

RESEARCH MONOGRAPH . COMPOUND PROFILE

Aficamten

A next-generation cardiac myosin inhibitor developed by Cytokinetics as CK-3773274, engineered for optimized pharmacokinetic properties relative to mavacamten, approved by the United States Food and Drug Administration in December 2025 for the treatment of symptomatic obstructive hypertrophic cardiomyopathy under the trade name MYQORZO.

DOCUMENT	KDC-MN-1622
ISSUED	2026-05-21
REVISION	1.0
AUTHOR	Kodi <i>ac</i> biolabs Research
COMPOUND CLASS	Selective small-molecule allosteric inhibitor of cardiac beta-myosin heavy chain (MYH7) ATPase activity

RESEARCH USE ONLY

ABSTRACT

Aficamten (CK-3773274, trade name MYQORZO) is a selective, allosteric, reversible small-molecule inhibitor of cardiac myosin motor activity developed by Cytokinetics, Inc. for the treatment of hypertrophic cardiomyopathy (HCM). The compound reduces myocardial contractility by stabilizing a weak actin-binding, pre-power-stroke state of the beta-cardiac myosin head, thereby decreasing the number of functional myosin cross-bridges available during each cardiac cycle and attenuating the left ventricular outflow tract (LVOT) obstruction that drives symptoms in obstructive HCM. Aficamten binds to an allosteric site between the upper 50 kDa and lower 50 kDa subdomains of the myosin catalytic domain, overlapping with the blebbistatin binding pocket but distinct from the mavacamten binding site, and dramatically slows phosphate release from the myosin ATPase cycle to a rate slower than the conventional super-relaxed state.

The compound was engineered to address pharmacokinetic limitations of mavacamten, the first-in-class cardiac myosin inhibitor. Aficamten achieves a plasma elimination half-life of approximately 75 to 100 hours (compared to 7 to 9 days for mavacamten), reaches steady-state plasma concentrations within approximately 2 weeks of daily dosing (compared to approximately 6 weeks for mavacamten), demonstrates reversibility of pharmacodynamic effects within 24 to 48 hours, exhibits a shallow exposure-response relationship that widens the therapeutic window, and is metabolized by multiple cytochrome P450 enzymes (CYP2C9, CYP3A4, CYP2D6, CYP2C19) rather than predominantly by the polymorphic CYP2C19, thereby reducing

the drug-drug interaction burden and eliminating the requirement for CYP metabolizer genotyping.

Clinical development of aficamten has proceeded through a comprehensive program. The Phase 1 dose-escalation study in 102 healthy participants demonstrated dose-proportional pharmacokinetics, dose-dependent reductions in left ventricular ejection fraction (LVEF), and favorable tolerability with no serious adverse events. The Phase 2 REDWOOD-HCM trial in patients with symptomatic obstructive HCM demonstrated statistically significant reductions in resting and post-Valsalva LVOT gradients, with 78.6 to 92.9 percent of patients achieving target gradient reduction at 10 weeks. The pivotal Phase 3 SEQUOIA-HCM trial randomized 282 patients with symptomatic obstructive HCM to aficamten or placebo for 24 weeks and met its primary endpoint of improved peak oxygen uptake (pVO₂), with a least-squares mean difference of 1.74 mL/kg/min ($p = 0.000002$), along with statistically significant improvements in all 10 prespecified secondary endpoints including NYHA functional class, Kansas City Cardiomyopathy Questionnaire scores, and LVOT gradient reduction. The Phase 3 MAPLE-HCM trial demonstrated superiority of aficamten monotherapy over metoprolol monotherapy, with a pVO₂ least-squares mean difference of 2.3 mL/kg/min ($p < 0.0001$). The Phase 3 ACACIA-HCM trial in 516 patients with non-obstructive HCM met both dual primary endpoints for symptom burden and exercise capacity improvement.

