
Sotatercept for Pulmonary Arterial Hypertension: Effectiveness and Value

Public Meeting — December 1, 2023

Meeting materials available at:

<https://icer.org/assessment/pulmonary-arterial-hypertension-2023/>



Patient Experts

Julia Feitner, Patient Expert

- *Julia previously served as Secretary on the Board of Directors for Team PHe-nomenal Hope, which receives greater than 25% of its funding from health care companies.*

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.*

Clinical Experts

Deborah Jo Levine, MD, Professor of Medicine, Stanford University

- *No conflicts to disclose.*

Marc A. Simon, MD, MS, Professor of Medicine & Director of Pulmonary Vascular Disease, University of California San Francisco

- *Dr. Simon has received consulting fees in excess of \$5,000 from Merck & Co.*



Why are we here today?

“I was diagnosed with Pulmonary Arterial Hypertension about 8 years ago. At the time, the statistics showed, on average, patients lived 3-5 years after diagnosis. As you might imagine, this kind of news radically changes your life. Not only was I trying to learn about the disease I have, manage the plethora of treatment steps, as well as deal with the basics of everyday life, but I was also trying to wrap my head around the idea I could die in the next few years. It was a terribly scary time. And at times, still is...

As a result of Pulmonary Hypertension, I have given up and lost many things. Sometimes I'm sad and long for when I was 'normal.' Other times, however, I see in the midst of loss, I've gained so much including an incredible appreciation for life..."

Nikole DuTemple Nichols

Losses and Gains - Keeping the Balance. [Blog] *Just Breathe*. Available at: <https://justbreathepah.blogspot.com/2019/11/losses-and-gains-keeping-balance.html>

Why Are We Here Today?

- What happens the day these treatments receive FDA approval?
- Questions about:
 - What are the risks and benefits?
 - How do new treatments fit into the evolving landscape?
 - What are reasonable prices and costs to patients, the health system, and the government?
 - What lessons are being learned to guide our actions in the future?

The Impact on Rising Health Care Costs for Everyone



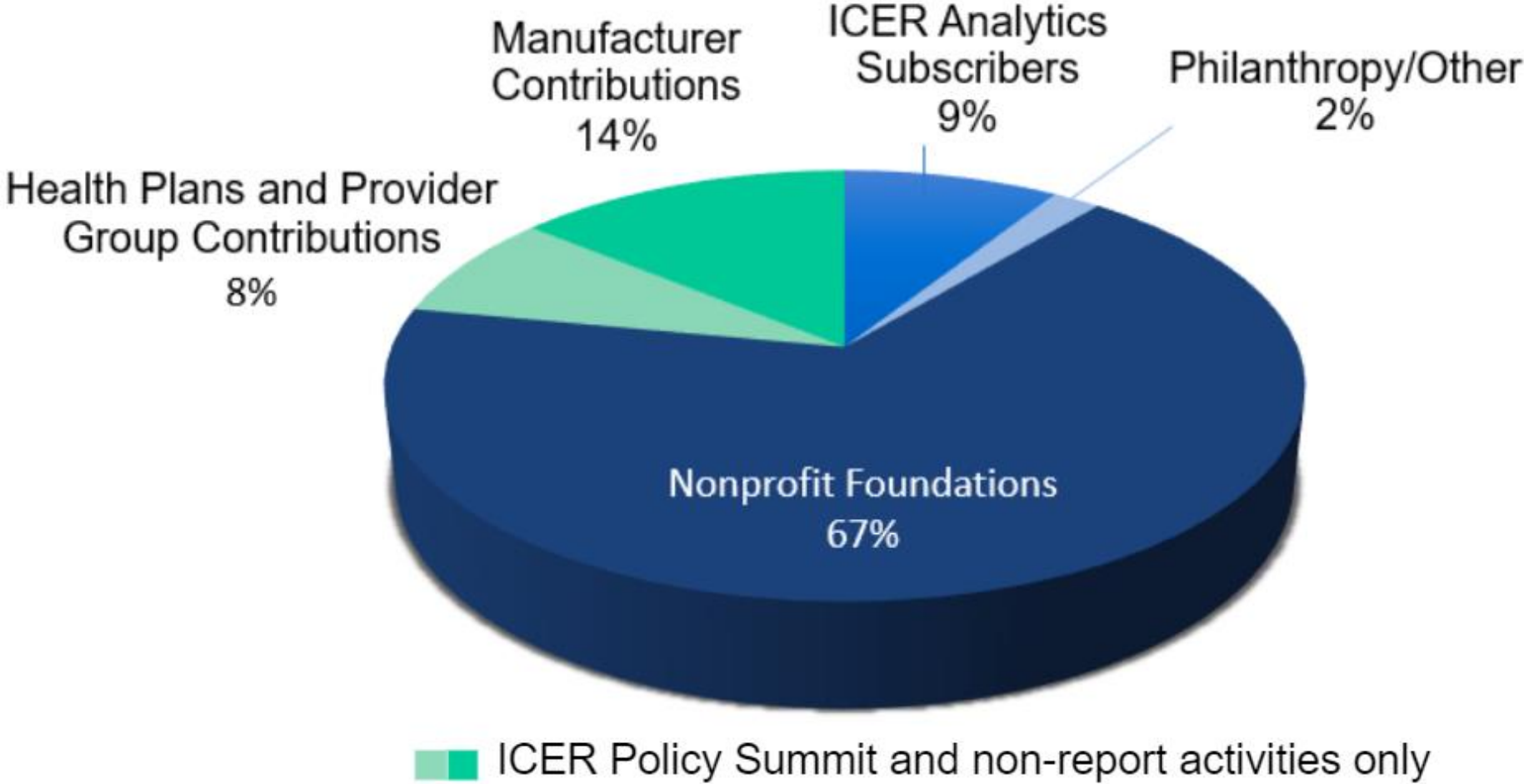
<https://khn.org/news/article/diagnosis-debt-investigation-100-million-americans-hidden-medical-debt/>



