CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Mavacamten (Camzyos)

Indication: For the treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM) of New York Heart Association (NYHA) class II to III in adult patients

Sponsor: Bristol Myers Squibb

Recommendation: Reimburse with Conditions

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that mavacamten be reimbursed for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM) of New York Heart Association (NYHA) Class II-III in adult patients only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Two phase III, randomized, double-blind, placebo-controlled trials (EXPLORER-HCM [n = 251] and VALOR-HCM [n = 112]) demonstrated that treatment with mavacamten resulted in added clinical benefit in adult patients with symptomatic oHCM. In EXPLORER-HCM, mavacamten was statistically significantly more efficacious than placebo in improving the NYHA class and exercise capacity (pVO2) in patients with symptomatic oHCM of NYHA class II to III. Results of the primary composite outcome showed that 37% of patients on mavacamten versus 17% of patients on placebo met the primary endpoint at week 30 with a between group difference of 19.4%, (95% CI, 8.7 to 30.1; P = 0.0005). Compared to patients in the placebo group, patients in the mavacamten group also had greater reductions in post-exercise LVOT gradient with a mean difference of -36 mmHg, (95% CI, -43.2 to -28.1; P < 0.0001), greater increases in pVO2 with a mean difference of 1.4 mL/kg per min (95% CI, 0.6 to 2.1; P = 0.0006), and improvements by ≥ 1 NYHA functional class (65% of patients in the mavacamten group vs 31% of patients in the placebo group) with a between group difference of 34% (95% CI, 22.2 to 45.4; P < 0.0001). Patients treated with mavacamten also reported greater improvement in health-related quality of life (HRQoL) as assessed by the scores on the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ CSS) with a mean difference of 9.1 (95% CI, 5.5 to 12.7; P < 0.0001), and greater reductions in severity of HCM symptoms as assessed by the Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness of Breath (HCMSQ SoB) domain score with a mean difference of -1.8, (95% CI, -2.4 to -1.2; P < 0.0001). The VALOR-HCM study was conducted in patients with symptomatic oHCM of NYHA class III to IV or class II with exertional syncope or near syncope. In this study, results of the primary composite outcome showed that at week 16, 17.9% of patients on mavacamten continued to meet guideline criteria for being eligible for septal reduction therapy (SRT) or elected to undergo the procedure compared to 76.8% of patients on placebo, with a treatment difference of 58.9% (95% CI, 44.0% to 73.9%; P < 0.001). Compared to patients in the placebo group, patients in the mavacamten group also had a greater reduction in post-exercise LVOT gradient with a mean difference of -37.2 mmHg (95% CI, -48.1 to -26.2; P < 0.001), improvements by ≥ 1 NYHA functional class with a between group difference of 41.1% (95% CI, 24.5% to 57.7%; P < 0.001), and greater improvement in HRQoL as assessed by the KCCQ CSS with a mean difference of 9.4 points (95% CI, 4.9 to 14.0 points; P < 0.001). Although the place in therapy of mavacamten for the management of oHCM is not completely clear, CDEC considered that mavacamten is an additional second-line treatment option after beta-blockers or calcium channel blockers.

Patients identified a need for treatment options that reduce the risk of heart failure and sudden cardiac death, and the debilitating symptoms that affect daily living activities and quality of life. Patients also expressed a need for treatments which are better non-invasive alternatives to SRT, that target the underlying cause of HCM, potentially reverse the course of the disease, and that are more efficacious. Patients identified a particular need for additional options for those who are intolerant of the side effects of beta-blockers and calcium channel blockers. CDEC concluded that based on the evidence, mavacamten appears to address some of the needs identified by patients, by reducing HCM symptoms and improving patients' HRQoL.

Using the sponsor submitted price for mavacamten and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for mavacamten when added to beta-blockers or calcium channel blockers (BB or CCBs) was $576,295 per quality-adjusted life-year (QALY) compared with BB or CCBs alone. At this ICER, mavacamten is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold for adult patients with symptomatic oHCM of NYHA Class II–III. A price reduction is required for mavacamten to be considered cost-effective at a $50,000 per QALY threshold.

Table 1. Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with mavacamten should be reimbursed when initiated in patients with all the following: 1.1. documented LVEF ≥ 55% at rest determined by echocardiography 1.2. LV wall thickness ≥ 15 mm (or ≥ 13 mm with a family history of HCM) 1.3. LVOT peak gradient ≥ 50 mmHg at rest, after Valsalva maneuver, or post exercise as confirmed by echocardiography	Patients enrolled in the EXPLORER-HCM and VALOR-HCM trials had to have LVEF of at least 55% and 60% at screening, respectively. In addition, patients enrolled in both studies had to have LV wall thickness ≥ 15 mm (or ≥ 13 mm with a family history of HCM), LVOT peak gradient ≥ 50 mmHg at rest, after Valsalva maneuver, or post exercise as confirmed by echocardiography and adequate acoustic windows to enable accurate TTEs	LVEF must be measured via echocardiography
2. Patients must be receiving beta-blocker or calcium-channel blocker therapy and experience clinical deterioration in symptoms or echocardiography while receiving either of these treatments	The majority of patients (90%) enrolled in the EXPLORER-HCM and VALOR-HCM trials were on some form of background therapy with a beta-blocker or calcium channel blocker	Based on clinical expert opinion, clinical deterioration should be defined as either worsening of symptoms or echocardiographically demonstrated deterioration in outflow tract obstruction.
Discontinuation		
3. Treatment with mavacamten should be permanently discontinued if the patient has either of the following: 3.1. LVEF ≤ 30% 3.2. Receives SRT	In both EXPLORER-HCM and VALOR-HCM trials, treatment with mavacamten was permanently discontinued if LVEF decreased to 30% or less. No evidence was identified to demonstrate an efficacy or safety benefit of mavacamten in patients who have undergone SRT.	LVEF must be measured via echocardiography. The product monograph also states that mavacamten should be discontinued if LVEF <50% on two consecutive occasions with 2.5 mg daily.
Prescribing		
4. The patient should be under the care of a cardiologist	Accurate diagnosis and follow-up of patients with oHCM is important to ensure that mavacamten is prescribed to the most appropriate patients.	—
Pricing		
5. A reduction in price	The ICER for mavacamten plus beta-blocker or calcium-channel blocker is $576,295 when compared with beta-blocker or calcium-channel blocker alone. A price reduction of at least 73% for mavacamten would be required for mavacamten plus beta-blocker or calcium-channel blocker to achieve an ICER of $50,000 per QALY gained compared to	—

Reimbursement condition	Reason	Implementation guidance
	beta-blocker or calcium-channel blocker alone.	

