

# A Systematic Review of Clinical Trials on Mavacamten in Hypertrophic Cardiomyopathy

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**Introduction:** Hypertrophic cardiomyopathy (HCM) is characterised by unusual thickening of the interventricular septum leading to dynamic left ventricular outflow tract obstruction, mitral valve regurgitation, impaired diastolic function and arrhythmias. Mavacamten (MYK-461) is a first-in-class, selective allosteric modulator of cardiac myosin adenosine triphosphatase and received US Food and Drug Administration (FDA) approval on 28 April 2022 to treat symptomatic obstructive HCM (oHCM). **Methods:** A systematic search of Medline/PubMed and ClinicalTrials.gov was conducted using advanced search strategies with the terms 'mavacamten/MYK-461' and 'hypertrophic cardiomyopathy/HCM' to identify and include all clinical trials published to date. **Results:** The clinical efficacy of mavacamten has been consistently demonstrated in the PIONEER-HCM, MAVERICK-HCM, EXPLORER-HCM, VALOR-HCM, EXPLORER-CN-HCM and HORIZON-HCM clinical trials – there was a notable decrease in the left ventricular outflow tract gradient. Apart from the MAVERICK experiment, which revealed no discernible change in functional class or peak volume of oxygen uptake ( $pVO_2$ ) in non-oHCM patients, improvements were reported in New York Heart Association functional class,  $pVO_2$  and quality-of-life metrics. Except for the PIONEER trial, which didn't report biomarker data such as N-terminal pro B-type natriuretic peptide (NT-proBNP) and troponins, mavacamten significantly reduced biomarkers in all investigations. Additionally, the VALOR trial showed that there was a reduced need for septal reduction therapy. Although systolic dysfunction is a major safety risk that requires careful monitoring, mavacamten was generally well tolerated. **Conclusion:** Mavacamten offered a promising, non-invasive pharmacological therapy for patients with symptomatic oHCM, particularly for those who are not candidates for or who have failed conventional treatments.

## Keywords

Diastolic dysfunction, hypertrophic cardiomyopathy, interventional, left ventricular outflow tract gradients, mavacamten, myosin heavy chains, quality of life, treatment outcome

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Hypertrophic cardiomyopathy (HCM) is a genetic cardiac abnormality characterized by left ventricular hypertrophy and diastolic dysfunction, primarily attributed to mutations in genes that encode sarcomeric proteins.<sup>1,2</sup> The disease manifests in two broad phenotypes: obstructive HCM (oHCM), defined by dynamic left ventricular outflow tract obstruction (LVOTO), and non-obstructive HCM (nHCM), which lacks significant left ventricular outflow tract gradients (LVOTGs).<sup>3</sup> The management of HCM has traditionally centred on relieving symptoms and minimizing LVOTO, especially in cases of oHCM. Pharmacologic therapies, including  $\beta$ -blockers, disopyramide and non-dihydropyridine calcium channel blockers, have offered symptomatic relief but have failed to address the underlying pathophysiology or alter the disease course.<sup>4,5</sup> Septal reduction therapy (SRT), an invasive procedure used for refractory cases, effectively reduces LVOTO but carries surgical risks and demands specialized expertise.<sup>6</sup>

A novel therapeutic approach has emerged with mavacamten/MYK-461 (MYK), a first-of-its-kind allosteric inhibitor of cardiac-specific myosin adenosine triphosphatase (ATPase). Over the past decade, six pivotal clinical trials – PIONEER-HCM (A Phase 2 Open-label Pilot Study Evaluating MYK-461 in Subjects With Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction; ClinicalTrials.gov identifier: NCT02842242), MAVERICK-HCM (A Phase 2 Study of Mavacamten in Adults With Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy; ClinicalTrials.gov identifier: NCT03442764), EXPLORER-HCM (Clinical Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy; ClinicalTrials.gov identifier: NCT03470545), VALOR-HCM (A Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive HCM Who Are Eligible for Septal Reduction Therapy; ClinicalTrials.gov identifier: NCT04349072), EXPLORER-CN-HCM (A Study to Evaluate the Efficacy and Safety of Mavacamten in Chinese Adults With Symptomatic Obstructive HCM; ClinicalTrials.gov identifier: NCT05174416) and HORIZON-HCM (A Study of Mavacamten in Obstructive Hypertrophic Cardiomyopathy; ClinicalTrials.gov identifier: NCT05414175) – have investigated the safety and effectiveness of MYK in managing HCM.<sup>7–14</sup> These studies have offered valuable insights into its potential to improve functional capacity, alleviate symptoms and mitigate LVOTO. This systematic review combines data from all six original clinical trials and provides a comprehensive analysis of MYK's role in HCM management. By synthesizing the available data, this review aims to provide a thorough understanding of MYK's therapeutic potential, identify gaps in knowledge and highlight areas for further research.

## Materials and methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocol for clinical trials was followed for reporting this systematic review.<sup>15</sup> *Figure 1* presents the PRISMA flow diagram outlining the study selection process. *Figure 2* illustrates the bias assessment of the trials included. The inclusion criteria encompassed primary human clinical trials published in English, with final results available. Excluded studies comprised animal research, secondary analyses, case reports, case series and clinical trials with interim results. A systematic search of PubMed/Medline and ClinicalTrials.gov was carried out using advanced search strategies with the terms 'mavacamten/MYK-461' and 'hypertrophic cardiomyopathy/HCM'. The search was performed to identify and include all clinical trials of mavacamten in HCM published up to November 2024. The validity of the included trials was assessed with the Cochrane Risk of Bias Tool.<sup>16</sup>

Each study's data extraction included the primary author, publication year, study duration, study type, country, comparison groups, follow-up period,

participant age and gender, dosage details, inclusion criteria, primary and secondary endpoints, adverse events, results and limitations. These data were systematically analysed and compared. Data extraction was independently conducted by two authors. Decisions regarding inclusion in the systematic review were made collaboratively. In instances of disagreement, a resolution was reached through discussion with the lead author.

