Clinical Value of Mavacamten in Symptomatic Obstructive Hypertrophic Cardiomyopathy:

APRIL 29, 2021
Introduction

Bristol Myers Squibb (BMS) acknowledges the importance of fully and accurately understanding the value that innovative therapies provide to patients, and we appreciate the opportunity to comment on the Institute for Clinical and Economic Review’s (ICER) draft scoping document for “Mavacamten for Hypertrophic Cardiomyopathy.” At BMS, our mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. Developing medicines that have the potential to be transformational, like mavacamten, is key to our vision: to transform patients’ lives through science. If approved by the Food and Drug Administration, mavacamten will be a first-in-class cardiovascular medicine for the treatment of symptomatic obstructive hypertrophic cardiomyopathy—a chronic heart disease for which no current targeted treatment options exist.

At the same time, BMS recognizes that value assessment reviews in the early stages of a medicine’s lifecycle, prior to approval by the FDA, present a number of challenges given the fast-evolving body of scientific evidence. The FDA has granted a Prescription Drug User Fee Act target or action date for mavacamten of January 28, 2022.1

We recommend that ICER’s review and model focus on patients with symptomatic obstructive hypertrophic cardiomyopathy who remain symptomatic and/or functionally limited when receiving currently available treatments. In this document, we emphasize the key elements underpinning the clinical value of mavacamten for the treatment of patients with symptomatic obstructive hypertrophic cardiomyopathy who represent a clinically distinct patient population with a substantial unmet clinical need.

Disease and prevalence

Cardiomyopathies are defined as structural and functional abnormalities of the heart muscle despite the absence of typical causes such as hypertension, coronary artery disease, or valvular disease that are sufficiently severe to justify such a defect.2, 3 Hypertrophic cardiomyopathy is a type of cardiomyopathy, of which symptomatic obstructive hypertrophic cardiomyopathy is a distinct and specific sub-group.

Patients with symptomatic obstructive hypertrophic cardiomyopathy experience dysfunction of the contractile unit of the heart known as the sarcomere, leading to remodeling and a subsequent worsening of cardiac function.2 The hallmark of symptomatic obstructive hypertrophic cardiomyopathy is a pathologic thickening of the heart muscle of the left ventricle2 that may limit and even block the ability of the left ventricle to pump blood to the rest of the body.3, 4 Often a progressive disease,5 symptomatic obstructive hypertrophic cardiomyopathy can be debilitating and life-changing for patients, leading to a reduced ability to function day-to-day, with symptoms limiting even routine daily activities, and impaired health-related quality of life.3, 6

Based on the assumption that 70% of patients diagnosed with hypertrophic cardiomyopathy in United States have obstructive disease,7 of which 40–60% of patients are estimated to be
symptomatic, the approximate prevalence of diagnosed symptomatic obstructive hypertrophic cardiomyopathy, based on publicly available data, is ~0.8-1.3 per 10,000 people in the United States.

The patient burden is daily

The burden of symptomatic obstructive hypertrophic cardiomyopathy is ever-present in affected patients. Symptoms include shortness of breath, fatigue, exercise intolerance, palpitations, and fainting. Simple activities of day-to-day life such as ironing, cleaning, and personal care can leave the patient exhausted for days. Priscilla, a patient interviewed as part of the Public Patient-Focused Drug Development Meeting notes that “taking a shower, a flight of stairs, and walking from my car to a building was a challenge. I would have palpitations, dizziness, chest pain, and I felt tired all the time.” These symptoms were shared by more than half of those interviewed. This takes an emotional and physical toll on the patient, which can manifest in chronic anxiety, depression, isolation, failed relationships, and lost employment opportunities.

Limitations of current therapy and unmet need

Effective treatment options for symptomatic obstructive hypertrophic cardiomyopathy are limited. Currently prescribed medications are predominantly symptom-focused with no evidence to suggest that they change or delay disease progression, and at present, there are no available therapies for patients with symptomatic obstructive hypertrophic cardiomyopathy that target the underlying pathophysiology of the disease.

Medications originally developed for other cardiovascular disorders, such as beta blockers, calcium channel blockers, and disopyramide, have been used to treat this patient population with the goal of reducing symptoms. An estimated 90% of patients with symptomatic obstructive hypertrophic cardiomyopathy take at least one of these medications with varying degrees of tolerability and symptom relief. Invasive and costly surgical intervention can be the next and final option for patients whose symptoms cannot be controlled by pharmacological intervention. Thus, these patients represent a population with a substantial unmet need for novel disease-specific therapies that not only improve their daily life but can also alter disease progression and mitigate the need for invasive surgical intervention.

The value of mavacamten

Mavacamten, which will potentially be the first drug in a new therapeutic class called myosin inhibitors, was designed to specifically target excess myosin-actin cross-bridging formation, the underlying cause of hypertrophic cardiomyopathy (and therefore, symptomatic obstructive hypertrophic cardiomyopathy). This strategy has been validated in both clinical and preclinical studies, which showed improvements in the structure and function of the heart with mavacamten, leading to improvements in symptoms, exercise capacity, and health status.
EXPLORER-HCM, the key mavacamten trial in patients with symptomatic obstructive hypertrophic cardiomyopathy, was the largest phase 3 randomized controlled trial in this clinical population to date. Study patients, like those in real-world clinical practice, were symptomatic (New York Heart Association [NYHA] Class II-III) at study entry and obstructed with left ventricular outflow gradients >50 mmHg despite the majority receiving beta blockers or calcium channel blockers.