LV = left ventricular; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; oHCM = obstructive hypertrophic cardiomyopathy; QALY= quality-adjusted life-year; SRT = septal reduction therapy; TTE = transthoracic echocardiography.

Discussion Points

- CDEC discussed that symptomatic oHCM is a chronic disease and that while descriptive results for the VALOR-HCM trial are available through to week 32, it is uncertain if mavacamten can reduce the need for SRT among patients with symptomatic oHCM in the long-term. Furthermore, there is no direct evidence of mavacamten compared to SRT available. In addition, it is unknown what impact mavacamten will have on the natural history of the disease.
- Given that mavacamten was evaluated in EXPLORER-HCM as an add-on to first-line treatment of beta-blocker or calcium channel blocker therapy, CDEC discussed the clinical efficacy of mavacamten as a first-line therapy but there is no evidence available for the use of mavacamten as a first-line, in addition, there is limited evidence for the addition of mavacamten to beta-blockers or calcium channel blockers plus disopyramide. Hence CDEC recommended that mavacamten be prescribed as a second line treatment after patients demonstrate clinical deterioration while taking a beta-blocker or calcium-channel blocker therapy.
- CDEC discussed that while the clinical practice guidelines recommend disopyramide as a second-line treatment for patients with symptomatic oHCM, the clinical expert, noted that disopyramide is not widely used in clinical practice in Canada given the concerns that disopyramide may increase the QT interval on the ECG, likely requiring first doses to be administered in hospitals and emergency rooms, with all the attendant resource consequences.
- CDEC discussed that there is a limited number of centres in Canada that conduct SRT, that SRT is associated with potentially severe complications, as well as the potential need for pacemaker implantation and re-intervention, and that mavacamten could potentially improve the symptoms and delay the time when SRT is required.
- The estimated price reduction required to achieve cost-effectiveness is uncertain. The long-term efficacy of mavacamten is highly uncertain given the lack of clinical data available to support the modelled long-term relative benefit of mavacamten plus BB or CCB compared with BB or CCB alone. If the long-term relative effectiveness of mavacamten plus BB or CCB compared to BB or CCB is worse than predicted, a greater price reduction will be required for mavacamten to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained.
- CDEC noted that clinical experts believe that patient registries for oHCM would be of great value as there are still evidence gaps and the therapeutic pathways are still unclear. Jurisdictions may want to discuss the need for a registry for patients with oHCM with the sponsor.

Background

Hypertrophic cardiomyopathy (HCM) is a common genetic heart disease characterized by increased left ventricular wall thickness. About 30% to 60% of HCM patients have identifiable familial disease caused by mutations in cardiac sarcomere protein genes and each offspring of an affected family member has a 50% chance of inheriting the altered gene, although not all family members who inherit an HCM mutation will develop the disease. The distribution of HCM is equal by sex, although women have been diagnosed less frequently than men. The age of symptom onset and the severity of symptoms varies significantly across HCM patients. Among HCM patients who do develop symptoms, the most common symptoms include chest pain, shortness of breath with exertion, fatigue, palpitations, and lightheadedness. Obstructive HCM (oHCM), a subclassification of HCM, is characterized by left ventricle outflow tract (LVOT) obstruction, with the obstruction impeding blood flow from the heart to the rest of the body, defined in the 2020 American Heart Association/American College of Cardiology (AHA/ACC) clinical guidelines as a peak LVOT gradient ≥ 30 mmHg. Patients with oHCM are more likely to develop symptoms such as increased myocardial wall stress, myocardial ischemia, and eventually, cell death and replacement scarring. Associated complications include heart failure, stroke due to atrial fibrillations, arrhythmias, and sudden cardiac death. The estimated prevalence of HCM in the general population is 1 in 500 adults, although most of these cases remain undiagnosed. The 2020 AHA/ACC clinical guidelines suggest that oHCM is present or develops over

time in most patients with HCM, with about a third of HCM patients remaining nonobstructive. Estimates for the proportion of HCM patients who have oHCM ranges from 22% in a study from western Sweden to 70% in a US study.

Mavacamten is a first-in-class cardiac myosin inhibitor. Mavacamten modulates the number of myosin heads that can enter power generating states, reducing force-producing systolic and residual diastolic cross-bridge formation. Mavacamten also shifts the overall myosin population towards an energy sparing, recruitable, super relaxed state. This is the first CADTH review for mavacamten. The Health Canada indication is for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM) of New York Heart Association (NYHA) class II to III in adult patients. Mavacamten is available as a 2.5 mg, 5 mg, 10 mg, or 15 mg capsule. The product monograph recommended starting dose of mavacamten for oHCM is 5 mg orally once daily. Patients should be assessed 4 weeks after initiation to for a clinical response. If LVOT gradient with Valsalva maneuver is < 20 mgHg, the dose should be decreased to 2.5 mg once daily. Otherwise, 5 mg once daily dosing should be maintained. Thereafter, follow-up visits should occur at 8 and 12 weeks after treatment initiation, with dose adjustments as appropriate. The product monograph for mavacamten contains serious warnings and precautions regarding the risk of heart failure and note that mavacamten reduces left ventricular ejection fraction (LVEF) and can cause heart failure due to systolic dysfunction, and that echocardiogram assessments of LVEF and LVOT gradient are required prior to, and regularly during treatment with mavacamten. It also notes that initiation of mavacamten in patients with LVEF < 55% is not recommended and that mavacamten treatment should be interrupted if LVEF is < 50% at any visit or if the patient experiences heart failure symptoms or worsening clinical status. The product monograph also states that concomitant use of mavacamten in patients on combination therapy of a calcium channel blocker (e.g., verapamil, diltiazem) and a beta-blocker should be avoided.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- A review of 2 RCTs in adult patients with oHCM
- Patient perspectives gathered by 2 patient groups, Canadian Heart Patient Alliance (CHPA) and HeartLife Foundation
- Input from public drug plans that participate in the CADTH review process
- 1 clinical specialist with expertise diagnosing and treating patients with cardiovascular disease
- Input from 2 clinician groups, including a community-based cardiology clinic Cardio1 and from an independent cardiologist
- A review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

