Mavacamten for Hypertrophic Cardiomyopathy: Effectiveness and Value

Public Meeting — October 22, 2021
Patient and Clinical Experts

Gwen Mayes, JD, MMSC, Patient Advocate; Founder, GwenCo Health

- Gwen Mayes serves as a consultant to the Hypertrophic Cardiomyopathy Association, which receives 20% of its sponsorship for educational programming from Bristol Myers Squibb/MyoKardia. She also consults for cardiac device companies including Edwards Lifesciences and Paragonix.

Lisa Salberg, Founder and CEO, Hypertrophic Cardiomyopathy Association

- The Hypertrophic Cardiomyopathy Association receives 20% of its sponsorship for educational programming from Bristol Myers Squibb/MyoKardia.

Milind Desai, MD, MBA, Director of Clinical Operations; Director, Hypertrophic Cardiomyopathy Center, Department of Cardiovascular Medicine; Heart, Vascular & Thoracic Institute, Cleveland Clinic

- Dr. Desai serves as an investigator for the VALOR study of mavacamten.

Martin S. Maron, MD, Director, Hypertrophic Cardiomyopathy Center, Tufts Medical Center; Co-Director, Chanin T. Mast Hypertrophic Cardiomyopathy Center Morristown Medical Center, Atlantic Health System

- Dr. Maron served as a site investigator for a Phase I mavacamten study and serves as a steering committee member for a Phase II Cytokinetics study of a second-generation myosin inhibitor.
“HCM has a huge impact on my life, and it affects my job. I can’t walk more than 10 minutes without stopping to catch my breath, I can’t workout like I used to, I am gaining weight, I can only walk up one flight of stairs at a time, I am embarrassed to be around people who may see me struggling to breathe – it keeps me secluded in my home. And what is most depressing is seeing how I am getting worse and can’t stop it.”
Why Are We Here Today?

• What happens the day these treatments are approved by the FDA?
• Patients can have difficulty accessing drugs
  • Coverage eligibility
  • Costs (out-of-pocket and insurance premiums)
• What happens to patients and others in the health care “system”?
The Impact of Rising Health Care Costs

Leonard Edloe
Richmond, Virginia

The Whitman family
Bird City, Alaska

The Maccoux family
Brooklyn Park, Minnesota
Organizational Overview

- California Technology Assessment Forum Public Advisory Council
- The Institute for Clinical and Economic Review (ICER)
Sources of Funding, 2021
https://icer.org/who-we-are/independent-funding/

- Nonprofit Foundations: 68%
- Manufacturer Contributions: 12%
- Government: 10%
- Health Plans and Provider Group Contributions: 9%
- Other*: 1%

*Individual / matching contributions and speech stipends

ICER Policy Summit and non-report activities only
How Was the ICER Report Developed?

• Scoping with guidance from patient groups, clinical experts, manufacturers, and other stakeholders
• Internal ICER staff evidence analysis
• University of Illinois at Chicago cost-effectiveness modeling
• Public comment and revision
• Expert reviewers
  • Milind Desai, MD, MBA, Director of Clinical Operations; Director, Hypertrophic Cardiomyopathy Center, Department of Cardiovascular Medicine; Heart, Vascular & Thoracic Institute, Cleveland Clinic
  • Martin S. Maron, MD, Director, Hypertrophic Cardiomyopathy Center, Tufts Medical Center; Co-Director, Chanin T. Mast Hypertrophic Cardiomyopathy Center Morristown Medical Center, Atlantic Health System
  • Steve R. Ommen, MD, Medical Director, Mayo Hypertrophic Cardiomyopathy Clinic, Mayo Clinic
  • Lisa Salberg, Founder and CEO, Hypertrophic Cardiomyopathy Association
• How is the evidence report structured to support CTAF 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

<table>
<thead>
<tr>
<th>Time (PT)</th>
<th>Activity</th>
</tr>
</thead>
</table>
| 9:00 am – 9:20 am | Meeting Convened and Opening Remarks  
Steven D. Pearson, MD, MSc, President, ICER |
| 9:20 am – 10:00 am | Presentation of the Clinical Evidence  
Jason H. Wasfy, MD, MPhil, Associate Professor, Harvard  
Medical School, Massachusetts General Hospital |
| 10:00 am – 10:40 am | Presentation of the Economic Model  
Surrey M. Walton, PhD, Associate Professor, University of  
Illinois at Chicago College of Pharmacy |
| 10:40 am – 11:15 am | Public Comments and Discussion |
| 11:15 am – 11:25 am | Break |
| 11:25 am – 12:15 pm | CTAF Vote on Clinical Effectiveness and Value |
| 12:15 pm – 1:00 pm | Lunch Break |
| 1:00 pm – 2:30 pm | Policy Roundtable |
| 2:30 pm – 3:00 pm | Reflections from CTAF |
| 3:00 pm | Meeting Adjourned |
Presentation of the Clinical Evidence

Jason H. Wasfy, MD, MPhil
Associate Professor, Harvard Medical School
Medical Director, Massachusetts General Physicians Organization
Director of Outcomes Research, Massachusetts General Hospital Heart Center
Massachusetts General Hospital
Key Collaborators

• Molly Beinfeld, MPH, Senior Research Lead, Evidence Synthesis, ICER
• Emily Nhan, Research Assistant, ICER

Disclosures:

We have no conflicts of interest 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 manufacturers or insurers.