## Results

### Baseline characteristics of the clinical trials

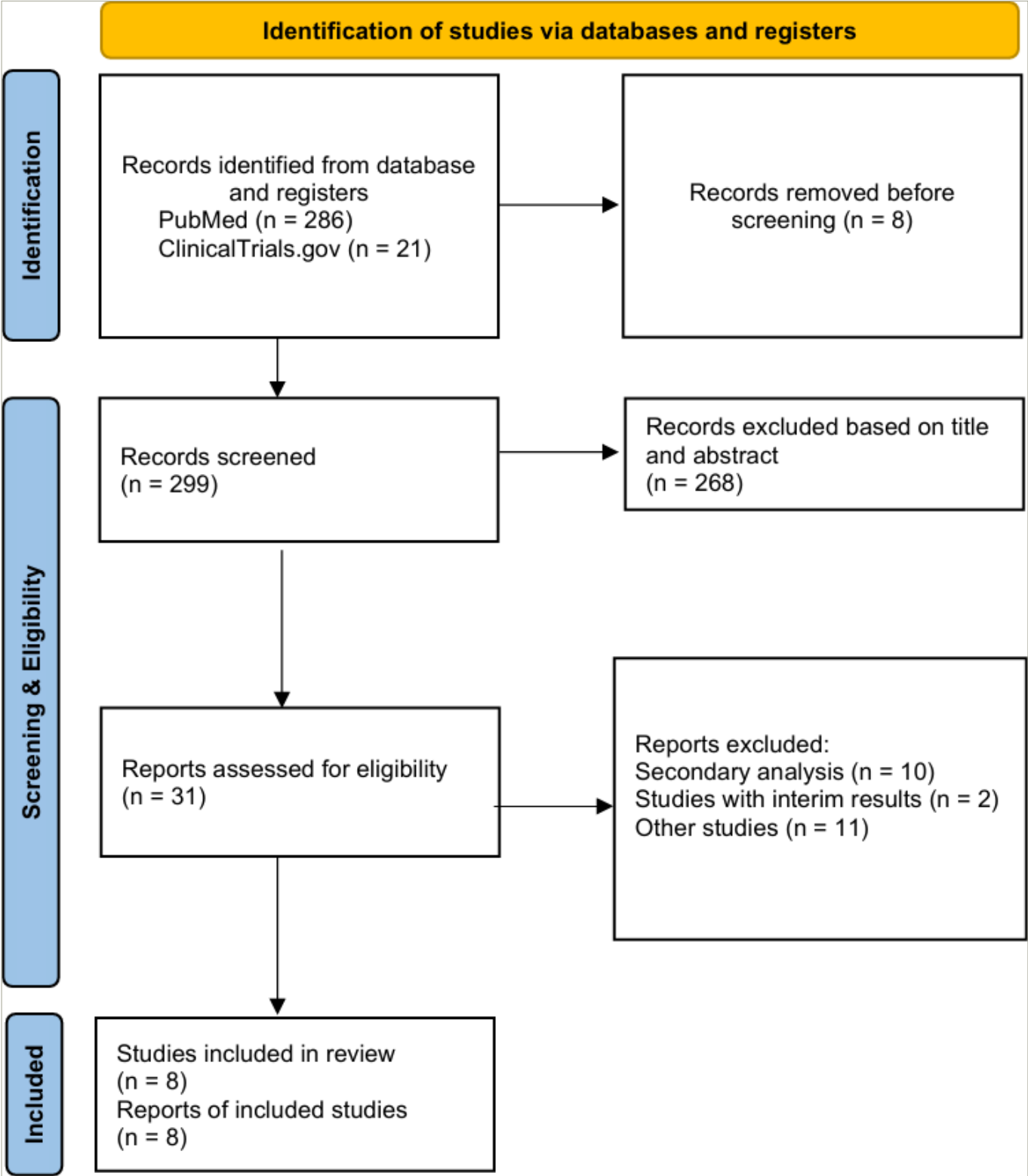
The included trials spanned phase II and phase III, with study designs varying from open-label to randomized, double-blind trials.<sup>7–14</sup> Most of these trials targeted symptomatic oHCM, while the MAVERICK trial explored the nHCM.<sup>8</sup> Geographically, PIONEER, MAVERICK, EXPLORER and VALOR were conducted in the USA, followed by two additional trials in China and Japan.<sup>7–12</sup> The EXPLORER-CN trial was conducted in China, and the HORIZON trial took place in Japan.<sup>13,14</sup> All the trials conducted were multicentric, ranging from 5 centres (in the PIONEER trial) to 68 centres (in the EXPLORER trial), reflecting varied scales and regional applicability.<sup>7,13</sup>

The VALOR trial published results in three separate papers at 16 weeks, 32 weeks and 56 weeks.<sup>10–12</sup> The initial publication presented outcomes at 16 weeks, with subsequent publications reporting results at 32 and 56 weeks. These additional publications, which followed the same aim and protocol over the study period, offered result data at different time points from the same study population and were not distinct investigations. Accordingly, all three publications were treated as a single study for this systematic review. To represent the unified study design and conclusions, the data from all three publications were extracted and combined into a single column. *Table 1* compares the baseline characteristics of trials: primary author, publication year, duration, type and country of study.<sup>7–14</sup>

### Baseline details of the study population

Population characteristics revealed sample sizes ranging from 21 (PIONEER trial) to 251 (EXPLORER trial) participants.<sup>7,9</sup> A minimum follow-up of 16 weeks was noted in all these trials. The mean age of participants in the studies was greater than 50 years, ranging between 51.9 (EXPLORER-CN trial) and 64.8 years (HORIZON trial).<sup>13,14</sup> Gender distribution varied significantly, with more male participation in the PIONEER, EXPLORER, VALOR and EXPLORER-CN trials, a pattern consistent with the reported higher incidence of HCM in males.<sup>7,9–13,15</sup> However, the MAVERICK and HORIZON trials had more female participation.<sup>8,14</sup> The VALOR trial had a nearly equal distribution of male and female participants — indicating a well-balanced gender representation.<sup>10–12</sup> The EXPLORER-CN trial had the highest difference between the two genders, followed by the HORIZON trial.<sup>13,14</sup> All the studies individualized MYK doses by titrations based on serum concentration or physiological measures such as LVOTG and left ventricular ejection fraction (LVEF). Each trial initiated a dose of 2.5 mg/day and progressed with up-titrations or down-titrations (2.5, 5, 10 and 15 mg/day) to achieve a satisfactory individualized MYK dose. No specific or generalized pattern of titration could be associated with age, gender or duration. Nevertheless, the studies' strengths lay in their comprehensive dose adjustments and targeted approaches, which are discussed below. Only Cohort B of the PIONEER trial, the EXPLORER-CN trial and the HORIZON trial allowed the use of other medical therapies, though these were limited to monotherapy.<sup>7,13,14</sup> *Table 2* compares the baseline characteristics of study population: comparison groups,

Figure 1: PRISMA flow diagram outlining the study selection process



dosage and duration of treatment, and age and gender details of participants.