Two patient advocacy groups, Canadian Heart Patient Alliance (CHPA) and HeartLife Foundation, provided input for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in adult patients. One patient group, HeartLife Foundation gathered information from in-depth interviews with expert physicians and patients across Canada, and review of study material and online literature. Another group (CHPA) conducted extensive interviews with three clinicians (two in the USA and one in Italy) involved with clinical trials for mavacamten. They also gathered information through meeting with staff from the US-based Hypertrophic Cardiomyopathy Association, and reviewing recorded panel discussions, patient testimonials, and educational videos. CHPA recruited participants through the US-based clinicians as well as outreach through the database for the CHPA in Canada, with additional patient profiles and confirmatory information provided by the Hypertrophic Cardiomyopathy Association. A total of 16 patient responses were gathered, among them 62.5% were female (10 out of 16), aged between mid-30s to mid-70s, and 31% (5 out of 16) were identified as Canadians (1 living in US) and 69% (11 respondents) as Americans. All participants reported being diagnosed with oHCM, and 40% also identified as diagnosed with NYHA functional class II and 40% with NYHA functional class III. About 25% participants mentioned being diagnosed with atrial fibrillation. Among the 16 respondents, 4 patients had been treated with mavacamten, and all of them were residents in the US.

Both patient groups agreed that HCM has a negative impact on patients' quality of life. Impact of delayed and misdiagnosis, shortness of breath, exercise intolerance, arrythmia, palpitations, chest pain, fatigue and fainting were some of the major issues experienced by the respondents. One patient group also mentioned about HCM affecting patients' families and friends both mentally and physically. While describing their experiences with currently available drugs, participants reported experiencing a variety of treatments, including heart surgery, implantable cardioverter defibrillators, alcohol septal ablation, and a variety of medications (such as beta-blockers, calcium channel blockers and antiarrhythmics). However, both patient groups reported concerns from both patients and healthcare providers regarding current treatments, and patients' symptoms and feelings of uncertainty and unresolved anxiety with the available treatment options.

While evaluating improved outcomes from new treatments, patients expressed a desire to see a reduction in the risk of heart failure including sudden death as a current unmet need, as well as reductions in the debilitating symptoms affecting daily living activities and quality of life, including shortness of breath, irregular heartbeat, palpitations, chest pain, fatigue, stress, and anxiety. Moreover, spending time with loved ones, the ability to go to work on regular basis, pursuing outdoor activities, and the ability to travel were some of the quality-of-life indicators and experiences patients and caregivers mentioned.

While describing the experiences with the current drug under review, 4 patients recruited by the CHPA reported "very positive" experiences, noting that they have more energy to perform daily tasks and they were hopeful that the drug will reduce their symptoms and risk of cardiac arrest. HeartLife Foundation described findings from a Cleveland Clinic led clinical trial (VALOR-HCM) demonstrating a reduced need for an invasive procedure like septal reduction therapy (SRT) in severely symptomatic, oHCM patients when mavacamten was used. However, CHPA reiterated the need of assessment for patients for their cardiac status and specifically by echocardiogram of left ventricular ejection fraction (LVEF) as well as other illnesses (e.g., infections or chronic disease), other cardiovascular symptoms (arrhythmias), and other medications prior to the approval for mavacamten. Moreover, patients must be closely monitored with echocardiogram for the first few months, as well as on a regular basis (every three months) and reported for any symptoms due to the risk of heart failure associated with mavacamten. CHPA mentioned that this limits the prescription of mavacamten to patients who have access to a high-volume clinic and are committed to regular monitoring and reporting of symptoms.

Clinician input

Input from clinical experts consulted by CADTH

According to the clinical expert, for patients with symptomatic oHCM, standard treatment has aimed to lessen the extent of LVOT obstruction and manage arrhythmias. Beta-blockers have been the traditional mainstay of therapy. Where beta-blockers cannot be used or are not tolerated, non-dihydropyridine calcium channel blockers, diltiazem or verapamil, can be prescribed. Should symptoms persist, then disopyramide is recommended as add-on therapy. These drugs, taken separately or in combination, improve symptoms and quality of life. According to the clinical expert consulted, mavacamten may meet an unmet need as an add-on therapy for patients not experiencing symptom relief with beta-blockers or calcium channel blockers with or without disopyramide.

The clinical expert consulted for this review noted that mavacamten has been evaluated in EXPLORER-HCM as an add-on to first-line treatment of beta-blocker or calcium channel blocker therapy in the context of improving symptoms and exercise capacity among patients with symptomatic oHCM. In terms of treatment paradigm, the clinical expert stated that mavacamten will provide another treatment option for symptomatic patients with oHCM. In their opinion, the current place in therapy for mavacamten is in fact unclear. It may be as an add-on to beta-blockers or calcium channel blockers, or more appropriately as a third line agent as an add-on to beta-blockers or calcium channel blockers plus disopyramide. The fact that mavacamten was not tested head-to-head with disopyramide raises uncertainty as to its relative position in the treatment algorithm according to the expert. The clinical expert stated that while it has its own issues, disopyramide is a class 1a antiarrhythmic with negative inotropic properties that have been argued to be more powerful than beta-blocker or calcium-channel blocker in controlling LVOT obstruction.