Organizational Overview

- Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC)
- Institute for Clinical and Economic Review (ICER)

Funding 2023



How Was the ICER Report Developed?

- Scoping with guidance from patients, clinical experts, manufacturers, and other stakeholders
- Internal ICER evidence analysis and cost-effectiveness modeling
- Public comment and revision
- Expert reviewers
 - Murali Chakinala, MD
 - Doug Coyle, MA, MSc, PhD
 - Katherine Kroner, MSW
 - Marc Simon, MD, MS
- How is the evidence report structured to support CEPAC voting and policy discussion?

Value Assessment Framework: Long-Term Value for Money

Special Social/Ethical Priorities

Benefits Beyond “Health”

Total Cost Overall
Including Cost Offsets

Health Benefits:
Return of Function, Fewer Side
Effects

Health Benefits:
Longer Life

Agenda (CT)

10:00 AM Meeting Convened and Opening Remarks

10:20 AM Presentation of the Clinical Evidence

11:00 AM Presentation of the Economic Model

11:40 AM Public Comments and Discussion

12:05 PM Lunch Break

12:50 PM Midwest CEPAC Deliberation and Vote

1:50 PM Break

2:00 PM Policy Roundtable Discussion

3:30 PM Reflections from Midwest CEPAC

4:00 PM Meeting Adjourned

Presentation of the Clinical Evidence

Grace Lin, MD

Medical Director for Health Technology Assessment, ICER

Professor of Medicine and Health Policy, UCSF



Key Collaborators

- **Dmitriy Nikitin, MSPH**, Senior Research Lead, Evidence Synthesis, ICER
- **Emily Nhan, BA**, Senior Research Assistant, ICER

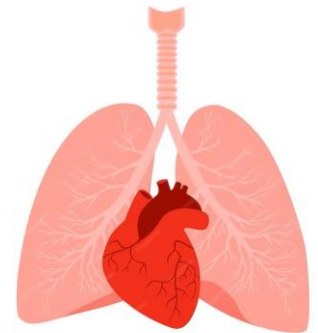
Disclosures:

Financial support was provided by ICER to the University of California, San Francisco.

No conflicts to disclose defined as more than \$10,000 in health care company stock or more than \$5,000 in honoraria or consultancies relevant to this report during the previous year from health care technology manufacturers or insurers.