Dr. Wasfy does not have conflicts of interest 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 manufacturers or insurers.
Background

• Hypertrophic cardiomyopathy (HCM) is a genetic disorder involving heart muscle that causes dysfunction and thickening

• Hypertrophic obstructive cardiomyopathy (HOCM) is a subtype of HCM in which the thickening leads to narrowing/obstruction in the left ventricular outflow tract

• Narrowing causes pressure drop, leading to symptoms with shortness of breath and chest discomfort with exertion. Reducing gradient is a core goal of therapy

• Palpitations, dizziness, syncope also prominent. Atrial fibrillation poorly tolerated

• Symptoms can be also be related to diastolic dysfunction, microvascular angina
Background

• HCM must be distinguished from other types of hypertrophy (hypertensive heart disease, athlete’s heart, amyloidosis)

• True prevalence unknown due to screening differences with imaging modalities (1 in 500 by echo but 1 in 70 by cMRI)

• With appropriate use of implantable cardioverter-defibrillators, rate of SCD has decreased to 0.5% per patient-year
Left Ventricular Outflow Tract Obstruction is Related to Cardiac Morphology

Naidu et al. ACC 2015
Bos et al. JACC 2009
Standard of Care and Management

• For patients with exertional symptoms attributable to LVOT obstruction:

  **First line**: Negative inotropic agents (beta blockers and calcium channel blockers) are first line

  **Then**: Disopyramide or septal reduction procedures
Septal Reduction Procedures

Nishimura *NEJM* 2004
Therapies Under Review

• Interventions
  • Mavacamten is an oral, first-in-class modulator of cardiac myosin
  • PDUFA date: January 28, 2022

• Comparators
  • Usual care
  • Disopyramide
  • Percutaneous septal ablation
  • Surgical myectomy

• Comparisons are informed by input from patients, ACC/AHA guidelines, and feedback from clinical experts and public commentary
Scope of Review

• Patients with symptomatic HOCM

• Outcomes included functional status, health-related quality of life, echocardiographic parameters, peak oxygen consumption (peak VO$_2$), serum cardiac biomarkers
Insights from Discussions with Patients

• In initial discussions with the Hypertrophic Cardiomyopathy Association, they sent out questions to patients

• We are grateful for these detailed responses! 641 responses from patients, caregivers, patient advocates

• Common themes:
  • Side effects of beta blockers
  • Difficulty accessing treatment (centers of excellence/knowledgeable specialists and drug shortage of disopyramide)
  • Impacts of both symptoms and drug side effects on work, education, family, relationships
  • Only 50% of patients say treatments “work well”
Clinical Evidence
Mavacamten: EXPLORER RCT (n=251)

- At 30 weeks, composite outcome of improvement in a physiological parameter (+1.5 mL/kg improvement in pVO$_2$) and clinician-defined symptom improvement (at least 1 NYHA class) or +3.0 mL/kg improvement with no NYHA worsening

  - Achieved by 37% of patients in the mavacamten arm at 30 weeks compared to 17% in the placebo arm (p=0.0005)

- Nearly 50% of patients on mavacamten achieved NYHA class I at 30 weeks compared to 21% of patients on placebo (p<0.0001)

<table>
<thead>
<tr>
<th></th>
<th>Mavacamten (n=123)</th>
<th>Placebo (n=128)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>30 Weeks</td>
</tr>
<tr>
<td>NYHA Class I (%)</td>
<td>0</td>
<td>49.6</td>
</tr>
<tr>
<td>NYHA Class II (%)</td>
<td>71.5</td>
<td>42.3</td>
</tr>
<tr>
<td>NYHA Class III (%)</td>
<td>28.5</td>
<td>6.5</td>
</tr>
<tr>
<td>Missing (%)</td>
<td>0</td>
<td>1.6</td>
</tr>
</tbody>
</table>
Kansas City Cardiomyopathy Questionnaire (KCCQ) is a measure of health status in heart failure

Change in KCCQ-OS at 30 weeks greater with mavacamten than placebo (+14.9 vs. +5.4, p<0.0001)

MCID: 4-6 points

Reverted to baseline after 8-week washout period

Spertus et al Lancet 2021
Olivotto et al Lancet 2020
Ho et al Circ HF 2020
Butler et al Eur J HF 2020
EXPLORER: Secondary Endpoints

