explained the presence of an outlier in WHO-FC II resulting in the mean cost for WHO-FC II to be greater than the mean cost for WHO-FC III. The median WHO-FC II cost was less than the median WHO-FC III cost, as would be expected clinically, and thus suggesting the outlier in WHO-FC II was driving the mean WHO-FC II cost to be greater than the mean WHO-FC III cost. Therefore, we used the relative difference between the median WHO-FC II cost and median WHO-FC III cost to estimate the mean WHO-FC II cost, by multiplying the mean WHO-FC III cost from the original source by the relative difference between the median WHO-FC II cost and median WHO-FC III cost from the original source.

Table E14. Health State Medical Costs, Per 12 Weeks

Health State	12-Week Cost	Source
WHO-FC I	$8,325	Dufour et al., 2017[37]
WHO-FC II	$11,838	
WHO-FC III	$15,964	
WHO-FC IV	$23,076	

WHO-FC: World Health Organization functional class

In addition to health state medical costs, an additional $68,906 was modelled per death event in alignment with recent evidence suggesting substantial end-of-life healthcare utilization and costs. The estimate of $68,906 was calculated by subtracting the six-month WHO-FC IV health state medical costs from the six-month end-of-life medical costs recently reported in Weiss et al., 2023.[63]

Productivity-Related Costs

Productivity-related costs were captured in the modified societal perspective. A study by Obgomo and colleagues reported the number of workdays missed by an individual with PAH per month. They reported 6.01 missed days per month. This estimate was not stratified by functional class; therefore, we assumed the 6.01 missed days per month was representative of individuals in WHO-FC III. We then applied the relative difference in non-drug health care costs between the other functional classes and WHO-FC III to estimate the missed workdays for WHO-FC I, WHO-FC II, and WHO-FC IV. Table E15 reports the workdays missed over the 12-week model cycle, by functional class. Productivity was monetized assuming eight hours worked per day and an average hourly wage based on data reported by the Bureau of Labor Statistics ($32.92 per hour).

Table E15. Lost Productivity, Per 12 Weeks

Health State	Missed Work Days over 12 Week Cycle	Source
WHO-FC I	8.65	Ogbomo et al., 2022 [5] and Dufour et al., 2017[37]
WHO-FC II	12.30	
WHO-FC III	16.59	
WHO-FC IV	23.98	

WHO-FC: World Health Organization functional class

Caregiver-Related Costs

Caregiver-related costs were captured in the modified societal perspective. We were not able to identify estimates of time spent caring for PAH patients by caregivers in the published literature. In the absence of data for PAH, we used evidence from heart failure as a proxy. We assumed no caregiving time was required for patients with WHO-FC I given the patient is symptom-free in this health state. A recent study by Lahoz and colleagues reported that caregivers of heart failure patients spent on average 18.1 hours per week providing care for patients categorized as NYHA Class II heart failure and 25.9 hours per week providing care for patients categorized as NYHA Class III or Class IV heart failure.[64] We assumed those numbers and that relationship held for the functional classes of PAH. Table E16 reports the time spent caregiving over the 12-week model cycle, by functional class. Time spent caregiving was monetized using an average hourly wage based on data reported by the Bureau of Labor Statistics ($32.92).

Table E16. Time Spent Caregiving, Per 12 Weeks

Health State	Hours Spent Caregiving over 12 Week Cycle	Source
Functional Class II	217	Assumed same as evidence by Lahoz et al., 2021[64] for heart failure patients
Functional Class III	311	
Functional Class IV	311	

E3. Results

Table E17 reports undiscounted outcomes over the lifetime time horizon.

Table E17. Undiscounted Outcomes, Lifetime Time Horizon

Undiscounted Outcome	Sotatercept plus Background Therapy	Background Therapy Alone
Years in WHO-FC **I**	**0.07**	**0.01**
Years in WHO-FC **II**	**2.65**	**0.92**
Years in WHO-FC **III**	**2.92**	**2.29**
Years in WHO-FC **IV**	**0.52**	**1.47**
Years without Symptoms at Rest*	**5.65**	**3.22**
Life Years	**6.16**	**4.69**
Quality-Adjusted Life Years	**3.84**	**2.75**
Equal-Value Life Years	**4.19**	**2.75**

WHO-FC: World Health Organization functional class

*Defined as years spent in Functional Class I, Functional Class II, and Functional Class III.