Details of inclusion criteria and study objectives

All the trials fairly shared similar inclusion criteria and study objectives, as outlined in Table 3.<sup>7-14</sup> Inclusion criteria typically focused on the diagnosis of HCM, LVEF percentages, LVOTG values and New York Heart Association (NYHA) class II or III symptoms.<sup>8-14</sup> Details regarding pregnancy during the initiation or course of treatment were not provided

in most trials, except the MAVERICK trial, which explicitly stated that pregnancy was not permitted during the study period.<sup>8</sup> The VALOR-HCM trial uniquely selected patients with a diagnosis of HCM who were referred for consideration of SRT (based on 2011 ACC/AHA guidelines), and it was also the only study to include participants with NYHA class IV symptoms, in addition to meeting the previously mentioned criteria.<sup>10-12</sup> However, the VALOR trial also had a distinct primary study objective – the effect of MYK on the need for SRT at 16, 32 and 56 weeks in patients with oHCM, which differed from the objectives of other clinical studies. The

Figure 2: Risk of bias assessment for the included trials, evaluated using the Cochrane Risk of Bias Tool

|                                                   | D1 | D2 | D3 | D4 | D5 | D6 |
|---------------------------------------------------|----|----|----|----|----|----|
| <b>Stephen B Heitner, 2019</b><br>(PIONEER TRIAL) | —  | +  | —  | —  | +  | +  |
| <b>Carolyn Y Ho, 2020</b><br>(MAVERICK TRIAL)     | +  | +  | +  | +  | +  | +  |
| <b>Lacopo Olivotto, 2020</b><br>(EXPLORER TRIAL)  | +  | +  | +  | +  | +  | +  |
| <b>Milind Y Desai, 2023</b><br>(VALOR TRIAL)      | +  | +  | +  | +  | +  | +  |
| <b>Zhuang Tian, 2023</b><br>(EXPLORER-CN TRIAL)   | +  | +  | +  | +  | +  | +  |
| <b>Hiroaki Kitaoka, 2024</b><br>(HORIZON TRIAL)   | ?  | ?  | —  | —  | +  | +  |

D1: Random sequence generation  
D2: Allocation concealment  
D3: Blinding of participants and personnel  
D4: Blinding of outcomes assessment  
D5: Incomplete outcome data  
D6: Selective reporting

High risk of Bias  
 Low risk of Bias  
 Unclear risk of Bias

study objectives of the other trials generally included changes in LVOTG, LVEF, cardiac biomarkers, improvement of  $\geq 1$  NYHA functional class from baseline and measures of patient-reported outcomes. The PIONEER and EXPLORER trials also examined peak oxygen uptake ( $pVO_2$ ).<sup>7,9</sup> Notably, the EXPLORER-CN trial was the first to assess the cardiac magnetic resonance imaging (CMR)-derived left ventricular mass index (LVMI).<sup>13</sup> Outcomes and adverse events are discussed in a separate section

below. To summarize, the MAVERICK trial's primary goal was to assess the safety and tolerability of a 16-week course of MYK, with additional objectives overlapping those of other trials.<sup>8</sup>

### Limitations

Trials included in this review exhibit several limitations that affected the generalizability and robustness of their findings. A common issue across

Table 1: Comparison of the baseline characteristics of trials<sup>7–14</sup>

| Trial name (year)                | ClinicalTrials.gov identifier | Primary author    | Study duration | Study type                                                                              | Country (number of centres)     | Condition        |
|----------------------------------|-------------------------------|-------------------|----------------|-----------------------------------------------------------------------------------------|---------------------------------|------------------|
| PIONEER (2019) <sup>7</sup>      | NCT02842242                   | Stephen B Heitner | 2016–2017      | Phase II, open-label, non-randomized trial                                              | USA multicentric (5)            | Symptomatic oHCM |
| MAVERICK (2020) <sup>8</sup>     | NCT03442764                   | Carolyn Y Ho      | 2018–2020      | Phase II, exploratory, double-blind, dose-ranging, randomized, placebo-controlled trial | USA multicentric (35)           | Symptomatic nHCM |
| EXPLORER (2020) <sup>9</sup>     | NCT03470545                   | Lacopo Olivotto   | 2018–2020      | Phase III, randomized, placebo-controlled, parallel-group trial                         | 13 countries, multicentric (68) | Symptomatic oHCM |
| VALOR (2023) <sup>10–12</sup>    | NCT04349072                   | Milind Y Desai    | 2020–2022      | Phase III, randomized, placebo-controlled, double-blind                                 | USA multicentric (19)           | Symptomatic oHCM |
| EXPLORER-CN (2023) <sup>13</sup> | NCT05174416                   | Zhuang Tian       | 2022–2022      | Phase III, randomized, placebo-controlled, double-blind                                 | China multicentric (12)         | Symptomatic oHCM |
| HORIZON (2024) <sup>14</sup>     | NCT05414175                   | Hiroaki Kitaoka   | 2022–2023      | Phase III, open-label, single-arm study                                                 | Japan multicentric (NA)         | Symptomatic oHCM |

HCM = hypertrophic obstructive cardiomyopathy; NA = not applicable; NCT = National Clinical Trial; nHCM = non-obstructive HCM; oHCM = obstructive HCM.

Table 2: Comparison of the baseline characteristics of study population<sup>7–14</sup>