According to the clinical expert, symptomatic oHCM patients who have not sufficiently responded to current treatment and/or whose symptoms are worsening would be eligible for treatment with mavacamten. Patients would need to be sufficiently symptomatic to need the drug (at least NYHA class II) despite treatment with beta-blockers or calcium channel blockers with or without disopyramide. The metrics of response to treatment with mavacamten according to the expert includes stabilization or improvement

of symptoms (e.g., fatigue, palpitations, lightheadedness, and chest pain), reduction in the frequency/severity of symptoms, and improved ability to perform activities of daily living. In the opinion of the clinical expert, treatment should be discontinued if drug side effects were to occur. If symptoms or LVOT gradient were to progress to the point that SRT was needed, then treatment with mavacamten should be discontinued. According to the clinical expert, mavacamten should be prescribed by specialists (cardiologists) or in specialty clinics.

Clinician group input

Clinician group input on the review of mavacamten for the treatment of oHCM was received from 2 clinician groups: a community-based cardiology clinic Cardio1, and from an independent cardiologist, who is a member of the HCM Clinic at the University of Calgary, the Stephenson Cardiac Imaging Center and the Libin Cardiovascular Institute at the University of Calgary.

The clinician groups mentioned that beta-blocker, calcium channel blocker and disopyramide are current treatments for oHCM. However, use of these treatments is for symptom management; they do not modify the underlying disease but serve to reduce symptoms. There are also potential adverse effects associated with these drugs which limit their use. Cadio1 also pointed out that septal reduction therapy (SRT) like surgical and percutaneous septal ablation may be beneficial to those who are refractory to drugs. However, they also have potential adverse effects and limitations and require proper and careful selection of patients, indicating an unmet medical need for better non-invasive alternatives to SRT.

There remains some unmet needs when current treatment options are deemed ineffective, are unable to reverse the course of the disease and used mostly for symptom relief. While both groups mentioned about data/study showing effectiveness of the drug under review in improving symptoms and reducing the need for surgery, Cardio1 focused on using available conventional therapy first and switching to the new therapy when they fail. The group also put importance on proper selection of patients, as well as checking for updates regarding long-term studies on the use of this new drug. The group added the need for timely assessment of patients' response to conventional treatment and switching to new treatment to prevent unnecessary suffering.

Regarding best suited patients for the new medication, one group identified patients with oHCM with severe left ventricular outflow tract (LVOT) obstruction who are highly symptomatic as most suitable ones, whereas Cardio1 mentioned patients unresponsive to currently available drug treatment as good candidates for this drug, as well as those who may not be a candidate for early SRT or those who want to delay SRT or those who do not want SRT. While one group mentioned their eagerness to offer the new medication to patients, referring to the compelling data behind the new medication, Cardio1 pointed out the ongoing importance to monitor the mortality, morbidity and hospitalization outcomes of this drug.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for mavacamten:

- relevant comparators
- considerations for initiation of therapy
- considerations for prescribing of therapy.

The clinical expert consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2. Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
In clinical practice, what is the typical treatment cascade for patients with oHCM?	The clinical expert noted to CDEC that patients diagnosed with symptomatic oHCM begin treatment with beta-blockers or non-dihydropyridine calcium channel blockers as first-line therapy. Patients who do not respond to or tolerate first-line therapy are candidates for disopyramide in combination with beta-blockers or non-dihydropyridine calcium channel blockers. Among patients in whom symptoms persist, SRT may be a treatment option.
Should mavacamten replace disopyramide as a combination therapy with a beta-blocker or calcium channel blocker or should it be used after a patient has tried combination therapy with disopyramide?	CDEC agreed with the clinical expert consulted by CADTH that the evidence as presented is for the use of mavacamten as an add-on to beta-blockers or calcium channel blockers. There is also limited evidence for the addition of mavacamten to beta-blockers or calcium channel blockers plus disopyramide. The current place in therapy for mavacamten is in fact unclear. It may be as an add-on to beta-blockers or calcium channel blockers, or perhaps more appropriately as a third line agent, given on top of beta-blockers or calcium channel blockers plus disopyramide. The fact that mavacamten was not tested head-to-head with disopyramide raises uncertainty as to its relative position in the treatment algorithm.
Is there a role for mavacamten monotherapy?	CDEC agreed with the clinical expert consulted by CADTH that there is no role for mavacamten monotherapy.
Mavacamten is a cardiac myosin inhibitor, which reduces the number of actin myosin cross bridges, which attenuates excessive contractility and improves cardiac function. Therefore, isn't it similar to beta-blockers or calcium channel blockers in that its function is to address the symptoms of oHCM?	CDEC agreed with the clinical expert consulted by CADTH that mavacamten is similar to beta-blockers or calcium channel blockers in terms of the effect of treatment. The clinical expert noted that mavacamten is more specific in its effect on contractility. There are some data showing reverse cardiac remodeling, as well as reductions in LV mass index and LV wall thickness with mavacamten. But whether this ultimately alters disease progression or impacts major clinical outcomes is unknown.
Is there any evidence in the available studies (EXPLORER-HCM, MAVA-LTE, or VALOR-HCM) that reliably demonstrates mavacamten improves outcomes of oHCM other than symptoms?	CDEC agreed with the clinical expert consulted by CADTH that the duration of the submitted trials were not long enough to reliably demonstrate that mavacamten improves outcomes of oHCM other than symptoms.
Considerations for initiation of therapy	
Are the eligibility criteria for EXPLORER-HCM reasonable for a clinical trial of patients with oHCM? Are the eligibility criteria in the EXPLORER-HCM trial possible to determine in clinical practice (i.e., able to be determined and available across Canada)? Would the eligibility criteria for the trial work as eligibility criteria for reimbursement of mavacamten (as requested by the sponsor)?	The clinical expert noted that patients more clearly eligible for mavacamten are those diagnosed with symptomatic oHCM who are not responding to treatment with disopyramide in combination with beta-blockers or non-dihydropyridine calcium channel blockers. CDEC however noted that the available evidence does not help answer questions in reference to disopyramide and mavacamten. CDEC agreed with the clinical expert consulted by CADTH that whether mavacamten should replace disopyramide as second line therapy remains uncertain in the absence of head-to-head trials. This could have been assessed if disopyramide had been used in lieu of placebo in the comparator arm.
If a patient progresses to NYHA class IV, should funding be discontinued?	CDEC agreed with the clinical expert consulted by CADTH that funding should not be discontinued in patients who progress to NYHA class IV, although other treatments such as SRT should be under consideration by that point.