• Greater reduction in post-exercise LVOT gradient with mavacamten (-43.2 mm Hg vs. -28.1 mm Hg, p<0.0001)

• Greater increase in peak VO\textsubscript{2} with mavacamten (+1.4 mL/kg/min, p=0.0006)

• Primary endpoint concordant with patient-reported outcomes, objective physiological endpoint, and purported mechanism

• Also concordant with large drops in LVOT gradient seen in PIONEER Phase II trial
Mavacamten: Longer Term Effects

- Of patients in EXPLORER that received cMRI, mavacamten patients had greater reduction in LV mass index and left atrial volumes

- Symptoms as reported by KCCQ return to baseline after stopping mavacamten

- Discordance of imaging and patient-reported outcomes?

Saberi et al. *Circulation* 2021
Spertus et al. *Lancet* 2021
Mavacamten: Uncertainties

- EXPLORER protocol required temporary treatment discontinuation for clinical endpoints including LVEF <50%
- 3 patients on mavacamten and 2 on placebo discontinued due to LVEF decreases during the study period
- In addition, 4 patients receiving mavacamten had LVEF <50% at week 30
- 3 patients recovered, 1 had persistent low LVEF after AF ablation with complications
- Clinical experts disagree about the relevance/importance of these findings
Evidence for disopyramide overall very limited
Mostly short term, small, and physiologic observational studies
Practical limitations – national shortage of the long-acting version
No trials
Among those who stayed on disopyramide, mean NYHA Class declined from 2.3 → 1.7 (p<0.0001)
40/134 (34%) required major interventions – among these patients, functional status did not improve
Selection bias (patients who were doing worse were not maintained on disopyramide) and unclear external validity (only patients appropriate for disopyramide were started on it)
Septal Reduction Therapies: Liebregts 2015

• Systematic literature review and meta-analysis of 16 myectomy cohorts and 11 septal ablation cohorts

• Pooled mean improvement in NYHA class before and after treatment was:
  • -1.16 for septal ablation
  • -1.51 for myectomy

• Large reductions in median LVOT gradients were associated with both procedures
  • 71% for septal ablation
  • 77% for myectomy
Harms of Mavacamten and Disopyramide

<table>
<thead>
<tr>
<th>Mavacamten</th>
<th>Disopyramide</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Generally well tolerated</td>
<td>• Risk of arrhythmia and prolonged QT interval</td>
</tr>
<tr>
<td>• ? Importance of decreasing LVEF</td>
<td>• Discontinuation due to side effects (7-23%)</td>
</tr>
<tr>
<td>• Discontinuation 1.6%</td>
<td>• Side effects include anti-cholinergic effects – xerostomia (dry mouth), constipation, urinary hesitancy</td>
</tr>
<tr>
<td></td>
<td>• Contraindications include narrow angle glaucoma, difficult to treat hypertension, risk of BPH</td>
</tr>
</tbody>
</table>
## Harms of Septal Reduction Therapy

<table>
<thead>
<tr>
<th></th>
<th>Septal Ablation</th>
<th>Myectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peri-Procedural Adverse Arrhythmic Events (VT and VF), %</td>
<td>2.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Peri-Procedural Mortality (&lt;30 Days), %, Weighted Mean (95% CI)</td>
<td>1.3 (0.7-1.8)</td>
<td>2.5 (1.4-3.6)</td>
</tr>
</tbody>
</table>

New pacemaker requirement – 4.4% for surgical myectomy and 10.0% for septal ablation
Reintervention – 1.6% for myectomy and 7.7% for septal ablation
Among studies after 2000, periprocedural mortality was no different for myectomy vs. septal ablation (1.1% vs. 1.3%, p=0.75)
Unpublished and Ongoing Trials

• 5-year long-term extension study (MAVA-LTE)

• Of 49 patients with a week 48 assessment, 71% improved by at least 1 NYHA class

Rader et al. ACC 2021
Disagreements about importance of decreased LVEF – longer term follow-up data is likely to address this. One patient in REDWOOD-HCM (a trial of aficamten) had decreased LVEF – data presented a few weeks ago.

More than 90% of patients in EXPLORER were white – concerns about representativeness.

No trials in key comparisons with septal reduction or disopyramide.

Discordance between imaging data in EXPLORER and patient-reported outcomes – durability of treatment effect of mavacamten is unclear.