EXPLORER-HCM met its primary endpoint, a trial-specific composite of functional capacity — (peak VO₂ [pVO₂] from cardio-pulmonary exercise testing) and symptom-based (NYHA) measures. EXPLORER-HCM demonstrated that, compared with placebo, the cohort of patients treated with mavacamten showed statistically significant and clinically meaningful benefit in the pre-specified primary and secondary outcomes (Appendix 1). The reduction of left ventricular obstruction with mavacamten was so substantial that over half of patients reduced their post-exercise gradient below 30 mmHg, the level defined by the American Heart Association/American College of Cardiology guideline as obstructive hypertrophic cardiomyopathy. Furthermore, more than a quarter of patients had gradient resolution under rest and provoked conditions below 30 mmHg, and had complete resolution of symptoms per the achievement of NYHA Class I (no limitation of physical activity). Additionally, patient-reported outcome assessments using the Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score and the novel Hypertrophic Cardiomyopathy Symptom Questionnaire-Shortness of Breath Score, specifically designed to evaluate symptomatic burden in patients with hypertrophic cardiomyopathy, showed a favorable effect of mavacamten on subjective wellbeing. This highlights the potential for mavacamten to not only alleviate patient-relevant disease symptoms such as shortness of breath, but for many patients, it may also alter the course of the underlying disease itself. Further evidence from EXPLORER-HCM showed improvement of independent predictors of morbidity and mortality such as pVO₂, cardiac remodeling, and reduction in serum biomarkers of cardiac wall stress and injury with mavacamten treatment in some patients.

Mavacamten has a safety and tolerability profile similar to placebo (Appendix 2). As expected with its mechanism of action, changes in baseline systolic function associated with mavacamten were small (i.e., the mean reduction in LVEF was -3.9% compared to -0.01% with placebo). Dosing was optimized to the individual based on their pharmacodynamic response. Overall, nine patients (mavacamten, n=7; placebo, n=2) had a transient decrease in left ventricular ejection fraction (LVEF) to less than 50% and protocol-driven temporary discontinuation of treatment less than 50% occurred in 5 patients (mavacamten, n=3; placebo, n=2) during the 30-week treatment period (median LVEF: 48%, range 35–49% among the 9 patients). LVEF normalized in all patients, and they resumed treatment and completed the study.

EXPLORER-HCM demonstrates the clinical value of using a disease-specific therapy approach in patients with a high unmet need currently managed by suboptimal or poorly tolerated pharmacological options recommended by treatment guidelines. The potential value of mavacamten has been recognized by the FDA who, in March 2021, accepted a New Drug Application for mavacamten use in patients with symptomatic obstructive hypertrophic cardiomyopathy based on evidence from EXPLORER-HCM.
## Appendix 1. Summary of efficacy outcomes from EXPLORER-HCM

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Change from baseline to week 30</th>
<th>Mavacamten</th>
<th>Placebo</th>
<th>Difference (95% CI; p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA improved by ≥ 1 class, n (%)</td>
<td>80 (65)</td>
<td>n=123</td>
<td>40 (31)</td>
<td>34 (22 to 45; p&lt;0.0001)</td>
</tr>
<tr>
<td>KCCQ-CSS, mean (SD)</td>
<td>+13.6 (14.4)</td>
<td>n=92</td>
<td>+4.2 (13.7)</td>
<td>+9.1 (5.5 to 12.7; p&lt;0.0001)</td>
</tr>
<tr>
<td>HCMSQ-SoB score, mean (SD)</td>
<td>−2.8 (2.7)</td>
<td>n=85</td>
<td>−0.9 (2.4)</td>
<td>−1.8 (−2.4 to −1.2; p&lt;0.0001)</td>
</tr>
<tr>
<td><strong>Function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO2 mL/kg/min, mean (SD)</td>
<td>1.4 (3.1)</td>
<td>n=120</td>
<td>−0.1 (3.0)</td>
<td>1.4 (0.6 to 2.1; p=0.0006)</td>
</tr>
<tr>
<td><strong>Cardiac Imaging</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>LAVI max, mL/m², mean (SD)</td>
<td>A greater reduction in maximum LAVI was observed with mavacamten (n=17) versus placebo (n=18)</td>
<td>−10.3 (−16.0 to −4.6; p=0.0004)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVMI, g/m², mean (SD)</td>
<td>−17.4 (12.1)</td>
<td>n=17</td>
<td>−1.6 (7.4)</td>
<td>−15.8 (−22.6 to −9.0; p&lt;0.0001)</td>
</tr>
<tr>
<td>Post-exercise LVOT peak gradient mmHg, mean (SD)</td>
<td>−47 (40)</td>
<td>n=117</td>
<td>−10 (30)</td>
<td>−35.6 (−43.2 to −28.1; p&lt;0.0001)</td>
</tr>
<tr>
<td><strong>Biomarkers</strong></td>
<td></td>
<td></td>
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<tr>
<td>NT-proBNP, ng/L</td>
<td>At week 30, the reduction in baseline NT-proBNP after mavacamten treatment (n=119) was 80% greater than for placebo (n=123; proportion of geometric mean ratio between the two groups, 0.202, 95% CI: 0.169 to 0.241).</td>
<td></td>
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<tr>
<td>hs-cTnI, ng/L</td>
<td>At week 30, the reduction in hs-cTnI was 41% greater for mavacamten (n=115) than for placebo (n=115; proportion of geometric mean ratio between the two groups, 0.589, 95% CI: 0.500 to 0.693).</td>
<td></td>
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</tr>
</tbody>
</table>

*Positive change is better. Negative change is better. CI, confidence interval; HCMSQ-SoB, Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath subscore; Hs-cTnI, high sensitivity cardiac troponin; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LAVI, left atrial volume index; LVMI, left ventricular mass index; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; pVO2, peak oxygen consumption; SD, standard deviation.
### Appendix 2. Summary of safety outcomes from EXPLORER-HCM¹⁴