The United States Food and Drug Administration approved aficamten on December 19, 2025, for the treatment of adults with symptomatic obstructive HCM to improve functional capacity and symptoms, marketed as MYQORZO. The approval includes a

boxed warning regarding the risk of heart failure due to systolic dysfunction and a Risk Evaluation and Mitigation Strategy (REMS) requiring echocardiographic monitoring. The principal adverse reaction observed at greater than 5 percent incidence above placebo was hypertension (8 percent versus 2 percent). LVEF reduction below 50 percent occurred in 3.5 percent of aficamten-treated patients in SEQUOIA-HCM compared to 0.7 percent on placebo; all instances were mild, reversible, and not associated with clinical heart failure events. This monograph reviews the chemistry, mechanism, pharmacokinetics, preclinical and clinical evidence, safety profile, handling considerations, and comparative assessment of aficamten against five alternative agents for the management of hypertrophic cardiomyopathy.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Aficamten.

Trade name: MYQORZO (Cytokinetics, Inc.; United States).

Development codes: CK-3773274, CK-274. The development code CK-3773274 is the canonical identifier in the preclinical and early clinical pharmacology literature. CK-274 is the abbreviated form used in clinical trial registrations and conference presentations [1].

Chemical Abstracts Service registry number: 2364554-48-1.

International Union of Pure and Applied Chemistry name: N-[(1R)-5-(5-ethyl-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1H-inden-1-yl]-1-methyl-1H-pyrazole-4-carboxamide.

Other identifiers: InChI Key: IOVAZWDIRCRMTM-OAHLLOKOSA-N.

1.2 Structural class and chemistry

Aficamten is a synthetic small-molecule heterocyclic compound incorporating a 1,2,4-oxadiazole ring system linked through an indanyl scaffold to a methylpyrazole carboxamide pharmacophore. The compound belongs to the cardiac myosin inhibitor class, a structurally novel group of agents that reduce cardiac contractility through direct inhibition of the beta-cardiac myosin heavy chain (MYH7) ATPase. The structural class is distinct from traditional negative inotropic agents (beta-adrenergic receptor antagonists, non-dihydropyridine calcium channel blockers, disopyramide) and from the first-in-class cardiac myosin inhibitor mavacamten (a pyrimidinone) [2].

Molecular formula: C₁₈H₁₉N₅O₂.

Molecular weight: 337.38 g/mol.

Physical properties: White to off-white crystalline solid. Soluble in dimethyl sulfoxide and organic solvents; limited aqueous solubility as the free base. The compound is formulated as immediate-release oral tablets at 5, 10, 15, and 20 mg strengths for clinical use.

Stereochemistry: Aficamten contains one stereocenter at the C-1 position of the indanyl ring and is supplied as the single (1R) enantiomer. The stereochemical configuration is essential for the allosteric binding to the cardiac myosin catalytic domain and was optimized during the medicinal chemistry program at Cytokinetics [2].

1.3 Synthesis

The published medicinal chemistry of aficamten describes its discovery through iterative structure-activity relationship optimization from an initial screening hit (CK-2172010) identified in a high-throughput biochemical assay for cardiac myosin ATPase inhibition [2]. The optimization program focused on five pharmacological properties: selectivity for cardiac over skeletal and smooth muscle myosin, a plasma half-life appropriate for once-daily dosing (target 3 to 4 days), attainment of steady-state within 2 weeks, a shallow concentration-response relationship to widen the therapeutic margin, and minimal cytochrome P450 interaction potential. The synthesis proceeds through construction of the 1,2,4-oxadiazole ring, coupling to the indanone scaffold, stereoselective reduction to establish the (1R) configuration, and amide bond formation with 1-methylpyrazole-4-carboxylic acid. Detailed synthetic routes and structure-activity relationship data are published in the Journal of Medicinal Chemistry [2].

2. Abstract

Aficamten (CK-3773274, MYQORZO) is a selective, allosteric, reversible inhibitor of cardiac beta-myosin heavy chain ATPase activity that reduces myocardial contractility by stabilizing a weak actin-binding state of the myosin motor domain and decreasing the number of functional cross-bridges during each cardiac cycle [1, 2]. The compound was developed by Cytokinetics, Inc. as a next-generation cardiac myosin inhibitor engineered to optimize the pharmacological properties of the class relative to mavacamten, the first approved agent.

The principal clinical application is the treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM), a genetic cardiomyopathy affecting approximately 1 in 500 individuals in which sarcomeric mutations (most commonly in MYH7 and MYBPC3) produce myocardial hypercontractility, left ventricular hypertrophy, dynamic LVOT obstruction, diastolic dysfunction, and progressive symptoms of heart failure, dyspnea, chest pain, and exercise intolerance [3]. The standard of care prior to cardiac myosin inhibitor approval consisted of beta-adrenergic blockers, non-dihydropyridine calcium channel blockers, and disopyramide, with septal reduction therapy (surgical myectomy or alcohol septal ablation) reserved for refractory disease.