| Trial name                | Comparison                                                                                                            | Duration of follow-up                                                                        | Population (n)                                                  | Mean age   | Gender           | Dosage                                                                                                                                                                                                                                                                                                                                                |
|---------------------------|-----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|-----------------------------------------------------------------|------------|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PIONEER <sup>7</sup>      | MYK (Cohort A) – MYK (Cohort B)                                                                                       | 16 weeks (12-week treatment + 4-week post-treatment)                                         | n=21; Cohort A=11; Cohort B=10                                  | 57 years   | M=57.1%; F=42.9% | Cohort A: 10–20 mg/dl MYK (other medical therapies were discontinued at least 14 days before the initial dose of MYK); Cohort B: 2–5 mg/dl MYK with $\beta$ -blockers allowed                                                                                                                                                                         |
| MAVERICK <sup>8</sup>     | MYK (Group 1) – MYK (Group 2) – placebo                                                                               | 24 weeks (16-week treatment + 8-week washout)                                                | n=59: Group 1=19; Group 2=21; Pooled (Group 1+2)=40; placebo=19 | 53.9 years | M=42.4%; F=57.6% | Participants received MYK for 16 weeks, with doses titrated at the sixth week to target one of two approximate serum drug concentrations; Group 1: 200 ng/mL; Group 2: 500 ng/mL; pooled median MYK dose: 5 mg/day                                                                                                                                    |
| EXPLORER <sup>9</sup>     | MYK – placebo                                                                                                         | 30 weeks                                                                                     | n=251; MYK=123; placebo=128                                     | 60 years   | M=59.4%; F=40.6% | Oral doses of 2.5, 5, 10 or 15 mg were administered to achieve a target reduction in LVOTG <30 mmHg and an MYK plasma concentration between 350 ng/mL and 700 ng/mL                                                                                                                                                                                   |
| VALOR <sup>10–12</sup>    | MYK – placebo for 16 weeks and then the placebo group was crossed over to dose-blinded MYK to 32 and then to 56 weeks | 16 weeks – 32 weeks – 56 weeks                                                               | n=112; MYK=56; placebo=56                                       | 60.3 years | M=50.9%; F=49.1% | Patients were titrated to receive 2.5, 5, 10 or 15 mg capsules of MYK once daily orally using core-lab measured echocardiogram LVOTG and LVEF at rest and Valsalva provocation                                                                                                                                                                        |
| EXPLORER-CN <sup>13</sup> | MYK – placebo                                                                                                         | 30 weeks                                                                                     | n=81; MYK=57; placebo=27                                        | 51.9 years | M=71.6%; F=28.4% | Started on oral MYK at 2.5 mg once daily, with individualized dose changes based on Valsalva LVOTG and LVEF measured by echo                                                                                                                                                                                                                          |
| HORIZON <sup>14</sup>     | Single arm study of MYK                                                                                               | 30-week primary treatment; 30 week–138 week long-term and an 8-week post-treatment follow-up | n=38                                                            | 64.8 years | M=34.2%; F=65.8% | Started on oral MYK at 2.5 mg once daily, with personalized dose adjustments (up or down titration) at 6, 8, 14 and 20 weeks based on Valsalva LVOTG and LVEF measured by echocardiography; monotherapy with stable dose $\beta$ -blockers/ diltiazem/verapamil was permitted if treatment was tolerated well for at least 2 weeks prior to screening |

F = females; LVEF = left ventricular ejection fraction; LVOTG = left ventricular outflow tract gradient; M = males; MYK = mavacamten; Wk = week(s).

these trials was the short follow-up period and small participant size, which limited the statistical power and the strength to draw definitive summaries. Trials such as PIONEER and HORIZON employed single-arm or open-label designs, reducing the ability to directly compare results with a control group.<sup>7,14</sup> Conservative dosing strategies observed across all trials may have contributed to potentially suboptimal outcomes in some patients. Despite reductions in cardiac biomarkers, the brief follow-up periods might not have been long enough to detect clinically significant changes in symptoms, quality of life or functional outcomes. Additional study-specific limitations, as noted by the authors, are outlined in *Table 3*. Potential remedies for these limitations are discussed in the ‘Future approaches and additional studies for follow-up’ section.

### Summary of outcomes

All trials demonstrated significant improvements in both primary and secondary outcomes. The efficacy of MYK was consistently evaluated across multiple trials, with a primary focus on reductions in LVOTG. The PIONEER, EXPLORER, EXPLORER-CN and HORIZON trials reported significant reductions in LVOTG, either from baseline or in comparison to control groups.<sup>7,9,13,14</sup> These reductions were consistently observed across resting, Valsalva manoeuvres and postexercise LVOTG measurements. Assessing the safety as well as tolerability of a 16-week regimen of MYK therapy was the main goal of the MAVERICK trial, which was carried out in patients with nHCM. Results indicated that MYK was

generally well-tolerated, with reported mild-to-moderate adverse effects.<sup>8</sup> Adverse events and treatment discontinuations, if any, across all trials are discussed collectively in a separate section below. The VALOR trial demonstrated that MYK lowered the proportion of participants qualifying for SRT after 16 weeks, accompanied by noticeable improvements in LVOTG and other symptoms.<sup>10–12</sup> These benefits were sustained at 32 and 56 weeks, with consistent reductions in LVOTG and continued symptomatic improvement. While these findings highlighted MYK as a promising treatment option, the risk of systolic heart failure necessitates ongoing close monitoring.

Except in the MAVERICK trial, improvements in the NYHA functional class have been consistent across all trials.<sup>8</sup> The HORIZON trial demonstrated particularly remarkable results, with 100% of patients achieving at least a one-class improvement by the study's conclusion, and no patients remaining in NYHA class III.<sup>14</sup> Conversely, the MAVERICK study reported no significant changes in NYHA class status or pVO<sub>2</sub> in the intention-to-treat population ( $p>0.05$ ).<sup>8</sup> However, significant increases in mean pVO<sub>2</sub> were observed in cohort A (10–20 mg/dL MYK with other medical therapies discontinued at least 14 days before the initial dose of MYK) compared to cohort B (cohort B: 2–5 mg/dL MYK with  $\beta$ -blockers allowed) in the PIONEER trial and in the MYK group compared to controls in the EXPLORER trial.<sup>7,9</sup> Biomarker analyses (N-terminal proB-type natriuretic peptide [NTproBNP], cardiac troponin I [cTnI] and cardiac troponin T

Table 3: Comparison of the inclusion criteria, outcomes measured and limitations of each study<sup>7–14</sup>