Likely strong patient preference dependence of therapy options (small risk of death with procedures a/w larger treatment benefit).
Potential Other Benefits and Contextual Considerations

• Patients with symptomatic HOCM are often at stage of lives when making decisions about families, careers, education

• Patient perspective about fear of death and unpredictability of symptoms – effects on relationships and career decisions

• Caregivers report needing to take time off from work, causing financial stress

• Mavacamten could provide more access to treatment options (although unclear if will be prescribed only at specialized centers)
Public Comments Received

• Gaps in data, particularly regarding comparisons of mavacamten to disopyramide and septal reduction procedures

• Importance of critical appraisal of data from trial populations

• Safety of initiation of disopyramide at home?
Summary

• Relative to usual care, mavacamten improves patient reported outcome (KCCQ), clinician-estimated functional status (NYHA), as well as objective physiological parameter (peak V0₂), concordant with mechanism (LVOT gradient)

• Trials have not been performed to compare mavacamten versus disopyramide, but evidence for disopyramide is relatively weak

• Trials have not been performed to compare mavacamten to septal reduction procedures – these decisions will likely be preference-sensitive
### ICER Evidence Ratings

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Comparator</th>
<th>ICER Evidence Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mavacamten Plus Usual Care</td>
<td>Usual care alone</td>
<td>P/I</td>
</tr>
<tr>
<td>Mavacamten Plus Usual Care</td>
<td>Disopyramide</td>
<td>P/I</td>
</tr>
<tr>
<td>Mavacamten Plus Usual Care</td>
<td>Septal reduction therapies</td>
<td>No rating</td>
</tr>
</tbody>
</table>

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.
Questions
Presentation of the Economic Model

Surrey M. Walton, PhD, MA
Professor, Pharmacy Systems, Outcomes, and Policy
Assistant Director, Center for Pharmacoepidemiology and Pharmacoeconomic Research
University of Illinois at Chicago College of Pharmacy
Key Review Team Members

• Jyotirmoy Sarker, MPharm, MBA, MBiotech, Graduate Student, Pharmacy Systems, Outcomes, and Policy, University of Illinois at Chicago

• Melanie D. Whittington, PhD, Associate Director of Health Economics, ICER

Disclosures:

Financial support was provided to the University of Illinois at Chicago from ICER.

University of Illinois at Chicago researchers have 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 cost effectiveness of mavacamten and standard of care compared with standard of care as well as disopyramide, myectomy, and septal ablation each with standard of care
Methods in Brief
Methods Overview

• **Model**: Semi Markov model

• **Setting**: United States

• **Perspective**: Health care sector perspective

• **Time Horizon**: Patient lifetime

• **Discount Rate**: 3% per year (costs and outcomes)

• **Cycle Length**: 4 weeks

• **Primary Outcomes**: Cost per QALY gained; cost per LY gained, cost per evLY gained, cost per NYHA I year gained
Model Schematic
Population Characteristics

- US patients with HOCM
  - Starting age: 58
  - 41% female
Key Model Assumptions

- Placeholder price of mavacamten: $75,000 per year
- Patient utilities are estimated via NYHA class
- Mortality is the same across all NYHA classes
- Discontinuation is not considered in the model

- For mavacamten and standard of care, treatment effect extrapolated for 8 cycles (32 weeks) based on EXPLORER trial data. After 8 cycles, proportion of live patients in different NYHA classes are held constant

- Proportion of patients in different NYHA classes in myectomy, septal ablation, and disopyramide arms held constant after applying a literature-based treatment effect in cycle 1
### Key Model Inputs: Treatment Effects

#### Treatment Effect of Mavacamten

<table>
<thead>
<tr>
<th></th>
<th>NYHA I</th>
<th>NYHA II</th>
<th>NYHA III</th>
<th>NYHA IV</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>0%</td>
<td>71.5%</td>
<td>28.5%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Week 14</strong></td>
<td>31.7%</td>
<td>55.3%</td>
<td>3.3%</td>
<td>0%</td>
<td>9.8%</td>
</tr>
<tr>
<td><strong>Week 30</strong></td>
<td>49.6%</td>
<td>42.3%</td>
<td>6.5%</td>
<td>0%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

#### Model Input

<table>
<thead>
<tr>
<th></th>
<th>NYHA I</th>
<th>NYHA II</th>
<th>NYHA III/IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>0%</td>
<td>71.5%</td>
<td>28.5%</td>
</tr>
<tr>
<td><strong>Cycle 4 (Week 16)</strong></td>
<td>36.85%</td>
<td>59.28%</td>
<td>3.87%</td>
</tr>
<tr>
<td><strong>Cycle 8 (Week 32)</strong></td>
<td>52.11%</td>
<td>40.78%</td>
<td>7.11%</td>
</tr>
</tbody>
</table>

Key Model Inputs: Treatment Effects

Treatment Effect of Standard of Care

<table>
<thead>
<tr>
<th></th>
<th>NYHA I</th>
<th>NYHA II</th>
<th>NYHA III</th>
<th>NYHA IV</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0%</td>
<td>74.2%</td>
<td>25.8%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Week 14</td>
<td>16.4%</td>
<td>64.1%</td>
<td>14.8%</td>
<td>0%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Week 30</td>
<td>21.1%</td>
<td>57.8%</td>
<td>19.5%</td>
<td>0%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