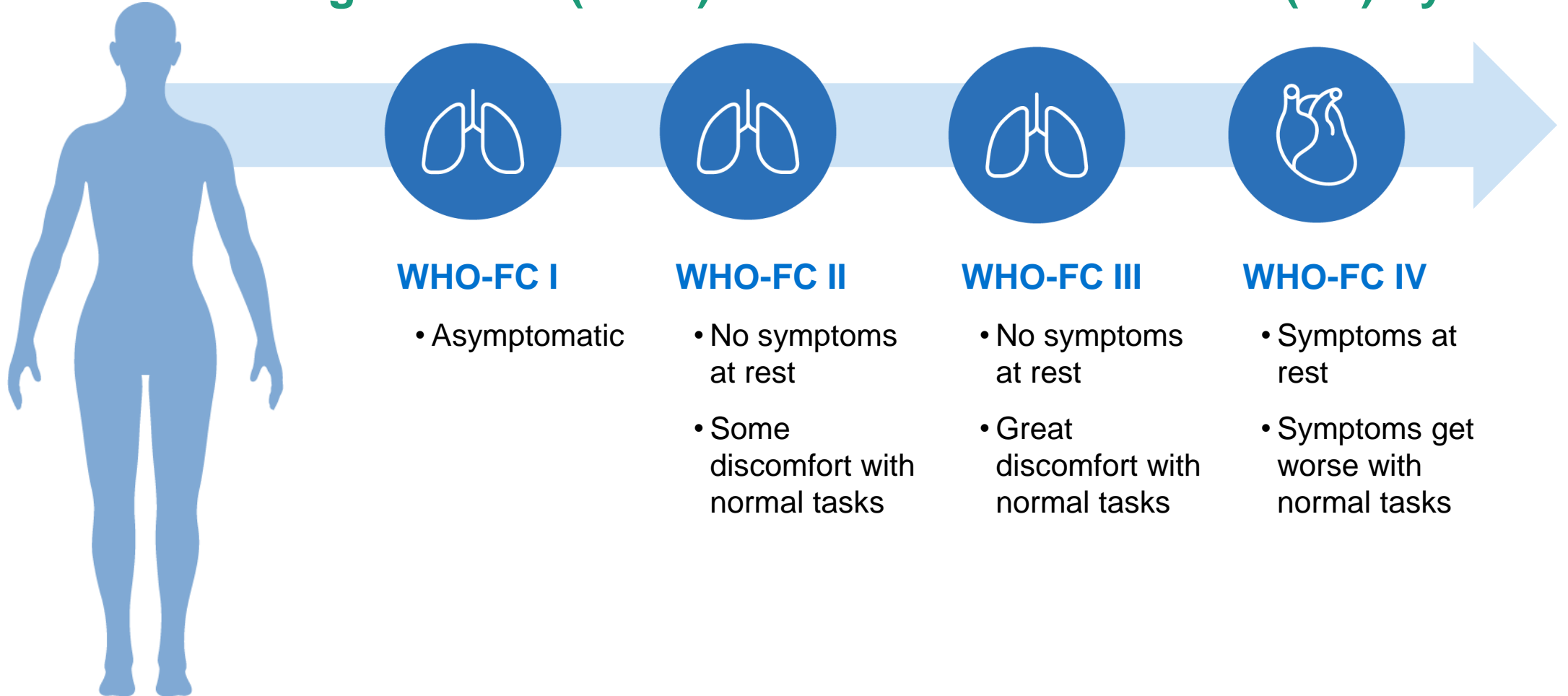
Pulmonary Arterial Hypertension (PAH)

- Type of pulmonary hypertension
 - High blood pressure in arteries carrying blood from right side of heart to lungs
 - Symptoms include dyspnea, fatigue, chest pain, cognitive difficulties
 - Can lead to right-sided heart failure, high mortality rate
- Causes: idiopathic, genetic, associated with connective tissue diseases or drug use, congenital heart disease, HIV
- More than 50,000 Americans affected, women > men
- Annual medical costs of \$100,000+ per person



Measurement of Functional Status

World Health Organization (WHO) Functional Classification (FC) System



PAH Standard of Care and Management

- Goals of care: slow progression, improve symptoms
- First line is combination therapy with phosphodiesterase-5-inhibitor (PDE5i) + endothelin receptor antagonist (ERA)
- Additional agents (IV or SC prostacyclin analogues, selexipag) may be added for high-risk or symptomatic patients
- Lung or heart-lung transplantation is only curative option



Patient Insights

- Symptoms cause significant disruption to life
- High caregiving burden
- High treatment burden
 - Oral and inhaled treatments need to be taken several times per day
 - Infused therapy requires around-the-clock administration
- Access to PAH therapies is often difficult due to high costs, insurance coverage issues, delivery issues
- Patients expressed hope for more user-friendly treatments



New Therapy: Sotatercept

- New mechanism of action from existing PAH therapies
 - Activin signaling inhibitor, may affect vascular remodeling by blocking abnormal signaling between cells
 - Reduces pulmonary vascular resistance, improving blood flow
 - Potentially disease-modifying
 - Delivered subcutaneously every 3 weeks
- FDA decision expected by March 26, 2024



Scope of Review

- Population
 - Adult patients with PAH WHO-FC II or III who are on stable background therapy
- Intervention
 - Sotatercept (Merck & Co, Inc.)
- Comparator
 - Standard of care/stable background PAH therapy

Clinical Evidence

Key Clinical Trials

Trial	Design	N	Follow-Up	Baseline Characteristics
STELLAR	Phase III, double-blind, placebo-controlled, RCT	323	24 Weeks	<p>Mean age: 47.9 Time since PAH diagnosis, years: 8.8 PAH Subtype: Idiopathic: 58.5% Heritable: 18.3% Connective tissue disease: 14.9% Drug/toxin-induced: 3.4% WHO-FC: Class II: 48.6%; Class III: 51.4% Background therapy: Dual: 34.7%; Triple: 61.3%</p>