| Name of the trial         | Inclusion criteria                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Outcomes measured                                                                                                                                                                                                                                                                                                                                               | Limitations stated by authors                                                                                                                                                                                                                                                                                                                                                                                                                   |
|---------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PIONEER <sup>7</sup>      | <ul style="list-style-type: none"> <li>- HCM diagnosis</li> <li>- LVOTO (resting LVOTG <math>\geq 30</math> mmHg and postexercise LVOTG <math>\geq 50</math> mmHg)</li> <li>- NYHA functional class II or III</li> <li>- LVEF <math>\geq 45\%</math></li> </ul>                                                                                                                                                                                                                                                                                 | <ul style="list-style-type: none"> <li># Change in postexercise LVOTG</li> <li># Change in NRS dyspnoea score and KCCQ-OSS</li> <li># Change in <math>pVO_2</math></li> <li># Change in resting LVEF</li> </ul>                                                                                                                                                 | <ul style="list-style-type: none"> <li>- Small size</li> <li>- Open-label design</li> </ul>                                                                                                                                                                                                                                                                                                                                                     |
| MAVERICK <sup>8</sup>     | <ul style="list-style-type: none"> <li>- nHCM diagnosis</li> <li>- NYHA functional class II or III</li> <li>- NTproBNP <math>&gt; 300</math> pg/mL</li> <li>- LVEF <math>\geq 55\%</math></li> <li>- No pregnancy allowed during the study period</li> </ul>                                                                                                                                                                                                                                                                                    | <ul style="list-style-type: none"> <li># Primary objective – evaluation of safety and tolerability of a 16-week period of MYK</li> <li># Change in the NTproBNP levels</li> <li># Change in the levels of cTnI</li> <li># Change in resting LVEF</li> </ul>                                                                                                     | <ul style="list-style-type: none"> <li>- Exploratory and dose-finding nature</li> <li>- Small size</li> </ul>                                                                                                                                                                                                                                                                                                                                   |
| EXPLORER <sup>9</sup>     | <ul style="list-style-type: none"> <li>- HCM diagnosis</li> <li>- LVOTG <math>\geq 50</math> mmHg at rest, after Valsalva manoeuvre or exercise</li> <li>- LVEF <math>\geq 55\%</math> NYHA class II or III symptoms</li> <li>- Able to safely perform upright cardiopulmonary exercise testing</li> </ul>                                                                                                                                                                                                                                      | <ul style="list-style-type: none"> <li># Change in <math>pVO_2</math></li> <li># Change in NYHA functional class</li> <li># Change in postexercise LVOTG</li> <li># Measures of patient-reported KCCQ-CSS and HCMSQSoB sub-score</li> <li># Change in the NTproBNP, cTnI levels</li> </ul>                                                                      | <ul style="list-style-type: none"> <li>- Participants on disopyramide and patients with severe symptoms (NYHA class IV)</li> </ul>                                                                                                                                                                                                                                                                                                              |
| VALOR <sup>10–12</sup>    | <p>Patients taking maximally tolerated medical therapy and referred for consideration of SRT based on 2011 American College of Cardiology/American Heart Association guidelines were selected for study with the following criteria:</p> <ul style="list-style-type: none"> <li>- HCM diagnosis</li> <li>- LVOTG <math>\geq 50</math> mmHg or greater at rest or with provocation</li> <li>- LVEF <math>\geq 60\%</math> NYHA class III/IV or II with exertional syncope or near syncope despite maximally tolerated medical therapy</li> </ul> | <p>Primary focus: effect of MYK on the need for SRT through 16 weeks, 32 weeks and 56 weeks in oHCM secondary outcomes:</p> <ul style="list-style-type: none"> <li># Improvement in NYHA class</li> <li># Measures of patient-reported outcomes – KCCQ-23 CSS</li> <li># Change in the NTproBNP, cTnI levels</li> <li># Change in postexercise LVOTG</li> </ul> | <ul style="list-style-type: none"> <li>- Sample size</li> <li>- Primary endpoint was solely affected by a decrease in guideline-based eligibility for SRT, rather than by patients deciding against the procedure</li> <li>- Study primarily involved White American patients (89.3%) treated at large-scale HCM centres with recognized expertise in SRT. Other patients were Asian (2.7%), Black (1.8%) or unsepcified race (6.2%)</li> </ul> |
| EXPLORER-CN <sup>13</sup> | <ul style="list-style-type: none"> <li>- HCM diagnosis</li> <li>- LVOTG <math>\geq 50</math> mmHg at rest or with provocation</li> <li>- LVEF <math>\geq 55\%</math> NYHA class II or III symptoms</li> </ul>                                                                                                                                                                                                                                                                                                                                   | <ul style="list-style-type: none"> <li># Change in Valsalva peak LVOTG</li> <li># Change in LVEF</li> <li># Change in LVMI</li> <li># Improvement in NYHA class</li> <li># Measures of patient-reported outcomes – KCCQ-CSS</li> <li># Change in the NTproBNP, cTnI levels</li> </ul>                                                                           | <ul style="list-style-type: none"> <li>- Lack of data on <math>pVO_2</math> and stress echocardiogram</li> <li>- Conservative titration strategy could lead to some patients being underdosed</li> <li>- Study population was relatively small</li> </ul>                                                                                                                                                                                       |
| HORIZON <sup>14</sup>     | <ul style="list-style-type: none"> <li>- HCM diagnosis</li> <li>- LVOTG <math>\geq 50</math> mmHg at rest or with provocation</li> <li>- Resting LVEF <math>\geq 60\%</math> NYHA class II or III symptoms</li> </ul>                                                                                                                                                                                                                                                                                                                           | <p>Primary study endpoint – 30-week change in postexercise peak LVOTG from baseline</p> <p>Secondary endpoints</p> <ul style="list-style-type: none"> <li># Measures of patient-reported outcomes – KCCQ-23 CSS</li> <li># Change in the NTproBNP, cTnI, cTnT</li> <li># Improvement in NYHA class</li> </ul>                                                   | <ul style="list-style-type: none"> <li>- Single-arm study</li> <li>- No comparison group</li> <li>- Relatively small sample and had a short follow-up period</li> <li>- Excluded participants on disopyramide or cibenzoline and participants with severe symptoms (NYHA class IV)</li> </ul>                                                                                                                                                   |

cTnI = cardiac troponin I; cTnT = cardiac troponin T; HCM = hypertrophic obstructive cardiomyopathy; HCMSQSoB = Hypertrophic Cardiomyopathy Symptom Questionnaire on Shortness of Breath; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire Overall Summary Score; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; LVOTG = left ventricular outflow tract gradient; LVOTO = left ventricular outflow tract obstruction; MYK = mavacamten; nHCM = non-obstructive HCM; NRS = numerical rating scale; NTproBNP = N-terminal proB-type natriuretic peptide; NYHA = New York Heart Association; oHCM = obstructive HCM;  $pVO_2$  = peak oxygen uptake; SRT = septal reduction therapy; Wk = Week(s).