E4. Sensitivity Analyses

Table E18 reports the tornado diagram inputs and results for the tornado diagram presented in Table 4.2 of the report.

Table E18. Tornado Diagram Inputs and Results for Sotatercept* plus Background Therapy as Compared to Background Therapy Alone

	Lower Input CE Ratio	Upper Input CE Ratio	Lower Input	Upper Input
Sotatercept effect on Functional Class worsening from FC II to FC III	$1,904,000	$3,005,000	RD56	RD61
Utility while in WHO-FC II	$2,889,000	$2,045,000	0.56	0.76
Utility while in WHO-FC IV	$2,174,000	$2,627,000	0.42	0.61
Sotatercept effect on Functional Class worsening from FC III to FC IV	$2,220,000	$2,616,000	RD57	RD62
Utility while in WHO-FC III	$2,508,000	$2,268,000	0.50	0.70
Increased mortality in WHO-FC II, vs. WHO-FC I	$2,272,000	$2,502,000	RD58	RD63
Increased mortality in WHO-FC IV, vs. WHO-FC I	$2,410,000	$2,351,000	RD59	RD64
Increased mortality in WHO-FC III, vs. WHO-FC I	$2,359,000	$2,396,000	RD60	RD65
Per cycle medical costs, WHO-FC IV	$2,397,000	$2,360,000	$18,775	$27,813
Per cycle medical costs, WHO-FC II	$2,363,000	$2,398,000	$9,631	$14,268

CE: cost-effectiveness; WHO-FC: World Health Organization functional class

*Assuming a placeholder price of $400,000 per year.

Table E19 reports additional results from the probabilistic sensitivity analysis.

Table E19. Results of Probabilistic Sensitivity Analysis for Sotatercept* plus Background Therapy as Compared to Background Therapy Alone

	Sotatercept plus Background Therapy	Background Therapy Alone Mean	Incremental
Costs	$3,045,000	$880,000	$2,165,000
QALYs	3.46 (2.85, 4.07)	2.51 (2.24, 2.78)	0.94
evLYs	3.75 (3.05, 4.43)	2.51 (2.24, 2.78)	1.23
Incremental CE Ratio ($/QALY)	$2,298,000		
Incremental CE Ratio ($/evLY)	$1,755,000		

CE: cost-effectiveness, evLYs: equal-value life year, QALY: quality-adjusted life year

*Assuming a placeholder price of $400,000 per year.

E5. Scenario Analyses

Scenario Analysis 1: Modified Societal Perspective

Table E20 and E21 report results from the modified societal perspective scenario analysis. In this scenario, patient productivity gains and caregiver time spent caregiving was included. Costs to the caregiver were greater for sotatercept-treated patients due to the longer duration of caregiving requirements.

Table E20. Model Outcomes for Sotatercept plus Background Therapy as Compared to Background Therapy Alone, Modified Societal Perspective Scenario Analysis

Treatment	Intervention Cost	Non-Intervention Health System Costs	Productivity Gains	Caregiver Time Spent Caregiving	Total Societal Costs
Sotatercept plus Background Therapy	$2,002,000*	$1,011,000	-$74,000†	$184,600	$3,123,000
Background Therapy Alone	$0	$880,000	$0	$162,200	$1,042,000

*Assuming a placeholder price of $400,000 per year.

†These are productivity gains due to additional time to be productive due to longer length of life and longer time spent in less severe health states. They are presented as a minus sign because they are cost savings.

Table E21. Incremental Cost-Effectiveness Ratios, Modified Societal Perspective Scenario Analysis

Treatment	Cost per Additional Year without Symptoms at Rest	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained
Sotatercept* plus Background Therapy	$1,021,000	$2,322,000	$1,749,000	$1,761,000

*Assuming a placeholder price of $400,000 per year.