Supporting Clinical Trials

- PULSAR: Phase II RCT (N=106), 24-week initial follow-up, 18-24 month open-label follow-up (N=97)
- SOTERIA: Phase III, open-label, long-term follow-up study of several sotatercept trials (N=409), ongoing follow-up to 7 years

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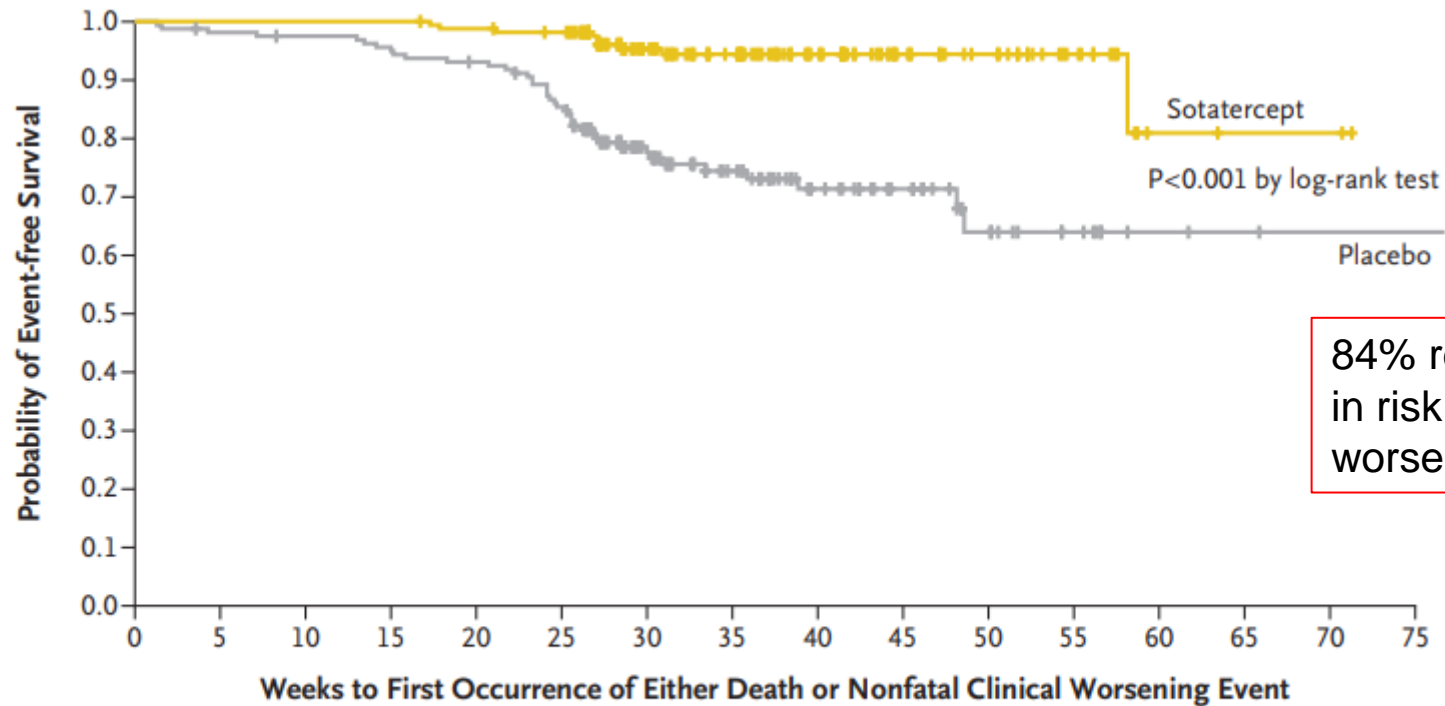
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Treatment with Sotatercept Improved Functional Status

- Change in Functional Status
 - Median difference in 6-Minute Walk Distance (6MWD) 40.8m (95% CI: 27.5-54.1)
 - Effect consistent across most subgroups (e.g., background therapy)
 - WHO-FC Improvement: 29.4% of participants in the sotatercept arm compared to 13.8% of participants in the placebo arm ($p < 0.001$)

Sotatercept Decreased Risk of Clinical Worsening



No. at Risk
Sotatercept
Placebo

Sotatercept	163	163	163	163	160	157	111	89	60	37	28	15	3	2	2	0
Placebo	160	156	154	151	146	133	83	59	38	27	16	9	3	2	1	1