<table>
<thead>
<tr>
<th>Event</th>
<th>Mavacamten group (n=123)</th>
<th>Placebo group (n=128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥1 treatment-emergent adverse event</td>
<td>108 (88%)</td>
<td>101 (79%)</td>
</tr>
<tr>
<td>Total number of serious adverse events</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>Patients with ≥1 serious adverse event</td>
<td>10 (8%)</td>
<td>11 (9%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2 (2%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Stress cardiomyopathy</td>
<td>2 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Sudden death</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Transient ischaemic attack</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Cardiac failure congestive</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Viral gastroenteritis</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>0</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Infection</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Contusion</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Forearm fracture</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Dehydration</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Vocal cord polyp</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Cholesteatoma</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

Data are n (%)
Sincerely,

Mitch Higashi, PhD
Vice President | Head Worldwide HEOR, Markets – US

John Whang, MD, FACC
Vice President | US Medical, Cardiovascular & Established Brands

Sandra Ibrahim, Pharm.D.
Director | Worldwide Scientific Content & US Market Capabilities, Cardiovascular
References


April 29, 2021

Institute for Clinical and Economic Review
2 Liberty Square, 9th Floor
Boston, MA 02109
Submitted Electronically: publiccomments@icer-review.org
Subject: Public Comments on Draft Scoping Document – Mavacamten

Dear Review Committee,

Thank you for the opportunity to provide feedback to ICER on its draft scoping document for comparative clinical effectiveness and value of mavacamten for hypertrophic cardiomyopathy. We appreciate your willingness to review comments and recommendations from the National Forum’s Value & Access Steering Committee and partners working on these issues.

The Value & Access Steering Committee and partners jointly offer the following feedback for ICER’s consideration in the development of the revised scoping document.

**Recommendations:**

**Population:**
- Focus on patients for whom there are data. The population studied in clinical trials were symptomatic HOCM patients who remained symptomatic despite treatment.

**Outcomes:**
- Revise “exercise restriction” to “exertional tolerance” or “capacity”
- Include measures that matter to HOCM patients, such as the characteristics captured in quality-of-life assessments such as the Kansas City Cardiomyopathy Questionnaire (KCCQ) or the Minnesota Living with Heart Failure Questionnaire.
  - Additional key symptoms and HOCM patient impacts[^1^], such as:
    - Tiredness
    - Shortness of breath with physical activity
    - Dizziness/light-headedness
    - Chest pain
    - Chest pain with physical exertion
    - Palpitations
    - Limitations on physical activities
    - Emotional impacts (anxiety, depression)
    - Impacts on work

- Evaluate lifestyle factors:

[^1^]: Additional key symptoms and HOCM patient impacts.
HOCM is a condition that affects every patient differently. Due to this variability, we suggest looking as broadly as possible at lifestyle factors, including those highlighted in “The Voice of the Patient Report for Hypertrophic Cardiomyopathy (HCM): Proceedings from an Externally Led Public Patient-Focused Drug Development (PFDD) Meeting Corresponding to the FDA’s Patient-Focused Drug Development Meeting.”

- Include measures such as:
  - Drop in gradient across the left ventricular outflow tract
  - Improvement in shortness of breath
  - Improvement in New York Heart Association (NYHA) class

- For future consideration:
  - Once properly diagnosed, patients with HOCM face life-long management of the condition. As patients are being identified earlier and younger, we suggest looking at evidence examining the impact on children and teens with HOCM.

Again, thank you for your consideration. We look forward to reviewing and providing additional comments throughout the review process.

Sincerely,

Members of the Value & Access Steering Committee and Partners representing the following organizations:

National Forum for Heart Disease & Stroke Prevention (convener)
American Association of Heart Failure Nurses
American College of Cardiology
American Heart Association
American Pharmacists Association Foundation
American Society for Preventive Cardiology
Association of Black Cardiologists
Association of State and Territorial Health Officials
BallengeRx Consulting
Global Healthy Living Foundation
Hypertrophic Cardiomyopathy Association
Independent Health
Institute for Patient Access
Mended Hearts
National Alliance of Healthcare Purchaser Coalitions
Partnership to Advance Cardiovascular Health
Partnership to Improve Patient Care
Preventive Cardiovascular Nurses Association
University of Michigan Center for Value-Based Insurance Design
WomenHeart

April 29, 2021

Institute for Clinical and Economic Review
Submitted Electronically: publiccomments@icer-review.org

Subject: Public Comments on Draft Scoping Document – Mavacamten

Dear Review Committee,

The Hypertrophic Cardiomyopathy Association (HCMA) appreciates the opportunity to provide feedback the draft scoping document for comparative clinical effectiveness and value of mavacamten for hypertrophic cardiomyopathy with obstruction (HOCM). HCMA is a non-profit, 501(c)3 patient advocacy organization representing 15,000+ families living HCM spectrum disorders including HOCM. Founded in 1996, the vision of the organization is to be the pre-eminent organization improving the lives of those with HCM, preventing untimely deaths, and advancing global understanding.

Of importance, HCMA hosted an Externally Led Patient Focus Drug Development meeting in June 2020 to identify the burden of disease and patients’ reactions to current and future treatment modalities. We encourage ICER to review the Voice of the Patient Report and a video recording of the meeting on its website at [www.4hcm.org](http://www.4hcm.org) for further guidance. HCMA respectively submits the following comments and recommendations:

**The Scope of the Clinical Evidence Review should be broadly assessed.** It is estimated that 1:500 Americans live with an HCM spectrum disorder and new data suggests estimates closer to 1:200. When first identified in the late 1950’s HCM was thought to be a deadly diagnosis, over the following five decades improvements in care made it a less grim diagnosis. Early diagnosis, advancements in treatments, and the development of specialized HCMA recognized Centers of Excellence (COEs) have lessened the mortality rate and provided a range of treatment options. HCMA recommends that the experiences of COEs are given high priority to determine the full scope of the clinical presentation and care of HCM. A common struggle of HCM patients is the delay in diagnosis and misdiagnosis, both of which add burdens in the development of unnecessary testing, lack of prompt attention to symptoms, risk factors, inappropriate drug therapies, and overall challenges to proper disease management. HCMA recommends that ICER refer to the recently issued 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients with Hypertrophic Cardiomyopathy for the most timely and comprehensive description of the patient population, clinical presentation, and treatment.