The Phase 3 SEQUOIA-HCM trial established the efficacy of aficamten in oHCM, demonstrating a 1.74 mL/kg/min improvement in peak oxygen uptake over placebo ($p = 0.000002$) with statistically significant improvements across all prespecified secondary endpoints [4]. The Phase 3 MAPLE-HCM trial demonstrated superiority of aficamten monotherapy over metoprolol monotherapy (pVO₂ difference 2.3 mL/kg/min, $p < 0.0001$) [5]. The Phase 3 ACACIA-HCM trial extended the evidence to non-obstructive HCM, meeting both dual primary endpoints [6].

The United States Food and Drug Administration approved aficamten on December 19, 2025, for the treatment of adults with symptomatic oHCM under the trade name MYQORZO [7]. The compound carries a boxed warning regarding the risk of systolic dysfunction and heart failure, with mandatory echocardiographic monitoring through a REMS program. Aficamten is available as 5, 10, 15, and 20 mg oral tablets for once-daily administration.

3. Discovery and Development History

3.1 Origin and medicinal chemistry

The cardiac myosin inhibitor class originated from research at MyoKardia (later acquired by Bristol-Myers Squibb), which developed mavacamten (MYK-461), the first small-molecule inhibitor of cardiac myosin, through the mid-2010s. Mavacamten was approved by the FDA in April 2022 under the trade name CAMZYOS for the treatment of symptomatic oHCM [8].

Cytokinetics, Inc., based in South San Francisco, California, initiated an independent cardiac myosin inhibitor program that identified aficamten through high-throughput screening of chemical libraries against purified human beta-cardiac myosin ATPase activity. The initial hit compound (CK-2172010) was optimized through several hundred analogs across multiple chemical series to yield CK-3773274 (aficamten), selected for development on the basis of potency against cardiac myosin (myofibril IC₅₀ 1.26 micromolar), selectivity over fast skeletal myosin (5.3-fold) and smooth muscle myosin (greater than 30-fold), predicted human half-life of 3 to 4 days, and favorable CYP interaction profile [2].

The medicinal chemistry program explicitly addressed limitations of mavacamten: the 7- to 9-day plasma half-life of mavacamten produces a 6-week time to steady state, prolonged pharmacodynamic effects that persist for weeks after discontinuation, and sensitivity to CYP2C19 polymorphism that necessitates metabolizer genotyping and dose adjustment. Aficamten was designed to achieve steady-state within 2 weeks, reversibility within 24 to 48 hours, and metabolism through multiple CYP pathways to reduce single-enzyme dependency [2].

3.2 Preclinical development

Aficamten advanced through comprehensive preclinical pharmacology and toxicology studies in rats, dogs, and in the R403Q knock-in mouse model of HCM. In vitro, the compound reduced fractional shortening in isolated cardiomyocytes to 12.0 plus or minus 2.0 percent of baseline at 10 micromolar ($p < 0.0001$) without altering calcium transients, confirming a myosin-directed mechanism independent of cal-

cium handling [1]. In R403Q HCM mice, aficamten produced dose-dependent reduction of fractional shortening with return to baseline by 24 hours and no heart rate changes [1].

3.3 Clinical development program

The clinical program comprised Phase 1 (healthy volunteer pharmacokinetics and pharmacodynamics), Phase 2 REDWOOD-HCM (dose-ranging in oHCM), Phase 3 SEQUOIA-HCM (pivotal efficacy in oHCM), Phase 3 MAPLE-HCM (comparison with metoprolol in oHCM), Phase 3 ACACIA-HCM (efficacy in non-obstructive HCM), and the ongoing FOREST-HCM long-term extension study [4, 5, 6, 9, 10].

3.4 Regulatory approval

The FDA approved aficamten (MYQORZO) on December 19, 2025, for the treatment of adults with symptomatic oHCM to improve functional capacity and symptoms [7]. The approval was based primarily on the SEQUOIA-HCM pivotal trial data. The approval included a boxed warning for heart failure risk due to reduced LVEF and a REMS program requiring prescriber certification, pharmacy participation, and echocardiographic monitoring before and during treatment. Aficamten became the second cardiac myosin inhibitor approved by the FDA, following mavacamten (April 2022).