Scenario Analysis 2: Treatment Discontinuation at Death

Table E22 and E23 report results from the scenario analysis that assumed treatment with sotatercept would continue until death. Unlike in the base-case that assumed treatment discontinuation in Functional Class IV, this scenario assumes treatment with sotatercept would continue through Functional Class IV and would only discontinue upon death or adverse event.

Table E22. Model Outcomes for Sotatercept plus Background Therapy as Compared to Background Therapy Alone, Treatment Discontinuation Scenario Analysis

Treatment	Intervention Cost	Non-Intervention Costs	Total Costs	Years without Symptoms at Rest†	QALYs	Life Years	evLYs
Sotatercept plus Background Therapy	$2,149,000*	$1,011,000	$3,160,000	5.02	3.41	5.46	3.69
Background Therapy Alone	$0	$880,000	$880,000	2.98	2.51	4.27	2.51

*Assuming a placeholder price of $400,000 per year.

†Defined as years spent in Functional Class I, Functional Class II, and Functional Class III.

Table E23. Incremental Cost-Effectiveness Ratios, Treatment Discontinuation Scenario Analysis

Treatment	Cost per Additional Year without Symptoms at Rest	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained
Sotatercept* plus Background Therapy	$1,118,000	$2,544,000	$1,916,000	$1,930,000

*Assuming a placeholder price of $400,000 per year.

Scenario Analysis 3: Halt Functional Class at 24 Weeks

Table E24 and E25 report results from the scenario analysis that assumed treatment with sotatercept would halt the functional class the patient was in at 24 weeks. Evidence on sotatercept's effect on functional disease improvement or worsening is limited to only 24 weeks. In

the base-case, we assume patients treated with sotatercept will continue to worsen in functional class after 24 weeks, but at a slower rate as compared to patients treated with background therapy alone.

Table E24. Model Outcomes for Sotatercept plus Background Therapy as Compared to Background Therapy Alone, Halt Functional Class Scenario Analysis

Treatment	Intervention Cost	Non-Intervention Costs	Total Costs	Years without Symptoms at Rest†	QALYs	Life Years	evLYs
Sotatercept plus Background Therapy	$2,693,000	$1,159,000	$3,852,000	6.85	4.50	6.86	4.99
Background Therapy Alone	$0	$880,000	$880,000	2.98	2.51	4.27	2.51

*Assuming a placeholder price of $400,000 per year.

†Defined as years spent in Functional Class I, Functional Class II, and Functional Class III.

Table E25. Incremental Cost-Effectiveness Ratios, Halt Functional Class Scenario Analysis

Treatment	Cost per Additional Year without Symptoms at Rest	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained
Sotatercept* plus Background Therapy	$770,000	$1,494,000	$1,148,000	$1,199,000

*Assuming a placeholder price of $400,000 per year.

Scenario Analysis 4: Functional Class Improvement Over the Lifetime

Table E26 and E27 report results from the scenario analysis that assumed functional class could improve over the lifetime time horizon, rather than being limited to 24 weeks as was assumed in the base-case. In this scenario analysis, we assume the transition probabilities observed in the trial for weeks 13 to 24 continue for all subsequent model cycles.

Table E26. Model Outcomes for Sotatercept plus Background Therapy as Compared to Background Therapy Alone, Lifetime Functional Class Improvement Scenario Analysis

Treatment	Intervention Cost	Non-Intervention Costs	Total Costs	Years without Symptoms at Rest†	QALYs	Life Years	evLYs
Sotatercept plus Background Therapy	$2,585,000	$1,123,000	$3,708,000	6.55	4.42	6.72	4.89
Background Therapy Alone	$0	$880,000	$880,000	2.98	2.51	4.27	2.51

*Assuming a placeholder price of $400,000 per year.

†Defined as years spent in Functional Class I, Functional Class II, and Functional Class III.