Model Input

<table>
<thead>
<tr>
<th></th>
<th>NYHA I</th>
<th>NYHA II</th>
<th>NYHA III/IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0%</td>
<td>74.2%</td>
<td>25.8%</td>
</tr>
<tr>
<td>Cycle 4 (Week 16)</td>
<td>18.22%</td>
<td>66.28%</td>
<td>15.50%</td>
</tr>
<tr>
<td>Cycle 8 (Week 32)</td>
<td>20.31%</td>
<td>57.96%</td>
<td>21.73%</td>
</tr>
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</table>

# Key Model Inputs: Treatment Effects

## Treatment Effect of Septal Ablation and Myectomy

<table>
<thead>
<tr>
<th>Procedure</th>
<th>NYHA Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septal ablation</td>
<td>45</td>
</tr>
<tr>
<td>Myectomy</td>
<td>45</td>
</tr>
</tbody>
</table>


## Model Input

<table>
<thead>
<tr>
<th></th>
<th>Myectomy</th>
<th>Septal Ablation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NYHA I</td>
<td>NYHA II</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.00</td>
<td>0.72</td>
</tr>
<tr>
<td>Cycle 1</td>
<td>0.76</td>
<td>0.21</td>
</tr>
</tbody>
</table>
### Key Model Inputs: Mortality from Procedure

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myectomy</td>
<td>1.3%</td>
</tr>
<tr>
<td>Septal Ablation</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

Key Model Inputs: Treatment Effects

Treatment Effect of Disopyramide

<table>
<thead>
<tr>
<th></th>
<th>NYHA I</th>
<th>NYHA II</th>
<th>NYHA III/IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Evaluation</td>
<td>9</td>
<td>40</td>
<td>29</td>
</tr>
<tr>
<td>Follow-Up Evaluation</td>
<td>29</td>
<td>42</td>
<td>7</td>
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Model Input

<table>
<thead>
<tr>
<th></th>
<th>Mavacamten</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NYHA I</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.12</td>
</tr>
<tr>
<td>Cycle 1</td>
<td>0.28</td>
</tr>
</tbody>
</table>
### Key Model Inputs: Costs

<table>
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<tr>
<th>Treatment and Health States Costs</th>
<th>Costs</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per Year Cost of Mavacamten</td>
<td>$75,000</td>
<td>Placeholder price</td>
</tr>
<tr>
<td>Per Year Cost of Metoprolol</td>
<td>$834</td>
<td></td>
</tr>
<tr>
<td>Per Year Cost of Verapamil</td>
<td>$730</td>
<td>Red Book</td>
</tr>
<tr>
<td>Per Year Cost of Disopyramide</td>
<td>$5,384</td>
<td></td>
</tr>
<tr>
<td>Septal Ablation Procedure Cost</td>
<td>$55,706</td>
<td></td>
</tr>
<tr>
<td>NYHA I Health State Cost (Per Cycle)</td>
<td>$751</td>
<td>EXPLORER trial</td>
</tr>
<tr>
<td>NYHA III Health State Cost (Per Cycle)</td>
<td>$2,826</td>
<td></td>
</tr>
</tbody>
</table>
## Key Model Inputs: Utilities

### Quality of Life (QOL) Parameters for Mavacamten and Standard of Care

<table>
<thead>
<tr>
<th>QOL</th>
<th>Utility for Mavacamten</th>
<th>Utility for Standard of Care</th>
<th>Average Used for Comparators</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA Class I</td>
<td>0.950</td>
<td>0.952</td>
<td>0.951</td>
</tr>
<tr>
<td>NYHA Class II</td>
<td>0.866</td>
<td>0.850</td>
<td>0.858</td>
</tr>
<tr>
<td>NYHA Class III/IV</td>
<td>0.708</td>
<td>0.704</td>
<td>0.706</td>
</tr>
</tbody>
</table>

An average disutility by age of 0.0007 per year was applied, which reflects average utility decrement in the US.

---

## Key Model Inputs: Utilities

### Disutility from Procedure

<table>
<thead>
<tr>
<th>Source of Disutility</th>
<th>Disutility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disutility of Pacemaker (Both Septal Ablation and Myectomy Arm)—Lifetime</td>
<td>0.045(^1)</td>
</tr>
<tr>
<td>Disutility of Septal Ablation Procedure—One Cycle</td>
<td>0.041(^2)</td>
</tr>
<tr>
<td>Disutility of Myectomy Procedure—Six Cycles</td>
<td>0.086(^3)</td>
</tr>
</tbody>
</table>

*Disutility of MI
†Disutility of coronary artery bypass graft (CABG)