STELLAR: Other Outcomes

- Improvement in multicomponent endpoint (6MWD + NT-proBNP level + WHO-FC) was in favor of sotatercept vs. placebo (38.9% vs 10.1%)
- Larger improvements in pulmonary vascular resistance, mean pulmonary arterial pressure and NT-proBNP in sotatercept vs placebo
- No change in quality of life overall on PAH-SYMPACT
 - Greater improvement in 2 out of 3 quality of life subdomains in sotatercept group vs placebo

Durability of Treatment Effect

- Maintenance of benefit in 6-MWD, NT-proBNP, WHO-FC, PVR to 18-24 months of f/u in PULSAR-OLE
- Maintenance of treatment benefit in 6-MWD, NT-proBNP, WHO-FC at 1 year in SOTERIA
 - Few patients (1.7%) experienced clinical worsening

Harms

- Fewer adverse events/severe AEs than in placebo group, no deaths
- Low treatment-related discontinuation (1.8%)
- Adverse events of special interest:
 - Increased hemoglobin (5%), telangiectasias (10.4%), bleeding events (21.5%) in sotatercept arm
- Long-term (1 year) safety events similar
 - Few drug-related TEAEs (0.7%) or discontinuations (1.2%)
 - 4 deaths due to adverse events; unknown causes

Uncertainties and Controversies

- Limited data in important subpopulations of PAH - connective tissue disease, congenital heart disease, and drug/toxin-induced
- STELLAR trial was not powered to look at mortality; multicomponent endpoints can be misleading
- More data are needed to determine if it is truly disease-modifying, can be discontinued after a period of treatment, and is effective in more severe or newly diagnosed patients

Potential Other Benefits and Contextual Considerations

- PAH is severe and affects younger people; effective therapy can have a significant impact on patients' and caregivers' abilities to achieve major life goals
- May simplify treatment regimen, particularly if it prevents or delays the need for infused therapy
- Treatment that is less complex and well-tolerated may decrease inequities in outcomes and access due to age, limited social support, or socioeconomic status

Public Comments Received

- Sotatercept may displace other therapies in the treatment algorithm

Summary

- Treatment with sotatercept improved 6MWD, WHO-FC, and hemodynamic endpoints, also decreased risk of clinical worsening
- Early, limited extension studies suggest maintenance of treatment benefit
- Impact on mortality remains uncertain
- High tolerability of treatment and overall safety profile is promising

ICER Evidence Ratings for Sotatercept

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

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

Questions?

Presentation of the Economic Evidence

Melanie D. Whittington, Ph.D.

Senior Fellow

Center for the Evaluation of Value and Risk in Health, Tufts Medical Center



Review Team Members

- **Marina Richardson, PhD, MSc**, Senior Health Economist, ICER

Disclosures:

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No conflicts to disclose defined as more than \$10,000 in health care company stock or more than \$5,000 in honoraria or consultancies relevant to this report during the previous year from health care technology manufacturers or insurers.

Objective

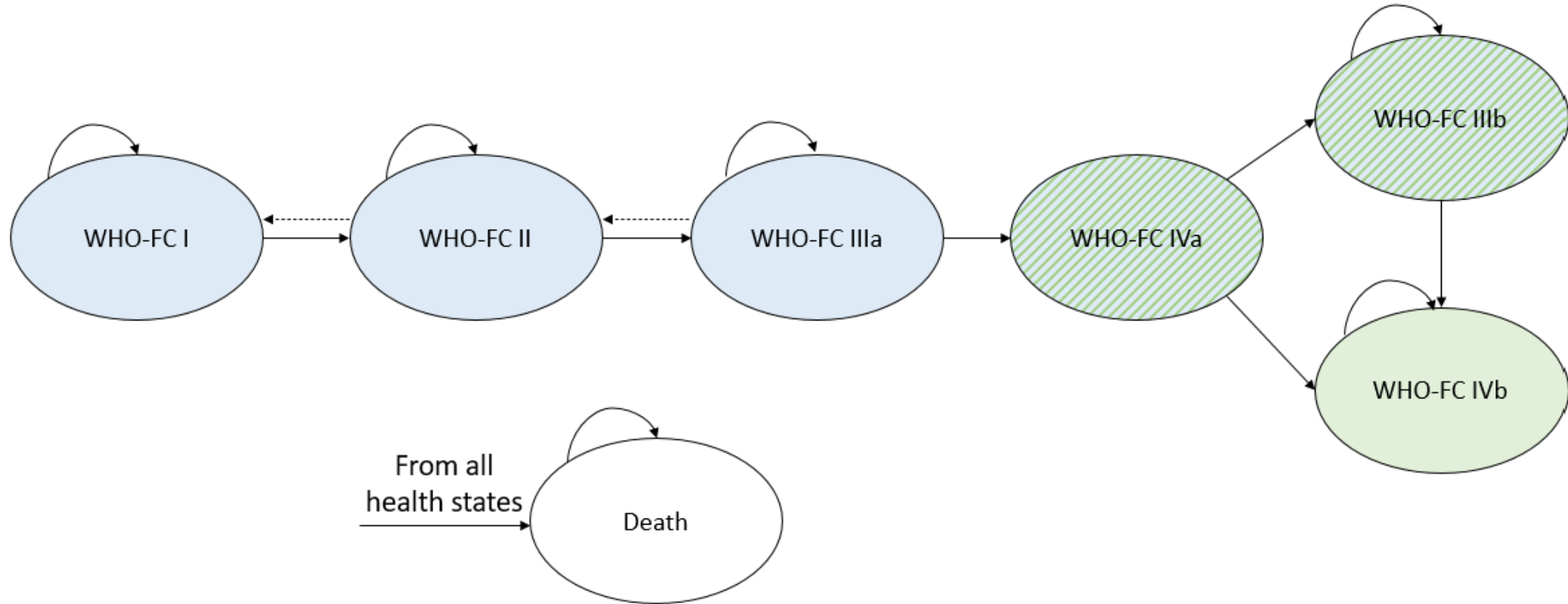
Estimate the lifetime cost-effectiveness of sotatercept added to background therapy as compared to background therapy alone for adults with pulmonary arterial hypertension in WHO-FC II or III.