**The Interventions and Comparators need to be clearly defined.** The draft scoping document refers to both as they relate to “usual care alone” and while reference is made to the similarities with the Phase III clinical trial for mavacamten, the trial was limited to only 2 underlying drug therapies and did not include other drugs (Norpace, Ranolozine, Sotalol or a combination of beta blockers and calcium channel blockers), interventions (alcohol septal ablation), or surgeries (myectomy). The variability of HCM patient experience and their symptoms necessitates a clear
understanding of the population characteristics, current treatments, and interventions to be included for an accurate review. Some patients have minimal symptoms; however more commonly, others are mild to debilitating lasting weeks or months and can shorten life expectancies even when on current therapies. In total, it is fair to say there is no one pathway to care as each patient progresses, advances, digresses, and experiences a unique course even once diagnosed and treated. These patients do not fit the typical mold of a “heart failure” patient (see below. A better understanding of how ICER will account for this degree of variability is needed in the scoping document.

**Patient-Important Outcomes should include considerations of side effects and interactions of non-specific drugs unstudied or unintended for use in HCM patients.** As ICER has noted, mavacamten is a first-in-class medication that “addresses the underlying disease process.” As such, patients have lived upwards of six or seven decades on an ever-changing “cocktail” of pharmaceuticals that results in a trial-and-error approach to medical management that creates side effects or interactions of dire consequences. This creates excessive testing, potential organ failure, ongoing monitoring, and a potentially life-threatening uncertainty of the patient’s underlying severity of illness. More specifically, HCMA has identified 50 different drugs in 10 different categories (calcium channel blockers, sodium channel blockers, antiarrhythmics, beta blockers, etc.) actively in use by patients. HCMA recommends that the clinical evidence account for the broad range and variability of medications when reviewing patient-reported outcomes and their economic impact.

**Potential Other Benefits and Contextual Considerations should be reviewed equally.** HCM is a lifelong illness; there is no cure. While mavacamten offers hope for additional improvement, patients experience an incalculable emotional, psychological, and financial burden of living with a chronic health condition that can instantly alter their life and the life of those around them. This results to chronic anxiety, PTSD, depression, isolation, failed relationships, and lost job opportunities. Critical decision points such as career and marital decisions, where to go to school, whether to have children, securing disability, retaining insurance, remaining financially secure, and where to live are dependent not only on the patient’s needs, but the ability of those around them to assist in their care and support. Budgeting for HCM care, which for many, includes traveling over 50 miles and lodging for multiple family members. Co-pays, deductibles, and medication costs can often place enormous barriers to access to care. This remains critical throughout the patient’s life and should be considered equally important in ICER’s evaluation at clinical data and reviewed with robust attention to the lifetime burden.

**The Comparative Value Analysis should reflect the lifetime cost of the patient’s journey, refrain from strict comparisons to heart failure patients, and include the compounded cost burden of managing multiple family members with HCM.**

Any economic model should include the full patient journey starting from the time of diagnosis, including events, treatments, and interventions that take place during the life of the patient as well as the quality-of-life impact on the patient, taking into consideration families with more than one member who is HCM positive. This includes the impact on earning potential, buying power, and productivity. As stated above, the emotional and psychological toll of HCM is extensive; costs associated with mental health treatments, antidepressants, cognitive therapies,
and counseling are obvious interventions to include. This is compounded in families with multiple members with HCM and this compounding effect should be studied beyond simply multiplying the individual burden by the number of HCM family members affected.

Of importance, HCMA wishes to stress that comparisons to heart failure patients is misleading. HCM is the most common inheritable heart condition, yet symptoms and complications are highly variable and can change dramatically in one month. For example, patients can be in NYHA Class II for years and suddenly experience months of demise requiring multiple treatments (classified as Class III or IV) and revert to Class II. This cycle may repeat throughout a patient’s life. Acknowledging this non-linear, non-predictable course and how it will be reflected in “predetermined annual cycles” is essential. HCMA cautions ICER from relying heavily upon comparisons to heart failure patients as this will not adequately reflect the HCM population. HCMA recognizes ICER may utilize quality of life measurement tools such as the Kansas City Cardiomyopathy Questionnaire or the Minnesota Living with Heart Failure Questionnaire; however, HCMA strongly recommends that ICER do so with full acknowledgement that while these tools may provide valuable insights, they will not sufficiently match the experiences of HCM patients.

Any economic model should include the impact of direct medical costs including ongoing echocardiograms, EKG, genetic testing, Holter monitoring, stress tests, imaging, atrial fibrillation management, and related travel and lodging costs. To achieve mavacamten’s optimal dosing, requires multiple testing and monitoring and these costs should be considered. It is not uncommon for HCM patients to have a cadre of providers in multiple centers necessitating coordination of care, multiple appointments, duplicative testing, and out-of-pocket expenses for denied medical claims, all of which are condition-related care expenses. This is especially true if managed by both a local cardiologist and at a COE. Condition-related costs should also include lost wages, childcare, complex social needs, surrogate care, in-home nursing care, and household expenses to correct for loss of function or serious adverse events including early death.

Finally, HCMA recommends that ICER evaluate the cost-effectiveness of mavacamten against the cost of treatment in its absence for HOCM, e.g., Combination drug therapy, Norpace CR, septal myectomy, alcohol ablation, pacemaker or ICD, atrial fibrillation management, transplantation, and related costs of hospitalizations, rehabilitation, and post-procedural care.

The HCMA looks forward to working closely with ICER to ensure the patient’s real-world experience is included in your work and welcomes the opportunity to provide valuable data on the economic, symptom and diagnostic burden of HCM as is needed to refine the analysis. Please contact me should you have any questions at lisa@4hcm.org.