Implementation issues	Response
Should mavacamten be continued in patients who have undergone SRT?	CDEC agreed with the clinical expert consulted by CADTH that mavacamten should be discontinued in patients who have undergone SRT
Are the exclusion criteria for EXPLORER-HCM reasonable for a clinical trial of patients with oHCM?	CDEC agreed with the clinical expert consulted by CADTH that it is unclear why patients with a history of syncope within 6 months prior to screening were excluded from the EXPLORER-HCM trial.
Are there any exclusion criteria in the EXPLORER-HCM or other clinical trials that should be used as reimbursement conditions of mavacamten?	The clinical expert noted to CDEC that patients with permanent atrial fibrillation who are either not on anticoagulation for more than four weeks or not adequately rate controlled for more than six months or any patients with paroxysmal atrial fibrillation present at screening were excluded in both pivotal trials. The reasoning for this is also unclear. CDEC agreed with the clinical expert consulted by CADTH that the exclusion criteria in EXPLORER-HCM of LVEF of at least 55% should be used as a reimbursement condition of mavacamten.
Considerations for prescribing of therapy	
Do patients with oHCM need to be managed by specialist (e.g., cardiologist), or a specialist with specific training in oHCM?	CDEC agreed with the clinical expert consulted by CADTH that patients with oHCM should preferentially be managed by a cardiologist or specialty clinic. Treatment could be started either on an inpatient or outpatient basis. In regions where no practicing cardiologist was available, specialist review and input could be provided virtually.
According to the sponsor's submission, there are only two sites in Canada that are established myectomy centers (Toronto General and St. Paul's Hospital in Vancouver). Is this accurate?	According to the clinical expert, these two sites are recognized specialty centers and will receive referrals for the more complex cases. However, other centers also perform SRT in Canada.

CDEC = Canadian Drug Expert Committee; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; oHCM = obstructive hypertrophic cardiomyopathy; pCPA = pan-Canadian Pharmaceutical Alliance; SRT = septal reduction therapy.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of studies

Two sponsor conducted phase 3, randomized, double-blind, placebo-controlled trials, EXPLORER-HCM and VALOR-HCM, which met the CADTH review protocol criteria were included in this systematic review.

The EXPLORER-HCM trial (68 sites in 13 countries, N = 251) evaluated the efficacy and safety of once-daily orally administered treatment with mavacamten (starting dose 5 mg) in adult patients with symptomatic oHCM with an LVOT peak gradient ≥ 50 mmHg at rest, after Valsalva maneuver, or post exercise, documented LVEF ≥ 55%, a maximum septal wall thickness determined by a core laboratory ≥ 15 mm or ≥ 13 mm with family history of HCM, and with NYHA functional class II or III symptoms. The primary outcome was composite functional response at week 30, defined as achieving an improvement of ≥ 1.5 mL/kg/min increase in peak oxygen consumption (pVO_2) and ≥ 1 NYHA functional class reduction or ≥ 3.0 mL/kg/min in pVO_2 without NYHA class worsening. Secondary outcomes prespecified in the statistical hierarchy included changes in post-exercise LVOT peak gradient, pVO_2, NYHA class, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ CSS), and Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness of Breath (HCMSQ SoB) domain score. Patients had a mean age of 58.5 years (SD 11.9), most patients (73%) had NYHA functional class II symptoms at baseline, and almost all patients (92%) were on background beta-blocker or calcium channel blocker therapy. Other exploratory outcomes assessed in the EXPLORER-HCM trial that were important to the CADTH review included HRQoL as assessed by the EQ-5D-5L questionnaire, changes in resting and Valsalva LVOT peak gradients, changes in cardiopulmonary exercise testing (CPET) parameters, cardiac structure, and biomarker-based assessments.

The VALOR-HCM trial (19 sites in the US, N = 112) evaluated the efficacy and safety of once-daily orally administered treatment with mavacamten (starting dose 5 mg) in adult patients with symptomatic oHCM with a dynamic LVOT gradient at rest or with provocation (i.e., Valsalva or exercise) of 50 mmHg or greater, a documented LVEF ≥ 60%, a maximum septal wall thickness determined by a core laboratory ≥ 15 mm or ≥ 13 mm with family history of HCM and NYHA functional class III, IV, or class II with exertional syncope or near syncope. Patients must have been referred within the past 12 months for SRT and actively considering scheduling the procedure. The primary outcome was a composite of the decision to proceed with SRT prior to or at week 16 or be considered guideline eligible for SRT at week 16. Guideline eligibility criteria were based on the 2011 ACCF/AHA HCM clinical and hemodynamic criteria. For the primary composite outcome, patients with maximum LVOT ≥ 50 mm Hg gradient (from rest, Valsalva, or post-exercise) and no improvement in NYHA functional class at week 16 were considered eligible for SRT. Secondary outcomes prespecified in the statistical hierarchy included changes in post-exercise LVOT peak gradient, ≥ 1 class of NYHA improvement, changes in KCCQ CSS, and changes in N-terminal pro b-type natriuretic peptide (NT-proBNP) and cardiac troponin I biomarkers.

Efficacy Results

Both pivotal trials comparing mavacamten with placebo detected a statistically significant difference in their primary outcomes and all prespecified secondary outcomes were statistically significant in favour of mavacamten.