---


Results
# Base-Case Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total Drug Cost</th>
<th>Total Cost</th>
<th>QALYs</th>
<th>Life Years</th>
<th>NYHA I Years</th>
<th>evLY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mavacamten*†</td>
<td>$1,258,000</td>
<td>$1,568,000</td>
<td>14.75</td>
<td>16.58</td>
<td>8.50</td>
<td>14.75‡</td>
</tr>
<tr>
<td>Standard Treatment</td>
<td>$12,600</td>
<td>$434,000</td>
<td>13.78</td>
<td>16.58</td>
<td>3.33</td>
<td>13.78</td>
</tr>
<tr>
<td>Disopyramide*</td>
<td>$116,000</td>
<td>$509,000</td>
<td>14.06</td>
<td>16.58</td>
<td>4.69</td>
<td>14.06</td>
</tr>
<tr>
<td>Septal Ablation*</td>
<td>$67,800</td>
<td>$297,000</td>
<td>14.97</td>
<td>16.40</td>
<td>12.49</td>
<td>N/A</td>
</tr>
<tr>
<td>Myectomy*</td>
<td>$135,000</td>
<td>$364,000</td>
<td>14.97</td>
<td>16.37</td>
<td>12.47</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Each of these treatments includes use of standard first-line therapy
†Cost estimates for mavacamten were based on a placeholder price of $75,000 per year
‡evLY for mavacamten is calculated as compared to standard treatment
# Base-Case Incremental Results

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comparator</th>
<th>Cost per QALY Gained</th>
<th>Cost per Life Year Gained</th>
<th>Cost per evLY Gained</th>
<th>Cost per Additional NYHA I Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mavacamten</td>
<td>Standard treatment</td>
<td>$1,200,000</td>
<td>Undefined</td>
<td>$1,200,000</td>
<td>$219,000</td>
</tr>
<tr>
<td></td>
<td>Disopyramide</td>
<td>$1,500,000</td>
<td>Undefined</td>
<td>$1,500,000</td>
<td>$278,000</td>
</tr>
<tr>
<td></td>
<td>Myectomy</td>
<td>Dominated</td>
<td>$5,600,000</td>
<td>N/A†</td>
<td>Dominated</td>
</tr>
<tr>
<td></td>
<td>Septal ablation</td>
<td>Dominated</td>
<td>$7,000,000</td>
<td>N/A†</td>
<td>Dominated</td>
</tr>
</tbody>
</table>

*Incremental cost ratios are based on a placeholder price of $75,000 per year for mavacamten
†Incremental cost per evLY gained not applicable due to fewer lifetime QALYs for mavacamten as compared to myectomy and septal ablation
# One Way Sensitivity Analyses

## Mavacamten vs. Standard of Care Incremental Cost

<table>
<thead>
<tr>
<th>Model Input</th>
<th>$900,000</th>
<th>$1,000,000</th>
<th>$1,100,000</th>
<th>$1,200,000</th>
<th>$1,300,000</th>
<th>$1,400,000</th>
<th>$1,500,000</th>
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</thead>
<tbody>
<tr>
<td>Discount Rate for Cost</td>
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<td></td>
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<td></td>
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<tr>
<td>Mavacamten Treatment Effect</td>
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<tr>
<td>NYHA III Health State Cost</td>
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<tr>
<td>SoC Treatment Effect</td>
<td></td>
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</tr>
<tr>
<td>NYHA II Health State Cost</td>
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<tr>
<td>NYHA I Health State Cost</td>
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</tr>
<tr>
<td>Percent of Patients in Mavacamten Group Taking Metoprolol</td>
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<tr>
<td>Percent of Patients in SoC Group Taking Metoprolol</td>
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<tr>
<td>Percent of Patients in Mavacamten Group Taking Verapamil</td>
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<tr>
<td>Percent of Patients in SoC Group Taking Verapamil</td>
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</tbody>
</table>

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# One Way Sensitivity Analyses

## Mavacamten vs. Standard of Care Incremental QALY

<table>
<thead>
<tr>
<th>Model Input</th>
<th>-2.00</th>
<th>-1.50</th>
<th>-1.00</th>
<th>-0.50</th>
<th>0.00</th>
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<th>1.50</th>
<th>2.00</th>
<th>2.50</th>
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<tbody>
<tr>
<td>Utility of NYHA class 2 for SoC</td>
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<tr>
<td>Utility of NYHA class 1 for Mavacamten</td>
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<tr>
<td>Utility of NYHA class 2 for Mavacamten</td>
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<tr>
<td>Utility of NYHA class 1 for SoC</td>
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<tr>
<td>Utility of NYHA class 3 &amp; 4 for SoC</td>
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<tr>
<td>Discount rate for outcomes</td>
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</tr>
<tr>
<td>Mavacamten treatment effect</td>
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<tr>
<td>Utility of NYHA class 3 &amp; 4 for Mavacamten</td>
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</tr>
<tr>
<td>SoC treatment effect</td>
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</tr>
</tbody>
</table>