Methods in Brief

Methods Overview

- **Model:** Markov
- **Setting:** United States
- **Perspective:** Health Care Sector Perspective, Modified Societal Perspective
- **Time Horizon:** Lifetime
- **Discount Rate:** 3% per year (costs and outcomes)
- **Cycle Length:** 12 weeks
- **Primary Outcomes:** costs, equal-value life years (evLYs), quality-adjusted life years (QALYs), life years (LYs), years without symptoms at rest

Model Schematic



WHO-FC: World Health Organization functional class

Key Model Assumptions

- Improvement in functional class occurred only over the first 24 weeks.
- Patients who discontinued sotatercept due to adverse events discontinued after the second model cycle.
- If an individual had been on sotatercept and an infused prostacyclin for one model cycle and did not improve, or if they transitioned back to WHO-FC IV after initially improving once starting an infused prostacyclin, they discontinued sotatercept.

Health State Transitions

- First 24 weeks:
 - Comparator: transition probabilities from the placebo arm of STELLAR
 - Intervention: transition probabilities from the sotatercept arm of STELLAR
- After 24 weeks:
 - Comparator: adjusted STELLAR transition probabilities to remove improvement in functional class
 - Intervention: applied sotatercept's effect on slowing the worsening of functional class to the comparator probabilities

Utility Inputs

Health State	Utility
WHO-FC I	0.729
WHO-FC II	0.668
WHO-FC III	0.598
WHO-FC IV	0.515

WHO-FC: World Health Organization functional class

Cost Inputs

Treatment	Annual Cost	On Treatment	Notes
Sotatercept	\$400,000	Patients in intervention arm except FC IVb	Placeholder cost
Double therapy	\$74,664	100% of alive patients	Basket of 9 different double therapy regimens
Third therapy (oral or inhaled)	\$169,004	20% of patients in FC II and IIIa	59% selexipag, 11% oral Treprostinil, 1% inhaled iloprost, 29% inhaled treprostinil
Third therapy (infused)	\$55,783	Patients in FC IV and IIIb	72% epoprostenol, 28% treprostinil

Results

Base-Case Results

Drug	Total Costs*	LYs	QALYs	evLYs	Years without Symptoms at Rest†
Sotatercept + Background Therapy	\$3,013,000	5.46	3.41	3.69	5.02
Background Therapy Alone	\$880,000	4.27	2.51	2.51	2.98

evLYs: equal-value life years, QALYs: quality-adjusted life years

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

†Defined as years spent in WHO-FC I, WHO-FC II, and WHO-FC III.