Sincerely,

Lisa Salberg
Lisa Salberg
Founder and CEO
Hypertrophic Cardiomyopathy Association
April 29, 2021

**Submitted electronically to:** publiccomments@icer-review.org

Steven D. Pearson, MD, President  
Institute for Clinical and Economic Review  
Two Liberty Square, Ninth Floor  
Boston, MA 02109

*Re: Scoping document for hypertrophic cardiomyopathy therapy*

Dear Dr. Pearson:

On behalf of the Institute for Patient Access, I thank you for the opportunity to provide comments regarding ICER’s scoping document titled “Mavacamten for Hypertrophic Cardiomyopathy,” dated April 8, 2021.

**About the Institute for Patient Access**

The Institute for Patient Access (IfPA) is a physician-led policy research organization dedicated to maintaining the primacy of the physician-patient relationship in the provision of quality health care. To further that mission, IfPA produces educational materials and programming designed to promote informed discussion about patient-centered care. IfPA was established in 2012 by the leadership of the Alliance for Patient Access, a national network of health care providers committed to shaping a patient-centered health care system. IfPA is a 501(c)(3) public charity nonprofit organization.

**Scoping Document Comments**

To ensure that the results of the forthcoming evidence report are applicable to the patient community, the mavacamten cost-effectiveness analysis should account for the following issues.

First, there are important differences between obstructive and non-obstructive hypertrophic cardiomyopathy. All hypertrophic cardiomyopathy patients report certain symptoms: fatigue, shortness of breath upon exertion, light-headedness, exercise intolerance, palpitations, dizziness after exertion, chest pain and fainting.¹ Patients living with obstructive hypertrophic cardiomyopathy, however, are more likely to report more of these symptoms, more severe symptoms and worsening symptoms after their diagnosis.² Patients with obstructive hypertrophic cardiomyopathy are also more likely to have symptoms that impact their ability to work. Since patients living with obstructive hypertrophic cardiomyopathy experience a greater number of

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² Ibid.
symptoms that are more severe and tend to worsen over time, an effective treatment for them will have greater value than an effective treatment for patients living with the non-obstructive form of the disease.

This conclusion is strengthened by the clinical costs associated with obstructive hypertrophic cardiomyopathy. According to one study, the average hospitalization cost for a patient diagnosed with the disease was $25,433, and the patient stayed in the hospital for an average of 4.9 days.\(^3\) Of note, these costs do not include the considerable expenditures many patients required after discharge.

These results are important with respect to mavacamten because the Food and Drug Administration is evaluating the medicine’s efficacy for adults with obstructive hypertrophic cardiomyopathy.\(^4\) Given the different burdens posed by the two different forms of the disease, and the intention of mavacamten to treat obstructive hypertrophic cardiomyopathy patients specifically, the evidence report should evaluate only the costs and benefits for patients with that form of the disease.

Second, according to the scoping document, the economic model will compare cost outcomes to patients with “related conditions such as heart failure.” While there are some common strategies, such as lifestyle changes, for treating heart disease regardless of the type, treatment options vary depending on the type of heart disease a patient has. Considering the important differences between heart failure and obstructive hypertrophic cardiomyopathy, the evidence report should not compare mavacamten’s cost effectiveness to that of treatment options for other types of heart disease.

Third, care should be taken when comparing the cost-effectiveness of mavacamten to “usual care” alone. The usual care that many patients experience is not ideal; it can entail invasive surgical procedures or medications aimed at treating symptoms of the disease rather than the cause. When comparing mavacamten to usual care, ICER economists should consider not just cost differences but also the significant potential improvements that mavacamten, as an oral therapy that treats the underlying cause of the disease, may offer patients.

Fourth, it is important that ICER adjusts the cost thresholds used in the analysis. The obstructive hypertrophic cardiomyopathy population is relatively small, but the patient burden from the disease, as measured in its financial costs and its impact on patients’ quality of life, is high. Without adjustment, the typical cost thresholds used by ICER will be biased against patients living with obstructive hypertrophic cardiomyopathy.

Fifth, the evidence report should account for the large non-health care costs imposed by the disease. As the Zaiser et al. (2020) study documented, obstructive hypertrophic cardiomyopathy meaningfully reduces patients’ quality of life and impacts patients’ ability to work. The

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\(^4\) https://clinicaltrials.gov/ct2/show/NCT03470545.
meaningful impact on patients’ ability to work means that, to the extent that mavacamten is efficacious, it will significantly reduce the non-health care costs that patients currently bear.

Some of these costs, such as patients’ improved ability to work or their ability to be more productive at work, will be easier to quantify. Other benefits, such as the improved ability to participate more fully in life without experiencing fatigue or dizziness, will be more difficult to quantify. For an accurate assessment of mavacamten, all potential benefits should be appropriately evaluated. Ignoring either type of cost in the evidence report will undervalue mavacamten and could inappropriately obstruct patients’ access to a drug that provides a net benefit.

Conclusion

An efficacious treatment that reduces the symptoms and risk factors associated with obstructive hypertrophic cardiomyopathy delivers great value to patients. Analyses that fail to consider all of the potential benefits, particularly the quality-of-life and productivity benefits, will undervalue this drug.

The evidence report will also undervalue mavacamten if it does not distinguish patients living with obstructive hypertrophic cardiomyopathy from those living with non-obstructive hypertrophic cardiomyopathy or heart failure. Conflating or combining these patient populations will lead to an understatement of the per-patient costs of this disease and, consequently, undervalue the benefits.

If IFPA can provide further detail or aid the Institute for Clinical and Economic Review in incorporating any of the above recommendations into its analysis, please contact us at 202-499-4114.