Lower QALY: Dark Green  
Upper QALY: Light Green
# Probabilistic Sensitivity Analysis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost-Effective at $50,000 per QALY</th>
<th>Cost-Effective at $100,000 per QALY</th>
<th>Cost-Effective at $150,000 per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mavacamten vs. Standard of Care</td>
<td>0.00%</td>
<td>0.00%</td>
<td>0.00%</td>
</tr>
</tbody>
</table>
## Scenario Analyses

### Incremental Cost-Effectiveness Ratios for Mavacamten in Scenario with Higher Mortality for NYHA Class III/IV

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Cost per QALY Gained</th>
<th>Cost per Life Year Gained</th>
<th>Cost per evLY Gained</th>
<th>Cost per Additional NYHA I Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Treatment</td>
<td>$893,000</td>
<td>$2,600,000</td>
<td>$693,000</td>
<td>$219,000</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>$1,100,000</td>
<td>$3,100,000</td>
<td>$874,000</td>
<td>$279,000</td>
</tr>
<tr>
<td>Myectomy</td>
<td>Dominated</td>
<td>$15,800,000</td>
<td>N/A</td>
<td>Dominated</td>
</tr>
<tr>
<td>Septal Ablation</td>
<td>Dominated</td>
<td>$29,900,000</td>
<td>N/A</td>
<td>Dominated</td>
</tr>
</tbody>
</table>
## Scenario Analyses

### Scenario Analysis with Employability Gain Assumptions

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Cost per QALY Gained</th>
<th>Cost per Life Year Gained</th>
<th>Cost per evLY Gained</th>
<th>Cost per Additional NYHA I Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full Employment for NYHA I and Not for Class II and III/IV (Both Mavacamten and Standard Treatment Group)</td>
<td>$876,000</td>
<td>N/A</td>
<td>$876,000</td>
<td>$165,000</td>
</tr>
<tr>
<td>Full Employment for All Patients in Mavacamten Group and Not for Standard Treatment Group</td>
<td>$242,000</td>
<td>N/A</td>
<td>$242,000</td>
<td>$46,000</td>
</tr>
</tbody>
</table>
Limitations

• Model results are based on a placeholder price for mavacamten

• Absence of long-term data on treatment efficacy (30 weeks trial length)

• Lack of evidence from direct comparison with myectomy, septal ablation, and disopyramide (also, insufficient data to conduct NMA)

• The utility scores are from the EXPLORER trial

• The evidence for myectomy, septal ablation, and disopyramide comes from observational studies

• Absence of data on actual societal costs of HOCM (the modified societal perspective scenarios are based on assumptions of productivity gain)

• Heterogeneity in HOCM patients not addressed in the model
Comments Received

• NYHA classes do not capture day to day utility adequately
• A societal perspective should have been used
• NYHA classes are related to mortality
• There is variability by gender and race in patient outcomes
• The model does not include discontinuation and adverse events
Conclusions

• Actual cost effectiveness of mavacamten will depend on its price

• At placeholder price, incremental cost per QALY of mavacamten and standard of care vs. standard of care is well beyond standard threshold levels

• When compared with disopyramide, the incremental cost per QALY is even higher

• At the placeholder price, mavacamten is dominated by myectomy and septal ablation

• Sensitivity and scenario analysis suggests findings are robust at the placeholder price
Questions
Manufacturer Public Comment and Discussion
John Whang, MD, FACC
Vice President, US Medical, Bristol Myers Squibb

Conflicts of Interest:

• Dr. Whang is a full-time employee of Bristol Myers Squibb.
Public Comment and Discussion
Conflicts of Interest:

- Billur T. Dowse has collaborated with the Hypertrophic Cardiomyopathy Association, which receives 20% of its sponsorship for educational programming from Bristol Myers Squibb/MyoKardia.
Gwen Mayes, JD, MMSc
Patient Advocate, Founder and Chief Concept Officer, GwenCo Health

Conflicts of Interest:

- Gwen Mayes serves as a consultant to the Hypertrophic Cardiomyopathy Association, which receives 20% of its sponsorship for educational programming from Bristol Myers Squibb/MyoKardia. She also consults for Edwards Lifesciences, Paragonix, and Natural Cycles.
Conflicts of Interest:

• No financial conflicts of interest to disclose.
Conflicts of Interest:

- No financial conflicts of interest to disclose.
Lisa Salberg
Founder & CEO, Hypertrophic Cardiomyopathy Association

Conflicts of Interest:

• The Hypertrophic Cardiomyopathy Association receives 20% of its sponsorship for educational programming from Bristol Myers Squibb/MyoKardia.
Break

Meeting will resume at 11:25 am
Voting Questions
Patient Population for all questions: Adults with symptomatic hypertrophic obstructive cardiomyopathy (HOCM) on background therapy with beta blockers and/or calcium channel blockers.
Clinical Evidence
1. Is the currently available evidence adequate to demonstrate that the net health benefit of mavacamten added to background therapy is superior to that provided by background therapy alone?