[cTnT]) across all trials highlighted the efficacy of MYK. Despite variations in the numerical data and statistical methods employed across trials, a consistent pattern of significant improvement was observed in patients treated with MYK.<sup>8–14</sup> Change in biomarker levels was not the objective of the PIONEER trial, and subsequently, no data were available to assess.<sup>7</sup>

The Kansas City Cardiomyopathy Questionnaire (KCCQ/KCCQ-23) is a 23-item self-administered tool designed to assess disease-specific outcomes.<sup>17</sup> The KCCQ overall summary score (KCCQ-OSS) and dyspnoea score used in the PIONEER trial showed improvement in both cohorts. The KCCQ clinical summary score (KCCQ-CSS) was used in EXPLORER, VALOR, EXPLORER-CN and HORIZON trials and reported improvement of scores at the time of analysis.<sup>7,9–14</sup> The EXPLORER trial used the Hypertrophic Cardiomyopathy Symptom Questionnaire on Shortness of Breath (HCMSQSoB), and the mean difference between the treatment group and placebo was  $-1.8$  (95% CI:  $-2.4$ ,  $-1.2$ ;  $p < 0.0001$ ;

negative change better).<sup>9</sup> Based on the data presented, it could be said that patients perceived a better quality of life during the trial period. The EXPLORER-CN trial demonstrated that the current titration scheme for MYK was effective without the need for CYP2C19 genotyping.<sup>13</sup> However, this did not imply that MYK was unaffected by CYP2C19. On the contrary, MYK is significantly influenced by CYP2C19, but the trial findings indicated that its effects could be effectively managed through careful titration.<sup>18</sup> The EXPLORER-CN trial used CMR in eligible patients after the research period and noted a reduction in LVMI, maximal wall thickness, LV mass and maximum left atrial volume index (LAVI).<sup>13</sup> Notably, this association was not investigated in any other clinical trial. Table 4 compares comprehensive information and a detailed comparison of study results.<sup>7–14</sup>

Table 4: Comparison of comprehensive information and a detailed comparison of study results<sup>7-14</sup>

| Trial name                | Endpoints                                  | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|---------------------------|--------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PIONEER <sup>7</sup>      | Post-exercise LVOTG†                       | At 12 weeks, mean decreased to 19 mmHg (SD, 13) from 103 mmHg (SD, 50); at baseline (mean change, -89.5 mmHg [95% CI: -138.3, -40.7]; p=0.008) in cohort A compared to a decrease to 64 mmHg (SD, 26) from 86 mmHg (SD, 43) in cohort B (mean change, -25.0 mmHg [CI: -47.1, -3.0]; p=0.020)                                                                                                                                                           |
|                           | Resting LVEF                               | Mean change of -15% (CI: -23%, -6%) and -6% (CI: -10%, -1%) in cohort A and B, respectively                                                                                                                                                                                                                                                                                                                                                            |
|                           | pVO <sub>2</sub>                           | Mean increase of 3.5 mL/kg/min (CI: 1.2, 5.9) is observed in cohort A compared to an increase of 1.7 mL/kg/min (CI: 0.03, 3.3) in cohort B                                                                                                                                                                                                                                                                                                             |
|                           | Dyspnoea score and KCCQ-OSS                | Both cohorts showed improvement in NRS dyspnoea scores and KCCQ-OSS                                                                                                                                                                                                                                                                                                                                                                                    |
| MAVERICK <sup>8</sup>     | Safety and tolerability†                   | MYK was generally well tolerated; 76% of reported adverse events were mild and 21% with moderate severity; most common symptoms include dizziness, fatigue, nausea and dyspnoea                                                                                                                                                                                                                                                                        |
|                           | NTproBNP                                   | 53% decrease in the pooled group; 1% decrease in the placebo group in geometric means (geometric mean differences of 435 and 6 pg/mL, respectively, p=0.0005)                                                                                                                                                                                                                                                                                          |
|                           | cTnI                                       | 34% decrease in geometric mean was noted in the pooled group, whereas 4% increase in the placebo group (geometric mean differences of 0.008 and 0.001 ng/mL, respectively, p=0.009)                                                                                                                                                                                                                                                                    |
|                           | LVEF                                       | Modest change noted: mean absolute change was -2.3 ± 5.3% in Group 1, -5.6 ± 9.7% in Group 2, -4.1 ± 8.0% in the pooled group and -2.3 ± 4.9% in placebo                                                                                                                                                                                                                                                                                               |
| EXPLORER <sup>9</sup>     | pVO <sub>2</sub> and NYHA functional class | No significant change in pVO <sub>2</sub> and NYHA functional class change in the ITT population (p>0.05)                                                                                                                                                                                                                                                                                                                                              |
|                           | NYHA functional class†                     | 80 (65%) of 123 patients in the MYK group had ≥1 NYHA class improvement compared with 40 (31%) of 128 in the placebo group; 50% in the MYK group and 21% in the placebo group reached NYHA class I status                                                                                                                                                                                                                                              |
|                           | pVO <sub>2</sub> †                         | Greater mean increase in pVO <sub>2</sub> of the MYK group by 1.4 mL/kg/min than the placebo group (95% CI: 0.6, 2.1; p=0.0006)                                                                                                                                                                                                                                                                                                                        |
|                           | NTproBNP and cTnI                          | At 30 weeks, the reduction in NTproBNP and cTnI after MYK treatment was 80% and 41% greater than that for placebo, respectively                                                                                                                                                                                                                                                                                                                        |
| VALOR <sup>10-12</sup>    | Peak post-exercise LVOTG                   | In the MYK group, a decrease from 86 mmHg (95% CI: 79.5, -91.8) to 38 mmHg (95% CI: 32.3, 44.0) is noted, whereas for placebo the change was from 84 mmHg (95% CI: 78.4, 91.0) to 73 mmHg (95% CI: 67.2, 79.6), showing a greater mean reduction with MYK                                                                                                                                                                                              |
|                           | Patient-reported outcomes                  | More improvement of KCCQ-CCS (positive change better) and HCMSQSoB (negative change better) scores in MYK than with placebo (KCCQ-CCS +9.1, 95% CI: 5.5, to 12.7; HCMSQSoB -1.8, 95% CI: -2.4, to -1.2; p<0.0001 for both)                                                                                                                                                                                                                             |
|                           | Need for SRT†                              | # At 16 weeks, 10 of 56 MYK participants and 43 of 56 placebo qualified for or underwent SRT<br># At 32 weeks, 6 of 56 MYK group participants and 7 of 52 in the placebo cross-over group qualified for or elected for SRT<br># At 56 weeks, 5 of 56 in MYK set and 10 of 52 patients in the placebo crossover group qualified for the composite endpoint                                                                                              |
|                           | Secondary outcomes                         | Significant differences favouring patients receiving MYK at 16 weeks, 32 weeks and 56 weeks were noted after the hierarchical testing of secondary outcomes, which include change in LVOTG, levels of NTproBNP, cTnI, NYHA functional class and patient-reported outcomes (KCCQ-23 CCS)                                                                                                                                                                |
| EXPLORER-CN <sup>13</sup> | LVOTG (in mmHg)†                           | Mean Valsalva peak LVOTG: decreased from 106.8 mmHg (SD, 43.2) at baseline to 48.9 mmHg (SD, 40.4) among the MYK group, whereas an increase from 99.8 (SD, 41.1) at baseline to 116.3 (SD, 52.2) was noted in the placebo group; resting peak LVOTG: a similar pattern was noted for resting peak LVOTG (LSM difference -55; 95% CI: -69.1, -40.9); this was consistently observed in all pre-specified subgroups (β-blocker use or CYP2C19 phenotype) |
|                           | LVMl                                       | 58 patients were eligible for CMR at the end of the study period and revealed favourable cardiac remodelling in the MYK group: reduction in LVMl (-26.4 g/m <sup>2</sup> versus 4.4 g/m <sup>2</sup> ; mean difference, -30.8 g/m <sup>2</sup> ; 95% CI -41.6, -20.1). A similar pattern was seen in LV mass, maximal wall thickness and maximum left atrial volume index                                                                              |
|                           | NTproBNP; cTnI                             | 82% greater reduction of NTproBNP for the MYK group compared with placebo (proportion of geometric mean ratio between treatments: 0.18; 95% CI: 0.13, 0.24) 66% greater reduction of cTnI for the MYK group compared with placebo (proportion of geometric mean ratio between treatments: 0.34; 95% CI: 0.27, 0.42)                                                                                                                                    |
|                           | NYHA functional class                      | 59.3% (32 of 54) in the MYK group had ≥1 NYHA functional class improvement and 14.8% (4 of 27) in placebo                                                                                                                                                                                                                                                                                                                                              |
|                           | Patient-reported outcomes                  | Improved health status noted in the MYK group compared with placebo, assessed by KCCQ-CSS, with a between-group LSM difference of 10.2 points (95% CI: 4.4, 16.1 points)                                                                                                                                                                                                                                                                               |