Base-Case Incremental Results

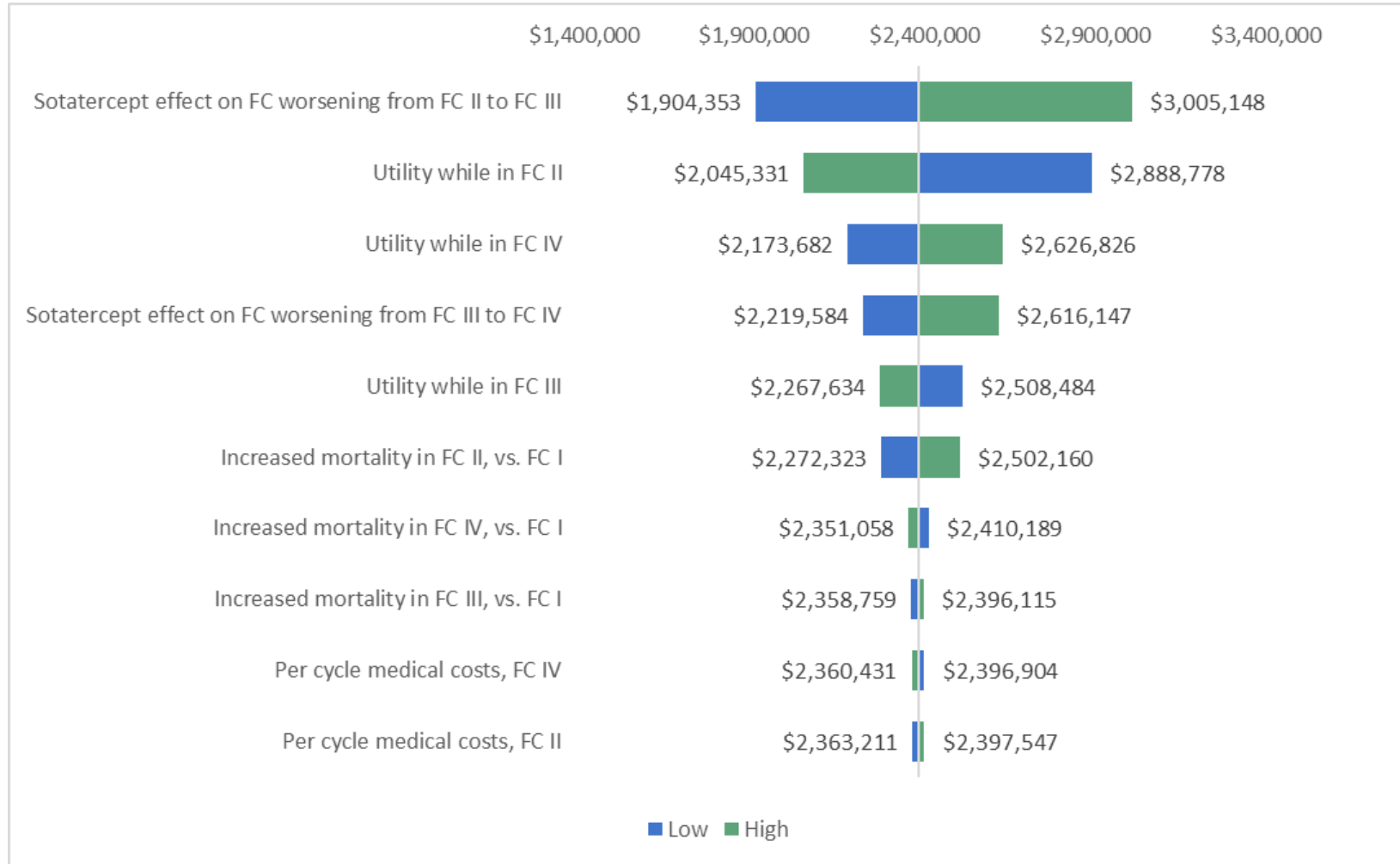
Drug	Cost per QALY Gained	Cost per evLY Gained	Cost per Additional Year without Symptoms at Rest†
Sotatercept* + Background Therapy	\$2,380,000	\$1,805,000	\$1,046,000

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.

One Way Sensitivity Analysis



Probabilistic Sensitivity Analysis

Drug	Cost-Effective at \$50,000 per evLY	Cost-Effective at \$100,000 per evLY	Cost-Effective at \$150,000 per evLY
Sotatercept* + Background Therapy	0%	0%	0%

evLY: equal-value life year

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

Scenario Analyses

Sotatercept* + Background Therapy	Cost per evLY Gained
Base-Case	\$1,805,000
Modified Societal Perspective	\$1,761,000
Treatment Continued Until Death	\$1,930,000
Halt WHO-FC at 24 Weeks	\$1,199,000
WHO-FC Improvement Over Lifetime	\$1,190,000

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

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

Health Benefit Price Benchmarks

	Annual Price at \$100,000 per Threshold	Annual Price at \$150,000 per Threshold
Per QALY Gained	\$17,900	\$26,900
Per evLY Gained	\$23,600	\$35,400

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

Limitations

- Controlled trial evidence for sotatercept is limited to 24 weeks.
- Limited evidence on sotatercept's independent effect on mortality or on functional class transitions when added on to an infused prostacyclin.