Sincerely,

Michelle M. D. Winokur, DrPH
Executive Director
April 29, 2021

Institute for Clinical and Economic Review
2 Liberty Square, 9th Floor
Boston, MA 02109
Submitted Electronically: publiccomments@icer-review.org
Subject: Public Comments on Draft Scoping Document – Mavacamten

Dear Review Committee:

Thank you for the opportunity to comment to the draft scoping document for ICER’s review of Mavacamten for Hypertrophic Cardiomyopathy. While our focus is heart valve disease, HCM patients experience many similar symptoms, such as shortness of breath, dizziness and chest discomfort, and are likewise underdiagnosed. Many patients actually have some form of mitral valve disease in combination with HCM and we are attempting to quantify the prevalence of these co-existing conditions so we can best serve our community.

One significant difference between heart valve disease and HCM, however, is that heart valve disease patients have specific treatment options; valve repair or replacement through surgery or a less invasive transcatheter procedure. At present, HCM patients have no available treatment for their underlying condition, only a range of imperfect options to treat the symptoms of the disease. Perhaps Mavacamten will fill this vital need.

Summary of Comments:

- The novel nature of Mavacamten and its role in filling an unmet patient need should be recognized and rewarded in any analysis of its value;
- Only through the development of real-world evidence (RWE) will the true benefits and risks of Mavacamten be known, as well gaining an understanding of its effectiveness on particular patient populations;
- Broader consideration of patient reported outcomes (PRO) should be included in the scope of this review;
- Patient preferences and quality of life measures are absent from the draft scope and must be included in any review;
- More direct patient input would inform this review and we encourage ICER to give full consideration to the recommendations of the Hypertrophic Cardiomyopathy Association (HCMA).

Because of the uniqueness of Mavacamten for this patient population, we urge ICER to reward innovation and to give greater weight to a drug developed specifically for this condition. One might argue that in the real world, there really is no comparator. We are optimistic that when/if
Mavacamten is available to a wider patient population, its value will become clearer as patients migrate from less desirable and less effective treatments.

The need for real world evidence to support any novel treatment also raises a concern regarding the timing of this review. While we understand issues of pricing and value are routinely considered prior to a product being granted market authorization, we are concerned there is insufficient evidence at this point to understand the full potential patient benefits of Mavacamten. A premature negative review could severely limit not only patient access but also the ability to gather evidence to support market adoption of the product or its potential benefits for particular patient populations.

We are similarly concerned that this draft scope does not provide for adequate consideration of a broader range of patient reported outcomes to include, for instance, the side effects of long-term off-label use of beta blockers, calcium channel blockers, and other drugs, such as Norpace (Disopyramide Phosphate). We further recommend greater consideration of quality-of-life measures in general.

The draft scope document lacks any mention of patient preferences. Currently, patients have a choice of using off-label medications with sometimes debilitating side effects or perhaps having a device implanted through open heart surgery (or a less invasive procedure) or an alcohol septal ablation. These drugs, devices, and procedures may treat symptoms of HCM, like arrhythmia, but not the underlying cause. Undoubtedly, if there were a drug developed specifically for HCM, that showed strong efficacy with minimal side effects, patients would choose this treatment. Based on the limited data that is publicly available at this point, Mavacamten could deliver on this promise. No true review of the value of a medical product can be complete without consideration of patient preferences.

In considering next steps, Heart Valve Voice US plans to survey its patient community to assess the prevalence and severity of HCM among heart valve patients, as well as their preferences for treatment. We will further encourage our community to complete the Patient Input Questionnaire to provide ICER with additional patient perspectives.

Thank you for your consideration. We look forward to continuing productive discussions on this topic to ensure the patient voice is provided meaningful consideration in your review.

Sincerely,

John Lewis
Executive Director
From: Nancy Weinstein  
Retired, Former College Administrator

I was diagnosed with obstructive HCM in 2003 at the age of 55. I had noticed symptoms like shortness of breath, fatigue and chest pain for about two years previously, particularly on stairs and walking up even slight inclines. After some trial and error, I have been managing solely with medications (Norpace CR and metoprolol) twice a day, as well as lifestyle adjustments like not exercising after I eat. However, several major pharmacy chains (CVS and Walgreens) no longer carry Norpace CR because of manufacturing shortages, and I can only order a one-month supply at a time from a New York pharmacy with a co-pay of $280 per month plus mailing charges. I live with the fear that next month they will no longer have a supply. If I do not take a dose as prescribed, I cannot catch my breath and can barely walk up the stairs to bed. I have tried taking the generic version four times a day (also no longer widely available), or cutting back on my dosage to save money, but the symptoms return full force. As far as I know, there is only one Pfizer factory manufacturing Norpace CR, and they are focusing on COVID vaccines instead. Doctors have warned me about ordering from Canada or another country because of counterfeits. A new, more targeted, drug is sorely needed. Coverage by Medicare, and a reasonable co-pay, would allow me to continue to lead a productive life without surgery. [You may use any portion of this message for your report]. Nancy Weinstein, Westport, MA
Thank you for allowing me to comment on the planned ICER assessment of mavacamten for patients with HCM. I will focus my comments on the proposed PICOTS framework and the comparative value assessment.

General comment:
As the adverse event rates in HCM are sufficiently low, the 30-week trial of mavacamten (EXPLORER-HCM) was underpowered to understand the impact of this new agent on several important outcomes. Similarly, the trial did not compare mavacamten to usual care. Rather it compared the new agent to first line therapy only.

Specific comments:
Population - no comment

Intervention - no comment

Comparator - As conducted, the EXPLORER-HCM trial only compares mavacamten to first line therapy. Usual care for HCM patients would be to offer advanced drug therapy (e.g. disopyramide) or invasive therapy for patients that remain symptomatic (this occurring in >50-70% of mavacamten treated patients in the trial). It would be important to also consider a qualitative assessment as compared to published data on disopyramide, myectomy, and septal ablation.