A. Yes

B. No
2. Is the currently available evidence adequate to demonstrate that the net health benefit of **mavacamten** is superior to that provided by **disopyramide**?

A. Yes

B. No
Contextual Considerations and Potential Other Benefits or Disadvantages
When making judgments of overall long-term value for money, what is the relative priority that should be given to *any* effective treatment for HOCM on the basis of the following contextual considerations:
3. Acuteness of need for treatment of individual patients based on the short-term risk of death or progression to permanent disability

A. Very low priority
B. Low priority
C. Average priority
D. High priority
E. Very high priority
4. Magnitude of the lifetime impact on individual patients of the condition being treated

A. Very low priority
B. Low priority
C. Average priority
D. High priority
E. Very high priority
5. Other (as relevant)

A. Very low priority
B. Low priority
C. Average priority
D. High priority
E. Very high priority
What are the effects of mavacamten on the following outcomes that inform judgment of the overall long-term value for money of mavacamten?
6. Patients’ ability to achieve major life goals related to education, work, or family life

A. Major negative effect
B. Minor negative effect
C. No difference
D. Minor positive effect
E. Major positive effect
7. Caregivers’ quality of life and/or ability to achieve major life goals related to education, work, or family life

A. Major negative effect
B. Minor negative effect
C. No difference
D. Minor positive effect
E. Major positive effect
8. Patients’ ability to manage and sustain treatment given the complexity of regimen

A. Major negative effect
B. Minor negative effect
C. No difference
D. Minor positive effect
E. Major positive effect
9. Society’s goal of reducing health inequities

A. Major negative effect
B. Minor negative effect
C. No difference
D. Minor positive effect
E. Major positive effect
10. Opportunity to improve access to treatment

A. Major negative effect
B. Minor negative effect
C. No difference
D. Minor positive effect
E. Major positive effect
11. Availability of a treatment with different timing and types of risks and benefits, relative to existing procedural and surgical options

A. Major negative effect
B. Minor negative effect
C. No difference
D. Minor positive effect
E. Major positive effect
12. Other (as relevant)

A. Major negative effect
B. Minor negative effect
C. No difference
D. Minor positive effect
E. Major positive effect
Lunch

Meeting will resume at 1:00pm
Policy Roundtable
## Policy Roundtable

<table>
<thead>
<tr>
<th>Policy Roundtable Participant</th>
<th>Conflict of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Milind Desai, MD, MBA</strong>, Director of Clinical Operations, Hypertrophic Cardiomyopathy Center, Cleveland Clinic</td>
<td>Dr. Desai serves as an investigator for the VALOR study of mavacamten sponsored by Bristol Myers Squibb/MyoKardia.</td>
</tr>
<tr>
<td><strong>Martin Maron, MD</strong>, Director, Hypertrophic Cardiomyopathy Center and Research Institute, Tufts Medical Center</td>
<td>Dr. Maron served as a site investigator for a Phase I study of mavacamten and currently serves as a steering committee member for a Phase II study of a second-generation myosin inhibitor sponsored by Cytokinetics.</td>
</tr>
<tr>
<td><strong>Gwendolyn Mayes, JD, MMSc</strong>, Founder and Chief Concept Officer, GwenCo Health</td>
<td>Gwendolyn Mayes serves as a consultant to the Hypertrophic Cardiomyopathy Association, which receives 20% of its sponsorship for educational programming from Bristol Myers Squibb/MyoKardia. She also consults for cardiac device companies, including Edwards Lifesciences and Paragonix.</td>
</tr>
<tr>
<td><strong>Carla McSpadden, RPh, BCGP, MBA</strong>, Director, Clinical Formulary Strategies, Humana</td>
<td>Carla McSpadden is a full-time employee of Humana.</td>
</tr>
<tr>
<td><strong>Lisa Salberg</strong>, Founder and CEO, Hypertrophic Cardiomyopathy Association</td>
<td>The Hypertrophic Cardiomyopathy Association receives 20% of its sponsorship for educational programming from Bristol Myers Squibb/MyoKardia.</td>
</tr>
<tr>
<td><strong>John Watkins, PharmD, MPH, BCPS</strong>, Residency Program Director, Premera Blue Cross</td>
<td>John Watkins is a full-time employee of Premera Blue Cross.</td>
</tr>
</tbody>
</table>
Next Steps

- Meeting recording posted to ICER website next week

- Final Report published on or around November 16, 2021
  - Includes description of CTAF votes, deliberation, policy roundtable discussion

Adjourn