In EXPLORER-HCM, a total of 37% of patients on mavacamten versus 17% of patients on placebo met the primary endpoint at week 30 with a between group difference of 19.4%, (95% CI, 8.7 to 30.1; P = 0.0005). In regards to key secondary outcomes tested in the statistical hierarchy from baseline to week 30, patients in the mavacamten group compared to those in the placebo group had: greater reductions in post-exercise LVOT gradient with a mean difference of -36 mmHg, (95% CI, -43.2 to -28.1; P < 0.0001), greater increases in pVO_2 with a mean difference of 1.4 mL/kg per min (95% CI, 0.6 to 2.1; P = 0.0006), more patients improving by ≥ 1 NYHA class (65% of patients in the mavacamten group vs 31% of patients in the placebo group) with a between group difference of 34% (95% CI, 22.2 to 45.4; P < 0.0001), greater improvement in scores on the KCCQ-23 CSS with a mean difference of 9.1 (95% CI, 5.5 to 12.7; P < 0.0001), and greater reductions in severity of HCM symptoms as assessed by the HCMSQ SoB domain score with a mean difference of -1.8, (95% CI, -2.4 to -1.2; P < 0.0001).

In VALOR-HCM, for the primary composite outcome, after 16 weeks treatment, 17.9% of mavacamten treated patients continued to meet guideline criteria for SRT or elected to undergo the procedure compared to 76.8% of placebo treated patients, with a treatment difference of 58.9% (95% CI, 44.0% to 73.9%; P < 0.001) favouring mavacamten. In regard to key secondary outcomes tested in the statistical hierarchy from baseline to week 16, patients in the mavacamten group compared to those in the placebo group had: a greater reduction in post-exercise LVOT gradient with a mean difference of -37.2 mmHg (95% CI, -48.1 to -26.2; P < 0.001), more patients with ≥ 1 class of NYHA functional class improvement with a between group difference of 41.1% (95% CI, 24.5% to 57.7%; P < 0.001), greater improvement in scores on the KCCQ CSS with a mean difference of 9.4 points (95% CI, 4.9 to 14.0 points; P < 0.001), and greater reductions in NT-proBNP and in cardiac troponin I with a geometric mean ratio difference of 0.33 (95% CI, 0.26 to 0.42; P < 0.001) and 0.53 (95% CI, 0.41 to 0.70; P < 0.001), respectively.

Harms Results

In EXPLORER-HCM, through to week 38, a total of 88% of patients in the mavacamten group and 79% of patients in the placebo group experienced ≥ 1 AE. The most common AEs were similar for both treatment groups. The proportion of patients who experienced ≥ 1 SAE was similar between treatment groups (8% vs 9%). A total of 1.6% of patients in the mavacamten group and 0.8% of patients in the placebo group discontinued treatments due to AEs. No AEs of decreased LVEF were reported. However, incidence of resting LVEF < 50% was a protocol-specified criterion for temporary treatment discontinuation in EXPLORER-HCM. Throughout the 30-week treatment period, 3.6% of patients met temporary treatment discontinuation criteria of LVEF < 50%, including 5.7% of patients in the mavacamten group and 1.6% of patients in the placebo group. No patients had a reduction in LVEF [redacted] necessitating permanent treatment discontinuation. One death was reported in the placebo group due to sudden death.

In VALOR-HCM, through to week 16, a total of 73.2% of patients in the mavacamten group and 61.8% of patients in the placebo group experienced at least 1 AE. The proportion of patients who had SAEs were similar for the mavacamten and placebo groups (5.4% vs 1.8%). Through to week 16, 3.6% of patients in the mavacamten group had LVEF < 50% resulting in temporary drug discontinuation, all of whom subsequently resumed mavacamten dosing. No patients had a reduction in LVEF ≤ 30% necessitating

permanent treatment discontinuation through to week 16. There were no reported treatment discontinuations due to AEs or deaths through to week 16.

Critical Appraisal

Internal validity

Both the EXPLORER-HCM and the VALOR-HCM trials appeared to have acceptable methods for blinding, allocation concealment, and randomization with stratification. The clinical expert consulted for this review stated that the differences in the proportion of patients taking neither beta-blockers nor calcium channel blockers at baseline in EXPLORER-HCM (3.3% mavacamten vs 12.5% placebo) may have introduced bias in favour of mavacamten as a greater proportion of patients in the placebo group were not receiving any background therapy. The baseline and demographic characteristics in the VALOR-HCM trial appeared to be generally balanced between the treatment groups. Treatment discontinuation and study discontinuation among patients was low in both pivotal trials. The clinical expert consulted for this review indicated that the primary efficacy outcome of EXPLORER-HCM, pVO_2 and NYHA functional class, are appropriate measures of functional capacity and symptom severity, respectively, in the indicated population. In both pivotal trials, HRQoL was measured using the KCCQ-23 CSS as a key secondary outcome. The clinical expert consulted indicated that such tools are not typically used in clinical practice but are used in multiple studies. Disease-related symptoms were assessed using the newly developed HCMSQ instrument with the HCMSQ SoB domain assessed as a key secondary outcome in EXPLORER-HCM. It should be noted that as approximately 28% of patients did not have KCCQ-23 CSS or HCMSQ SoB data collected at baseline or week 30 visit in EXPLORER-HCM, there is a risk of bias as those that completed the questionnaires may be fundamentally different than those who did not (i.e., differences in treatment response). However, for all imputation scenarios, ad-hoc sensitivity analyses were generally supportive of the findings of the primary analyses.

The VALOR-HCM trial is evaluating the use of mavacamten to reduce the need for SRT in patients who are guideline eligible and willing to participate in invasive therapies. As such, there is no direct evidence of mavacamten compared to SRT available for this review. There is also limited direct evidence comparing mavacamten to disopyramide. Patients taking disopyramide were excluded from the EXPLORER-HCM trial and less than 20% of enrolled patients (n = 22) used disopyramide at baseline as monotherapy or in combination with beta-blockers and/or calcium channel blockers in VALOR-HCM. Subgroup analyses based on disopyramide use at baseline was not available for the VALOR-HCM trial, as statistical comparisons were not performed when the sample size within a subgroup was less than 20% of the overall population. Therefore, the comparative effectiveness of disopyramide versus mavacamten in this patient population is unknown. In terms of subgroups of interest, both pivotal trials included subgroup analyses by baseline background therapy (beta-blocker or calcium channel blocker use) and the EXPLORER-HCM trial also examined NYHA class (II vs III) as a pre-specified subgroup. For the primary endpoint in the EXPLORER-HCM trial, there was no statistically significant difference for the subgroup of patients taking beta-blockers. However, all key secondary endpoints in EXPLORER-HCM showed benefit for mavacamten compared with placebo across the evaluated subgroups, irrespective of beta-blocker use. The subgroup analyses may not have been powered to detect a treatment difference and there were no adjustments made for multiplicity. As such, all subgroup analyses are exploratory in nature. It should be noted that there was no clinical study report or statistical analysis plan available for the VALOR-HCM trial at the time of this review which prevented CADTH from being able to fully appraise the potential for bias within the trial.