Outcomes - Patient-important outcomes - The trial duration was of insufficient duration (and insufficient person-years) to understand the impact of mavacamten on overall mortality, SCD, need for ICD, heart failure incidence, need for invasive therapies (see further comment below), AF, or stroke. Neither myectomy nor septal ablation are offered as emergency procedures, so the decision to proceed to these invasive options involves shared decision-making between the patient and HCM provider. The participation of an individual patient in a treatment specific drug trial practically delays consideration of invasive therapy until after the patient has completed the trial. Even without that assumption, 30 weeks is a reasonable time course of adjusting or switching between current standard front-line agents.

Timing - This will be a very difficult task for ICER as none of the published data on mavacamten has sufficient person-years at risk to assess important safety outcomes. This is particularly poignant given that 10% of treated patients develop significant left ventricular systolic dysfunction, which in turn is associated with long-term adverse outcomes in patients with HCM.

Contextual Consideration/Comparative Value - It will be important to consider that successful therapy with mavacamten would involve indefinite/lifetime use of this agent. Alternatively, patients who undergo successful myectomy or ablation can use much lower doses of stand first line agents, or importantly, many patient require no ongoing use of cardiac medications following these procedures.
Thank you again for undertaking this important assessment

Steve R. Ommen, MD
Professor of Medicine
Director, Mayo Hypertrophic Cardiomyopathy Clinic
April 29, 2021

Institute for Clinical and Economic Review
Submitted Electronically: publiccomments@icer.org
Subject: Public Comments on Draft Scoping Document – Mavacamten

Dear Review Committee,

As a woman living with hypertrophic cardiomyopathy (HCM) obstructive, I welcome this chance to comment on the ICER draft scoping document and review of the clinical and economic value of mavacamten. My comments include key points from my personal experiences alone and how they relate to the clinical evidence review and economic model.

When I was 33 years, half my age now, in 1988, the first thing a cardiologist at a renowned academic medical center in Washington, DC said to me upon diagnosis, was “Gwen, you will have a shorten life expectancy.” The following forty minutes I was numb frightened. My questions about longevity, exercise tolerance, whether to change jobs, or what to eat were all answered, “We don’t know.” I was advised against having children. I was told it could cause more emotional and psychological stress than medical problems. “Yes, you could die suddenly for no apparent reason,” he said when I inquired if I could still safely iron my clothes.

The news was not a complete shock. My mother’s hopes and dreams of going to college and leaving rural Kentucky were erased when she found her father dead of a sudden cardiac arrest on the bathroom floor her senior year in high school. She, too, had heard of her father’s father and brother dying of sudden “heart failure” at young ages. So when I was born with a heart murmur and started fainting when I was 8, she became depressed and filled with anxiety.

I have been fortunate over the years to receive good care, overcome emotional and psychological traumas, but it has not been easy. HCM comes into play every day of my life in some form – what I eat, what side I sleep on, whether I join others for travel, if I drink enough water, am alert enough to explain my condition to the EMTs, if I can convince a nurse I’m not exaggerating a heart rate of 180, how to keep from fainting, whether to lie on an insurance form, whether I’ll ever emotional recover from having an abortion (despite using birth control but told not to have children), should I change jobs, what will I do if I have brain fog while driving, who will care for me if I have surgery, why people distance themselves when they learn about my condition, whether I should buy a house with a bedroom on the first floor, how to make sense of the medical records between three medical centers, if I can afford medications, is my bra is too small and constricting my breathing, could I actually do CPR on myself if I went into ventricular fibrillation, and the list continues. Every day, I must answer these and more questions.

My clinical course began in earnest in graduate school in 1980 at Emory University where I was studying to be an Intensive Cardio-Respiratory Physician Assistant for the Post-Surgical Shock Trauma ICU. I was required to run an EKG on myself for practice. Mine (1 lead) was grossly abnormal and resembled nothing I had studied in school. Knowing my family’s history of sudden death, I felt doomed to repeat the pattern of dropping dead while brushing my teeth. The
following day I turned in the EKG of a 80 year old janitor as mine and began to lie. For the next eight years, despite having access to some of the best cardiologists, I kept quiet and mourned. I lied on medical records, defied my own advice and kept smoking, shunned any relationship of merit, skipped doctor appointments, and ignored the fear and anger that took root. In some ways, I lived a split world: I wore a handmade t-shirt that read “DAMAGED GOODS” when around my parents and rode ambulances in the inner-city keeping others alive.

Once diagnosed in 1988, I had the same cardiologist for 32 years until he retired. I was tested at least every six months – Holter monitors, stress tests, echocardiograms, weight reduction, EKGs, enzyme studies – and managed on a beta blocker (Betaxolol) and calcium channel blocker (Verapimil). I was evaluated for an ICD and declined due to the high rate of misfiring. I learned to conserve my energy buy resting for long periods of time, changing diets, stop smoking, joining a gym, and watching my fluid intact.

Despite these adjustments, I experienced (still do) near frequent bouts of ventricular tachycardia, atrial fibrillation, atrial tachycardia, heart blocks, syncope, brain fog, and shortness of breath. I have fainted on airplanes, at fairgrounds, at holiday parties, on the METRO, and in my backyard. I have been misdiagnosed (pulmonary embolism and heart attack) and on one occasion had to physically fight off an ER nurse who wanted to ‘shock’ me when she saw a HR of 150 on the monitor despite my attempts to explain it was ‘double counting’ (spiking “T” waves).

I have lost count of the times I have had to simply lie down on the floor of my office or at a park simply to catch my breath. When I took the Bar Exam, my cardiologist had me wear a Holter monitor – he recorded 700+ PVCs while taking the exam. Each of these experiences left me weakened, shaky, nervous, unable to work, bedridden, and scared of dying. On average, it takes about one week to stop ruminating about what happened and how it might happen again.