Continued

Table 4: Continued

| Trial name            | Endpoints                 | Results                                                                                                                                                                                                                                                                                                |
|-----------------------|---------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| HORIZON <sup>14</sup> | LVOT (in mmHg)†           | Post-exercise: mean at 30 weeks was 28.4±26.5, a mean change of -60.7 (95% CI: -71.5, -49.9) from baseline Resting; mean at 30 weeks was 15.0±16.0, a mean change of -61.1 (95% CI: -72.9, -49.2) from baseline Valsalva; mean at 30 weeks was 23.0±22.3, a mean change of -83.2, -58.0) from baseline |
|                       | LVEF                      | Decreased from baseline; mean change of -2.9 ± 8.7%                                                                                                                                                                                                                                                    |
|                       | NTproBNP, cTnI, and cTnT  | Improved from baseline, the geometric mean ratios to baseline at 30 weeks were 0.546 (CV 35.5) for cTnT, 0.180 (CV 156.9) for NTproBNP and 0.323 (CV 61.3) for cTnI.                                                                                                                                   |
|                       | NYHA functional class     | 100% improvement of ≥1 NYHA functional class from baseline; no patient had NYHA class III symptoms by the end of the study period                                                                                                                                                                      |
|                       | Patient-reported outcomes | Significant improvement noted from week 6 and sustained through week 30 in KCCQ-23 CSS (mean was 9.8 points; 95% CI: 4.1, 15.5)                                                                                                                                                                        |

†Primary outcome(s)

CMR=cardiac magnetic resonance imaging; cTnI = cardiac troponin I; cTnT = cardiac troponin T; CV = coefficient of variance; HCM = hypertrophic obstructive cardiomyopathy; HCMQSoB = Hypertrophic Cardiomyopathy Symptom Questionnaire on Shortness of Breath; ITT = intention to treat; KCCQ-CCS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire Overall Summary Score; LSM = least square means; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; LVOTG = left ventricular outflow tract gradient; MYK = mavacamten; nHCM = non-obstructive HCM; NRS = numerical rating scale; NTproBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; oHCM = obstructive HCM; pVO<sub>2</sub> = peak oxygen uptake; SD = standard deviation; SRT = septal reduction therapy; Wk = week(s).

Table 5: Comparison of the information regarding adverse events, treatment discontinuations and reported deaths<sup>7–14</sup>

| Name of the trial         | Tolerability                                                                                                                       | Adverse events (definitively or potentially associated with MYK)                                                                                                                                                                                                                     | Treatment discontinuation                                                                                                                    | Death of participants        |
|---------------------------|------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| PIONEER <sup>7</sup>      | MYK was generally well tolerated, with the majority of adverse events being mild (80%) or moderate (19%) or unrelated to treatment | Reduced LVEF, A-fib is most commonly reported; other symptoms include fatigue, headache, nausea and dyspnoea                                                                                                                                                                         | 1 in cohort A (4.8% of n) – patient had persistent A-fib and elected to opt-out                                                              | No deaths were reported      |
| MAVERICK <sup>8</sup>     | MYK was generally well tolerated; 76% of reported events were mild and 21% with moderate severity                                  | Dizziness, fatigue, nausea and dyspnoea; other reported events were unlikely due to MYK                                                                                                                                                                                              | 5 patients in the pooled group (12.5%) were discontinued as LVEF dropped to <45%                                                             | No deaths were reported      |
| EXPLORER <sup>9</sup>     | Adverse events were generally mild and well tolerated                                                                              | MYK group: serious adverse events in 10 patients (8%), accounting for 11 events (2 cases of A-fib and 2 of stress cardiomyopathy); placebo group: serious adverse events in 11 patients (9%), with a total of 20 events (3 cases of A-fib and 1 A-fib with congestive heart failure) | 5 patients: 2 in MYK (1.6%) – A-fib; syncope 1 in placebo (0.8%) – sudden death; 2 patients personally elected to opt-out, 1 from each group | 1 death in the placebo group |
| VALOR <sup>10–12</sup>    | MYK was generally well tolerated                                                                                                   | Fatigue, dyspnoea, dizziness and nausea                                                                                                                                                                                                                                              | 2 patients in the MYK group (3.6%) had temporary drug discontinuation due to LVEF <50%; no permanent drug discontinuation                    | No deaths were reported      |
| EXPLORER-CN <sup>13</sup> | MYK demonstrated good tolerability                                                                                                 | A-fib, sinus node dysfunction and arrest, atrial flutter and hypotension were reported                                                                                                                                                                                               | 2 patients from placebo (7.4%) for various reasons                                                                                           | No deaths were reported      |
| HORIZON <sup>14</sup>     | 63.2% of patients (n=24) reported adverse events – either mild (n=14) or moderate (n=10) and was fairly well tolerated             | COVID-19, A-fib, contact dermatitis, hypertension, nasopharyngitis, palpitations and pyrexia bronchitis were commonly reported, unclear if related to MYK                                                                                                                            | 2 patients (5.3% of n) have treatment interruption due to adverse events                                                                     | No deaths were reported      |

A-fib = atrial fibrillation; LVEF = left ventricular ejection fraction; MYK = mavacamten; Wk = week(s).