Compared to the Canadian population, the racial diversity in the pivotal trials was limited as most patients were White. In addition, no patients were recruited from Canada in both pivotal trials. However, the clinical expert noted that the lack of representation of Canadian patients does not reduce generalizability of results to Canadian clinical practice. While mavacamten has been approved by Health Canada for use in adult patients with symptomatic oHCM of NYHA functional class II to III, the VALOR-HCM trial included an unknown number of NYHA functional class IV patients. The VALOR-HCM trial is an ongoing RCT evaluating the use of mavacamten to reduce the need for SRT in patients who are guideline eligible for invasive therapies with descriptive data available through to week 32. As such, it is uncertain if mavacamten can reduce the need for SRT among symptomatic oHCM patients in the long-term.

Indirect Comparisons

No indirect evidence was available.

Other Relevant Evidence

Additional descriptive efficacy and safety data for the VALOR-HCM trial through to week 32 and data from 1 open-label extension study (MAVA-LTE) were summarized in this report.

Description of studies

An additional study report was published for the VALOR-HCM trial examining data up to week 32 among patients initially randomized to mavacamten (32 weeks of drug exposure) and for patients initially randomized to placebo who crossed over to mavacamten at week 16 (16 weeks of drug exposure). A total of 4 patients in the placebo group who elected to undergo SRT treatment or withdrew from the study during the first 16 weeks were not included in this analysis.

MAVA-LTE is an ongoing, dose-blinded, 5-year extension study to assess the long-term efficacy and safety of mavacamten following patients who completed the EXPLORER-HCM trial through to week 38 (the EXPLORER-LTE cohort) and MAVERICK-HCM (a phase 2 trial in nonobstructive HCM not assessed in this report). A total of 224 patients who enrolled in the EXPLORER-LTE cohort started mavacamten treatment at 5 mg once daily, regardless of their treatment group in the EXPLORER-HCM pivotal trial. Dose adjustments at week 4, week 8, and week 12 were based on site-read echocardiograms of Valsalva LVOT gradient and LVEF. At LTE baseline, a total of 5.8% of patients in the EXPLORER-LTE cohort were NYHA functional class I, 65.2% were NYHA functional class II, 29.0% were NYHA functional class III, and none were NYHA functional class IV.

Efficacy Results

In the VALOR-HCM trial, at week 32, ≥ 1 NYHA class improvement was observed in 48/53 (90.6%) patients of original mavacamten group and 35/50 (70%) patients in the crossover group. In the original mavacamten group, the mean change from baseline to week 32 in in KCCQ-23 CSS was 13.1 points (95% CI, 9.2 to 17.1), while in the placebo crossover group, the mean change in KCCQ-23 CSS from week 16 to week 32 was 8.0 points (95% CI, 3.2 to 12.8). At week 32, 6 (10.7%) patients in the original mavacamten group and 7 (13.5%) patients in the placebo crossover group continued to meet guideline criteria for SRT or elected to undergo the procedure. In the original mavacamten group, there was a reduction in resting, Valsalva, and post-exercise LVOT gradients from baseline to week 32. A similar reduction in LVOT gradients in the crossover group was seen after 16 weeks of mavacamten exposure.

Among patients in the EXPLORER-LTE cohort, from LTE baseline to week 48 of the extension study, 35 (71.4%) patients had an improvement of ≥ 1 NYHA class [redacted] Reductions from LTE study baseline were observed in both resting and Valsalva LVOT gradients with mavacamten treatment as assessed by both site- and central-readings in the extension study. However, the number of patients were relatively small during the end timepoints, making it difficult to draw any conclusion about the effects of mavacamten on LVOT gradients. [redacted] In line with the EXPLORER-HCM pivotal trial, NT-proBNP concentrations decreased at LTE week 4 and decreases were sustained over time to LTE week 72.

Harms Results

In the VALOR-HCM trial, through to week 32, the rate of SAEs was similar between the original mavacamten group and the placebo crossover group. There were no reported deaths, myocardial infarctions, or strokes in either group. Through to week 32, 9 patients, comprising of 7 (12.5%) patients in the original mavacamten group and 2 (3.8%) patients in placebo crossover group, required a temporary drug discontinuation due to LVEF < 50%. One patient in the placebo crossover group had a reduction of LVEF ≤ 30% at week 31 associated with paroxysmal atrial fibrillation and heart failure. Following permanent mavacamten discontinuation, there was recovery and normalization of LVEF.

Among patients in the EXPLORER-LTE cohort, 62.9% of patients experienced at least 1 AE. The most common adverse events (frequency ≥ 3%) were atrial fibrillation, [redacted] fatigue, nasopharyngitis, dizziness, headache, dyspnea, and pain in extremity. One death, due to bacterial endocarditis, occurred in the EXPLORER-LTE cohort, which was deemed unrelated to mavacamten by the investigator. The most common SAEs among patients were cardiac failure (1.3%), pneumonia (0.9%), and atrial fibrillation (0.9%). A total of 2 patients (0.9%) permanently discontinued treatment due to AEs, with 1 patient discontinuing due to worsening of systemic lupus erythematosus (SLE) and 1 patient due to cardiac failure. No patients met the permanent discontinuation criteria of LVEF < 30%. A total of 11 (4.9%) patients demonstrated a total of 13 qualifying events meeting the criteria for a temporary treatment discontinuation, 4 (1.8%) of whom experienced LVEF < 50%.