Approximately 15 years ago, I self-referred myself to Mayo Clinic in Rochester for a preemptive evaluation to determine what, if any, further treatment was needed. I go every three years for evaluation, however, a septal myectomy has not been recommended at this time. I have coordinated care with 7-8 general cardiologists and experts at the University of Maryland, and remained medically managed on Sotalol (antiarrhythmic) and Eliquis (blood thinner) the past year. Recently, I have had three trips to the ER due to atrial fibrillation and spent nine days in two hospitals last year due to uncontrollable arrhythmias. Every minor procedure – colonoscopy, dental work, eye surgery – requires stopping and readjusting medications. These, and other medications that have been tried, require months of adjustments, and have their own side effects – some of which, like palpitations and arrhythmias – they are intended to correct.

I am encouraged that ICER has included “contextual considerations” and “other benefits or disadvantages” in its review. The objective texts, drug choices, doctor trips, and time in the hospital are miniscule compared to the day-to-day adjustments that it takes to simply live with HCM. Top of mind for me are:

- **Access to insurance**. Until the passage of the ACA, I was uninsurable due to a pre-existing condition. Over the past 40 years, I’ve been tethered to demanding jobs, jobs that did not fit my education, turned down promotions, job hopped, committed insurance
fraud, lied on medical records, and destroyed medical records simply to have access to insurance. I always felt I was one step away from spiraling medical debt. Even in 2018, I lost a battle with Anthem BCBS over whether an echocardiogram at Mayo Clinic was covered as “medically necessary” because they did not get prior approval. I lost. $1700.

- **Psychological and emotional balance.** I have been on no less than five anti-anxiety medications and worked with psychologists on “healing trauma” and “body imaging” and “mindfulness” training for decades. I hire life coaches and yoga instructors to combat anxiety. These costs likely exceed hospital, provider, and drug costs.

- **Family support and healthy relationships.** HCM was devastating for me as a young woman. The man I was dating refused to see me (1988) because I was an “invalid”; and the next man refused to see because it would “interfere with our sex life.” I felt unlovable and unimportant as a woman knowing I could (or should not) have children. I never married and have lived alone since 1977. As a single woman living with a chronic health condition, the ‘costs’ maintaining a home, traveling, paying taxes, holidays, vacations, and something as simple as “can I get a parking space closer to my condo” have compounded over the years.

- **Relationships with bosses, friends, co-workers, etc.** Thankfully, I have had friends over the years who have sat with me in ERs, visited when I was hospitalized, and shown their care. But many have not. On one occasion, a neighbor refused to pick me up after I had fainted on a airplane, saying, “but what if you die while you’re in my car?” Another refused to go with me to the ER after work, saying, “I am supposed to meet the guys for drinks.” The isolation and feelings of being “different” never leave.

Finally, the economic model for evaluating HCM and mavacamten specifically will be critical to gaining access to this medication. HCM patients have lived a lifetime of bouncing from one drug to the next as if being blindfolded and trying to hit a piñata. The promise of a disease-specific drug is encouraging but will need to be affordable to provide benefit. Comparisons to heart failure patients will not give you a full picture. I have been in three different NYHA classifications in one year, stayed in the same for a decade, digressed, and then recovered. Currently, I live a normal life on the Chesapeake Bay in Annapolis, MD, sail, travel, volunteer, walk 2 miles/day, and kayak. Twenty years ago, my diastolic pressures were so high, my cardiologist said, “you will not survive a stress test.” You can read more about my story from the American Heart Association, one of the five organizations I serve with as a patient representative.

Please let me know how I can provide additional information that is of value to your review.

Sincerely,

**Gwen Mayes**

Gwen Mayes (65)
Annapolis, MD
My Name is Tim Westhaver I am 62 years old.

I Had My first Cardiac event 31 years ago.

At that time I had completed 11 Marathons and finished a half iron man.

The first indication of something being wrong was a shortness of breath and fatigue that lingered longer than was normal for me.

My wife was pregnant for our first child, little did I know the havoc that our decision to have children would unleash.

As my genes ( I have two that are known MYH7 and TTN2 ) started to express themselves my condition worsened.

A daily occurrence included dizziness, fatigue, chest pain and palpitations.

I was diagnosed with chronic fatigue syndrome, depression etc. etc.

Finally after the sudden cardiac death of two young members of our family I was referred for gene testing and was diagnosed with HCM.

An Icd was implanted. Case closed. A drug regime of beta blockers diuretics and ace inhibitors became my daily tonic to ward off the advances the disease had taken on me.

As time progressed and my symptoms worsened I was seen by a specialist I was diagnosed with HOCM a pressure gradient of 70 under provocation.

Disopyramide was prescribed. It has helped with the symptoms but as time goes by its effectiveness is waning.

HCM being genetic is a terrible disease for a parent. Watching your children grow and ultimately have their lives torn apart as icds were implanted and there sports careers ended.

Their lives torn asunder my son was a university lacrosse player my daughter a national class ringette and hockey player.

Then you wait and every time they are tired or sick you wonder is this the time?

The very thought that they are both considering not having children or maybe even worse that they are is heart rendering.

HCM is a Trojan horse that is wheeled into a family and then when nobody suspects it unleashes its lethal attack.

When I was 50 I was president of a successful print brokerage. Had 13 employees.

That ended.

Disability insurance is like jumping from the boil to the simmer.
It has left me as a person who lacks confidence. When you have a disease that comes and goes you become unreliable.

Dinners get cancelled dreams are left unfulfilled.

The sudden cardiac death is one thing the constant symptoms are another and maybe even worse.

It is entirely isolating you are filled with self-loathing for what your genetic gift is and self-doubt for your inability to know or have hope in the future.

It has cost me well over 1 million dollars from my loss of employment.

Not everybody everywhere can have a Myectomy. This is a promising alternative it would definitely change people’s lives in a very positive way.

Best Regards

Tim Westhaver