Table E27. Incremental Cost-Effectiveness Ratios, Lifetime Functional Class Improvement Scenario Analysis

Treatment	Cost per Additional Year without Symptoms at Rest	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained
Sotatercept* plus Background Therapy	$794,000	$1,478,000	$1,157,000	$1,190,000

*Assuming a placeholder price of $400,000 per year.

E6. Model Validation

We used several approaches to validate the model. First, we provided the preliminary model structure, methods and assumptions to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model, as needed. Second, we varied model input parameters to evaluate face validity of changes in results and performed model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we will also share the model with the manufacturer for external verification around the time of publishing this draft report. Finally, we compared results to other cost-effectiveness models in this therapy area. The outputs from the model were also validated against the trial data and relevant observational data.

Prior Economic Models

We did not identify any other cost-effectiveness analyses of sotatercept in the literature. The assumptions made in this analysis were similar to other published cost-effectiveness models in PAH. As compared to these other models, our model makes more favorable assumptions around the duration of functional class improvement. In our model, we allow for functional class improvement

for up to 24 weeks, whereas other published analysis in PAH only allow for functional class improvement for the first 12 weeks on treatment. Our model structure allowed for one increment changes in functional class per cycle and did not explicitly model transplantation, which aligns with the structural assumptions taken by other modelers.

A population health model with Merck co-authors predicting the long-term impact of sotatercept on morbidity and mortality has been published.[42] This model extrapolated the short-term clinical findings from the sotatercept evidence over a lifetime time horizon similar to our model; however, the published study did not incorporate costs or any other economic inputs. The population health model made two optimistic assumptions that our model did not in its base-case, including 1) assuming improvement in functional class could occur over the entire lifetime at the same rate as what was observed from week 13 to week 24 in the trial, and 2) that sotatercept has an independent effect on mortality (hazard ratio for all-cause mortality of 0.25).[42] When we assume those two optimistic assumptions in our model, our model generates similar findings as the published population model. Modeling both of these optimistic assumptions, our model produces 4 life years in the comparator arm and 15 life years in the sotatercept arm, resulting in 11 life years gained. The population health model reported 11.5 life years gained, suggesting good validity between the two models even while other differences in modeling existed (e.g., our model structure was based on functional class and their model structure was based on the four-strata risk assessment). The second assumption (i.e., sotatercept has an independent effect on mortality of 0.25) has the largest impact on the differences between the published population model and our base-case findings. Modeling only the first assumption (i.e., assuming improvement in functional class could occur over the entire lifetime at the same rate as what was observed from week 13 to week 24 in the trial) was addressed in our Scenario Analysis 4 results in 2.45 life years gained, far less than the 11 life years gained when also incorporating the second model assumption. Our model does not assume an independent effect of sotatercept on mortality at this time due to the small sample, short timeframe, double counting with mortality benefits downstream of functional class improvement, and the confidence interval on the 0.25 hazard ratio for all-cause mortality was not statistically significan

F. Potential Budget Impact: Supplemental Information

Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon. The five-year timeframe was chosen given the potential for cost offsets to accrue over time and to provide a more realistic uptake assumption on the number of patients treated with sotatercept.

This potential budget impact analysis included the estimated number of individuals in the US who would be eligible for treatment. To estimate the size of the potential candidate populations for treatment, we used the mid-range of the estimated 50,000 to 100,000 individuals living with PAH in the US (75,000).[1] Based on PHA Registry estimates, we limited the potential eligible patient population to those with WHO-FC II and III (80.9%) and assumed that 100% of patients are on background therapy.[9] Applying these sources resulted in an estimated 60,675 eligible patients in the US. For the purposes of this analysis, we assumed that 20% of these patients would initiate treatment in each of the five years, or 12,135 patients per year.

ICER's methods for estimating potential budget impact are described in detail elsewhere. The intent of our approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Once estimates of budget impact are calculated, we compare our estimates to a budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's Value Assessment Framework presentation, this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold reflects the running five-year average annual number of FDA new drug approvals, as well as estimates for current overall US medical spending, spending on prescription drugs and drugs administered by providers, and the five-year average annual growth in gross domestic product (GDP) + 1%.

For 2022-2023, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $777 million per year for new drugs.