### Safety profile of mavacamten

The clinical trials demonstrated a generally favourable profile across all studies. MYK demonstrated good tolerability, with most of the adverse events being mild or moderate and usually temporary. In the PIONEER trial, 80% of adverse events were mild and 19% were moderate, while the MAVERICK trial reported similar results with 76% and 21%, respectively.<sup>7,8</sup> The EXPLORER trial and the VALOR study showed similar patterns.<sup>9–12</sup> The EXPLORER-CN trial reported no new safety signals, and in the HORIZON trial, adverse events were mainly mild (36.8%) or moderate (26.3%).<sup>13,14</sup> Common adverse events included cardiovascular issues such as reduced LVEF, atrial fibrillation (A-fib) and sinus-related dysfunction. Other reported events likely related to MYK were fatigue, nausea, dyspnoea, dizziness and headache.

Discontinuation of MYK because of adverse events was infrequent. In the PIONEER trial, one patient (4.8% of n) discontinued due to persistent A-fib, while the MAVERICK trial reported five discontinuations linked to reduced LVEF (<45%). In the EXPLORER trial, five patients were discontinued, including two in the MYK group (12.5%) due to A-fib or syncope.<sup>7–9</sup> The VALOR trial observed temporary discontinuations due to reduced LVEF (<50%), but no permanent discontinuations.<sup>10–12</sup> In the EXPLORER-CN trial, two placebo group patients (7.4%) discontinued treatment, and in the HORIZON trial, two patients (5.3%) experienced treatment interruptions.<sup>13,14</sup>

Mortality was rare across the trials and primarily unrelated to MYK. No deaths were reported in the PIONEER, MAVERICK, VALOR, EXPLORER-CN and HORIZON trials.<sup>7–12,14</sup> In the EXPLORER trial, one death occurred in the placebo group. *Table 5* compares information regarding adverse events, treatment discontinuations (if any), and reported deaths (if any).<sup>7–14</sup>

### Discussion

MYK is a first-in-class allosteric modulator of cardiac myosin ATPase. MYK works on the sarcomeric hypercontractility of HCM by decreasing excessive cross-bridge formation of actin-myosin.<sup>19</sup> Specifically:

- Primary mechanism: MYK inhibits the phosphate release rate during the ATPase cycle, reducing cross-bridge formation – inhibition in the active state.<sup>20</sup>
- Secondary effects: MYK stabilizes myosin in the super-relaxed state, where myosin heads exhibit reduced ATP turnover, thus diminishing sarcomere hypercontractility – inhibition in the relaxed state.<sup>21</sup>

Pharmacokinetics- and pharmacodynamics-guided dose titration strategies, as demonstrated in the EXPLORER-CN trial, ensure the lowest effective dose to reduce LVOTG while maintaining normal LVEF.<sup>13,18</sup> Approved by the US Food and Drug Administration (FDA) on 28 April 2022, MYK is indicated for symptomatic NYHA class II–III oHCM.<sup>22</sup> MYK showed significant benefits in oHCM patients:

- Haemodynamic improvement: it markedly reduces LVOTG at rest and with provocation.
- Symptom relief: it improves exercise tolerance, patient-reported outcomes and NYHA functional class.
- Quality of life: it decreases dyspnoea symptom scores and enhances overall functional capacity.

MYK also reduces biomarkers like NTproBNP and LAVI, reflecting its favourable effects on myocardial structure and function.<sup>8–14</sup>

Over a range of 1–15 mg, MYK shows dose-proportional pharmacokinetics, with a bioavailability of ≥85% and peak plasma concentration achieved within 1 hour. It is highly protein-bound (97–98%) and exhibits a

steady-state peak-to-trough ratio of ~1.5.<sup>22</sup> As mentioned earlier in this article, MYK demonstrated good tolerability, with most of the adverse events being mild or moderate and usually temporary. However, MYK's use requires careful monitoring due to its potential to cause systolic heart failure. Evaluation of LVEF through echocardiogram is needed before initiation and while on MYK. Patients with LVEF <55% at baseline or who experience a decline in LVEF <50% during treatment may need to discontinue the drug. Its co-administration with disopyramide, verapamil or diltiazem is contraindicated due to the increased risk of systolic dysfunction.<sup>22</sup> In patients with oHCM, MYK's long-term safety and efficacy remain unknown.

### Future approaches and additional studies for follow-up

One of the primary limitations of current trials is the relatively short duration of follow-up. Continued follow-up is essential to definitively establish the efficacy of MYK in the treatment of HCM and to determine whether the observed benefits are sustained over time, ultimately ensuring long-term patient outcomes. Studies such as the PIONEER-OLE and EXPLORER-LTE are being conducted to address these gaps. However, only interim results are currently available, which is why the above studies were not included in this systematic review.<sup>23,24</sup> The EXPLORER-CN trial is currently undergoing a long-term follow-up study to further assess its outcomes and safety profile over an extended period.<sup>13</sup> Monitoring these final results closely will be critical to confirm whether the favourable changes associated with MYK are maintained in the long term. Several follow-up secondary analyses, in-depth analytical studies and post-hoc analyses

of the current trials are also available in the literature.<sup>25–34</sup> Integrating these studies with long-term follow-up results may offer a more thorough picture of MYK's ability, safety and efficacy. Another recommendation for future researchers is to conduct trials on larger populations. While the outcomes of current studies, albeit conducted on smaller cohorts, have been favourable, these findings cannot yet be generalized unambiguously to broader populations without additional data.

### Conclusion

Recent clinical trials assessing MYK's safety and efficacy in treating HCM have offered encouraging new information about the drug's therapeutic potential. MYK significantly decreased LVOTG and improved functional capacity across trials, as seen by favourable changes in NTproBNP and cTnI levels, improvement in NYHA functional class and increase in pVO<sub>2</sub>. Quality of life metrics and other patient-reported outcomes also demonstrated significant improvement. All these trials were constrained by limitations such as small sample sizes, short follow-up durations and population-specific characteristics, which restrict the generalizability of their findings. Larger, more varied cohorts and longer follow-ups are required for future research to validate these findings and fill in evidence gaps on stress echocardiography and long-term efficacy. Overall, MYK held promise as a transformative agent in the treatment of HCM, particularly for individuals with obstructive forms and refractory symptoms. □

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