4. Mechanism of Action

4.1 Cardiac myosin ATPase and the sarcomere

The beta-cardiac myosin heavy chain (MYH7) is the principal motor protein of the ventricular sarcomere, converting the chemical energy of ATP hydrolysis into mechanical force through cyclic interaction with actin filaments. During each cardiac cycle, myosin heads transition through defined biochemical states: ATP binding and hydrolysis in the detached state, weak actin binding in the pre-power-stroke state, phosphate release triggering the power stroke and strong actin binding, and ADP release followed by return to the detached state upon ATP rebinding [1].

In hypertrophic cardiomyopathy, mutations in sarcomeric genes (most frequently MYH7 and MYBPC3, collectively accounting for approximately 70 percent of genotype-positive cases) increase the proportion of myosin heads in the force-generating state, producing hypercontractility, increased energy consumption, impaired relaxation, and dynamic LVOT obstruction in the subset of patients with obstructive physiology [3].

4.2 Aficamten binding site and allosteric mechanism

Aficamten binds to an allosteric pocket in the catalytic domain of cardiac beta-myosin, located between the upper 50 kDa (U50) and lower 50 kDa (L50) subdomains near the phosphate release backdoor [1]. This binding site overlaps with that of blebbistatin (the two compounds are mutually exclusive in binding) but is distinct from the mavacamten binding site, which is located at the myosin mesa region at the interface between the catalytic and converter domains [1, 2].

Aficamten stabilizes a weak actin-binding, pre-power-stroke state by dramatically slowing phosphate release from the myosin ATPase cycle. The single ATP turnover rate is reduced from approximately 0.0014 per second to approximately 0.0004 per second, a rate slower than the conventional super-relaxed (SRX) state [1]. This effectively sequesters myosin heads in an inactive conformation, reducing the number of force-generating cross-bridges during systole and thereby reducing contractile force.

4.3 Selectivity

Aficamten demonstrates selectivity for cardiac myosin over skeletal and smooth muscle myosin isoforms. The cardiac myofibril IC₅₀ is 1.26 micromolar (95 percent confidence interval 1.20 to 1.33 micromolar), while fast skeletal myosin IC₅₀ is approximately 6.7 micromolar (5.3-fold selectivity) and smooth muscle myosin IC₅₀ exceeds 40 micromolar (greater than 30-fold selectivity) [1]. The selectivity for cardiac over smooth muscle myosin minimizes the risk of vasodilation and systemic hypotension. The selectivity for cardiac over skeletal myosin provides a margin against skeletal muscle weakness, although the 5.3-fold ratio is narrower than ideal and is a consideration in dose-finding.

4.4 Pharmacodynamic window

In preclinical models, aficamten demonstrates a pharmacodynamic window (IC₅₀/IC₁₀ ratio for contractility reduction) of approximately 7 to 10 across species: 10 in rats, 7.2 in beagle dogs, and 7.1 to 7.5 in R403Q HCM mice [1]. This window, combined with the shallow exposure-response relationship observed clinically, permits dose titration to therapeutic effect (meaningful LVOT gradient reduction) while maintaining an acceptable margin before clinically significant LVEF reduction occurs.

4.5 Comparison with mavacamten mechanism

Although both aficamten and mavacamten inhibit cardiac myosin ATPase activity and reduce the proportion of force-generating myosin heads, the two compounds bind to different sites and produce distinct biochemical phenotypes. Mavacamten stabilizes the super-relaxed (SRX) state, characterized by folded-back myosin heads with inhibited ATPase activity, through binding at the mesa-converter interface [8]. Aficamten instead stabilizes a weak actin-binding state through slowing of phosphate release at the U50-L50 backdoor pocket [1]. The distinction is reflected in different concentration-response slopes, different effects on the equilibrium between disordered relaxed (DRX) and SRX populations, and different time courses of pharmacodynamic effect reversal.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Aficamten is rapidly absorbed after oral administration, with a median time to peak plasma concentration (T_{max}) of approximately 2.0 hours (range 1.0 to 6.0 hours) [9, 11]. Oral bioavailability is high; mass balance studies indicate that at least 95 percent of an oral dose is absorbed [11]. In the Phase 1 food-effect cohort, administration with food increased peak concentration (C_{max}) by approximately 30 percent and reduced T_{max} from 2.3 to 1.5 hours, but did not meaningfully affect total exposure (AUC₀₋₂₄ 631 versus 601 nanogram-hours per milliliter for fed versus fasted conditions) [9].