Comments Received

- Allow for transitions to non-adjacent health states per model cycle.
- Define health states by risk strata rather than by functional class.
- Include an independent effect of sotatercept on mortality.

Conclusions

- Sotatercept produces improved clinical outcomes.
- At a placeholder price of \$400,000 per year, sotatercept would exceed commonly used thresholds.
- Findings primarily driven by the effectiveness of sotatercept on improving functional class and on slowing the worsening of functional class.

Questions?



Manufacturer Public Comment and Discussion

Swapnil Rajpathak, MD, MPH, DrPH
Associate Vice President, Center for Observational and
Real World Evidence, Merck & Co.

Conflicts of Interest:

- *Dr. Rajpathak is a full-time employee of Merck & Co.*

00 : 05 : 00

Public Comment and Discussion

Colleen Brunetti, M.Ed.

Pulmonary Hypertension Association Board of Trustees

Conflicts of Interest:

- *Pulmonary Hypertension Association (PHA) receives greater than 25% of its funding from health care companies.*

00 : 05 : 00

Colleen Connor

Patient Volunteer, Pulmonary Hypertension Association

Conflicts of Interest:

- *No conflicts to disclose.*

00 : 05 : 00

Katie Kroner, MSW

Vice President, Advocacy and Patient Engagement, Pulmonary Hypertension Association

Conflicts of Interest:

- *Pulmonary Hypertension Association (PHA) receives greater than 25% of its funding from health care companies.*

00 : 05 : 00

Katherine Tobias

Patient Advocate

Conflicts of Interest:

- *No conflicts to disclose.*

00 : 05 : 00

Lunch

Meeting will resume at 12:50 pm CT





Voting Questions

Patient population for all questions: Adults with World Health Organization WHO Functional Class (WHO-FC) II and III pulmonary arterial hypertension (PAH) who are on background therapy.



Clinical Evidence Questions

slido



1. Is the evidence adequate to demonstrate that the net health benefit of sotatercept added to background therapy is superior to that provided by background therapy alone?

① Start presenting to display the poll results on this slide.



Contextual Considerations and Potential Other Benefits or Disadvantages Questions

When making judgements of overall long-term value for money, what is the relative priority that should be given to any effective treatment for PAH, on the basis of the following contextual considerations:

slido



2. Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability.

① Start presenting to display the poll results on this slide.

slido



3. Magnitude of the lifetime impact on individual patients of the condition being treated?

① Start presenting to display the poll results on this slide.

What are the relative effects of sotatercept added to background therapy versus background therapy alone on the following outcomes that inform judgement of the overall long-term value for money of sotatercept:

slido



4. Patients' ability to achieve major life goals related to education, work, or family life.

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slido



5. Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life.

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slido



6. Patients' ability to manage and sustain treatment given the complexity of regimen versus currently available third-line or fourth-line treatments.

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slido



7. Society's goal of reducing health inequities.

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Long-Term Value for Money Question

Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment at current pricing with sotatercept added to background therapy versus background therapy alone?

slido



8. What is the long-term value for money of treatment at current pricing with sotatercept added to background therapy versus background therapy alone?

① Start presenting to display the poll results on this slide.

Break

Meeting will resume at 2:00 pm CT



Policy Roundtable

Policy Roundtable

Participant	Conflict of Interest
Mindy Bauer, PharmD, BCACP , Associate Director of Clinical Pharmacy, IPD Analytics	<i>Dr. Bauer is a full-time employee of IPD Analytics.</i>
Julia Feitner , Patient Expert	<i>Julia previously served as Secretary on the Board of Directors for Team PHe-nomenal Hope, which receives greater than 25% of its funding from health care companies.</i>
Katie Kroner, MSW , Vice President, Advocacy and Patient Engagement, Pulmonary Hypertension Association	<i>The Pulmonary Hypertension Association (PHA) receives greater than 25% of its funding from health care companies.</i>
Deborah Jo Levine, MD , Professor of Medicine, Stanford University	<i>No conflicts to disclose.</i>
Mckenzie McVeigh, PharmD, MS , Clinical Pharmacy Manager, MassHealth	<i>Dr. McVeigh is a full-time employee of MassHealth.</i>
Marc A. Simon, MD, MS , Professor of Medicine & Director of Pulmonary Vascular Disease, University of California San Francisco (UCSF)	<i>Dr. Simon has received consulting fees in excess of \$5,000 from Merck & Co.</i>

Midwest CEPAC Council Reflections

Next Steps

- Meeting recording posted to ICER website next week
- Final Report published on or around January 8, 2024
 - Includes description of Midwest CEPAC votes, deliberation, policy roundtable discussion
- Materials available at: <https://icer.org/assessment/pulmonary-arterial-hypertension-2023/#timeline>

Adjourn