Critical Appraisal

Results at week 32 of the VALOR-HCM trial provided additional data on the safety and efficacy of mavacamten. As all placebo patients crossed over to mavacamten treatment week at 16, there was no active comparator, and all outcomes were descriptive in nature, making it difficult to make causal conclusions of the findings. Once placebo patients crossed over to active treatment at week 16, investigators and patients were aware that all patients were receiving active treatment, and thus their expectations of treatment could affect reporting of subjective outcomes such as NYHA class, HRQoL, and adverse effects.

Among patients in the EXPLORER-LTE cohort, the baseline and demographic characteristics were similar to those seen in the pivotal trial. Treatment discontinuation and study discontinuation among patients were low in the extension study, as observed in both pivotal trials. Peak oxygen consumption from the pivotal trial was not assessed in the extension study, secondary and exploratory outcomes like HCMSQ and EQ-5D-5L data were collected in the extension study but were not assessed until the final analysis is conducted. The absence of these parameters in the interim analysis makes it difficult to interpret the efficacy results of mavacamten for the extension study. [redacted], the number of patients at later timepoints in all efficacy analyses were relatively few at the time of the data cut, therefore these results need to be interpreted with caution. The generalizability of the efficacy and harms outcomes and the lack of racial diversity mentioned in the main studies are applicable to the extension study.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with symptomatic obstructive hypertrophic cardiomyopathy (oHCM) of New York Heart Association (NYHA) Class II–III
Treatment	Mavacamten + beta-blockers or calcium channel blockers (BB/CCBs)
Dose regimen	5 mg once daily, with dose adjustments recommended based on left ventricular outflow tract (LVOT) gradient
Submitted price	Mavacamten, 2.5 mg, 5 mg, 10 mg, and 15 mg: $61.6000 per capsule
Treatment cost	$22,484 per year
Comparator	BB/CCB (73% of patients assumed to receive BB [53% metoprolol, 47% bisoprolol] and 23% assumed to receive CCB [50% diltiazem, 50% verapamil])
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (41 years)
Key data source	EXPLORER-HCM trial
Key limitations	• The full Health Canada population was not modelled. Effectiveness of mavacamten + BB/CCB in the pharmacoeconomic model was based on observations from the EXPLORER-HCM trial, in which most patients received mavacamten as second-line therapy. The cost-effectiveness of mavacamten as first- or third-line therapy is unknown. • Disopyramide was not included as a comparator, which was deemed inappropriate based on clinical practice guidelines and clinical expert feedback obtained by CADTH for this review.

Component	Description
	• The survival benefit predicted by the sponsor's submitted model for mavacamten + BB/CCB compared to BB/CCB is highly uncertain and has not been shown in clinical trials. • Several assumptions related to subsequent therapy are highly uncertain and not aligned with expected clinical practice. As a result of these assumptions, the sponsor's model predicts that more patients will undergo septal reduction therapy after mavacamten compared to BB/CCB, which is contradictory to the findings of the VALOR trial. • The sponsor's use of a shorter observation period for the efficacy of mavacamten + BB/CCB compared with BB/CCB biases the results in favour of mavacamten. • The relative long-term effectiveness of mavacamten compared to BB/CCB is highly uncertain. • The sponsor incorporated response-based stopping rules for mavacamten, which are not recommended in the product monograph or implemented in the pivotal trials. Clinical experts consulted by CADTH indicated that criteria adopted by the sponsor in the model are not aligned with how mavacamten is expected to be used in clinical practice.
CADTH reanalysis results	• In CADTH reanalyses, CADTH removed the survival benefit for mavacamten, adopted alternative assumption on subsequent treatment among patients on BB/CCB, adopted the same observation period to determine the efficacy of mavacamten and BB/CCB, and removed the response-based stopping rules for mavacamten. CADTH was unable to address the omission of disopyramide as a comparator. • Results of the CADTH reanalyses, suggest that mavacamten + BB/CCB is more costly (incremental costs: $264,737) and more effective (incremental QALYs: 0.46) than BB/CCB alone, resulting in an ICER of $576,295 per QALY gained when used in the second-line setting for patients with baseline NYHA Class II or III. A price reduction of 73% for mavacamten would be required for mavacamten + BB/CCB to be considered cost-effective compared to BB/CCB at a willingness-to-pay threshold of $50,000 per QALY. • The cost-effectiveness of mavacamten compared to disopyramide is unknown. Furthermore, the results were sensitive to the assumptions about the long-term relative effectiveness of mavacamten. The CADTH reanalysis estimated a smaller benefit in the extrapolated period compared to the sponsor although uncertainty remains regarding the expected magnitude of the clinical benefit. If treatment effectiveness waning occurs, a higher price reduction would be required.

BB = beta blocker; CCB calcium channel blocker; ICER = incremental cost-effectiveness ratio; LY = life-year; NYHA = New York Heart Association; oHCM = obstructive hypertrophic cardiomyopathy; QALY= quality-adjusted life-year; SRT = septal reduction therapy.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis:

- The number of patients eligible for mavacamten plus BB or CCB is highly uncertain. The sponsor's method of deriving the eligible population size may have double counted the proportion of patients who are diagnosed, thus underestimating the number eligible. Most of the epidemiological parameters utilized by the sponsor were based on expert opinion or data that could not be validated by CADTH.
- The uptake of mavacamten may be higher than estimated by the sponsor in some settings.

CADTH reanalyses included: removing the double counting of symptomatic patients by assuming that all patients diagnosed with oHCM are symptomatic and including mark-ups and dispensing fees. CADTH reanalyses suggest that the overall budget impact to the public drug plans of introducing mavacamten for the treatment of symptomatic oHCM in adult patients is $54,641,769 over three years (Year 1: $4,807,445; Year 2: $13,723,972; Year 3: $36,110,351).

The estimated budget impact is sensitive to assumptions about the number of patients eligible for mavacamten and the rate of uptake of mavacamten. Should the number of patients eligible to receive mavacamten increase or the rate of uptake of mavacamten among eligible patients increase, the budget impact of reimbursing mavacamten will be higher than the CADTH base case.

CDEC Information

Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Meeting date: February 23, 2023

Regrets:

Three of expert committee members did not attend.

Conflicts of interest:

None