5.2 Distribution

The apparent volume of distribution (V_z/F) is approximately 690 liters (coefficient of variation 35 percent), consistent with extensive tissue distribution [11]. The whole blood to plasma ratio is 0.566, indicating minimal partitioning into erythrocytes. Plasma protein binding is approximately 89.6 percent (10.4 percent unbound fraction) [11].

5.3 Metabolism

Aficamten is extensively metabolized in the liver through Phase I and Phase II pathways. Phase I metabolism is predominantly oxidative hydroxylation of the ethyl group and the indane moiety, with Phase II conjugation (glucuronidation and sulfonation) of the hydroxylated metabolites [11]. A reductive ring cleavage of the 1,2,4-oxadiazole ring by gut microbiota produces the fecal metabolite M18 (CK-4017583) [11].

Nine metabolites have been identified from seventeen detected chromatographic peaks. The principal circulating metabolites are M1b (CK-3834283, an omega-1-hydroxylated metabolite, representing 36.4 percent of plasma radioactivity), M1a (CK-

3834282, a second hydroxylated metabolite, 10.5 percent), and M5 (CK-4034051, a glucuronide conjugate of M1a, 10.3 percent) [11]. Unchanged aficamten represents 19.8 percent of total plasma radioactivity.

The primary CYP enzymes responsible for aficamten metabolism are CYP2C9 (approximately 50 percent contribution), CYP3A4 (approximately 26 percent), CYP2D6 (approximately 21 percent), and CYP2C19 (approximately 3 percent), with additional minor contributions from CYP2C8 [11, 12]. The distribution across multiple CYP pathways is a deliberate design feature that mitigates the impact of single-enzyme polymorphism or inhibition on overall drug exposure and differentiates aficamten from mavacamten (which is predominantly metabolized by CYP2C19 and CYP3A4 and requires CYP2C19 genotyping) [12].

5.4 Elimination

Elimination is predominantly metabolic. Total recovery of radioactivity following a single oral dose of [14C]-aficamten was 89.7 percent by 600 hours, with 57.7 percent excreted in feces and 32.0 percent in urine [11]. Unchanged drug accounted for 5.07 percent of the fecal dose and 0.554 percent of the urinary dose, confirming that metabolism rather than direct renal or biliary clearance is the dominant elimination pathway.

Total body clearance (CL/F) is approximately 4.50 liters per hour (coefficient of variation 32.1 percent). Renal clearance is negligible at 2.63 milliliters per hour [11].

The terminal elimination half-life is approximately 75 to 100 hours (median 99.6 hours in the mass balance study; 76.9 to 86.4 hours in the Phase 1 multiple-ascending-dose cohorts) [9, 11]. Steady-state plasma concentrations are achieved within approximately 10 to 14 days of once-daily dosing. The accumulation ratio on repeated dosing is approximately 4.6 to 4.9 [9].

5.5 CYP2D6 poor metabolizer pharmacokinetics

In a dedicated CYP2D6 poor metabolizer cohort in the Phase 1 study (n = 9), the half-life was modestly prolonged to approximately 110 hours (compared to 85 hours in extensive metabolizers), and total exposure (AUC₂₄) was not clinically meaningfully increased (495 versus 679 nanogram-hours per milliliter) [9]. The modest im-

pact reflects the distributed metabolism across multiple CYP pathways. CYP2D6 genotyping is not required for aficamten dosing, in contrast to the CYP2C19 genotyping requirement for mavacamten.

5.6 Routes of administration

Aficamten is administered exclusively by the oral route. The commercial formulation (MYQORZO) is available as immediate-release tablets in 5, 10, 15, and 20 mg strengths for once-daily dosing [7].

5.7 Special populations

No dose adjustment is required for mild to moderate hepatic impairment based on comparable pharmacokinetic parameters observed in these populations. Pharmacokinetic parameters are comparable between healthy participants and patients with obstructive HCM [11]. The compound has not been approved for pediatric use. Use in pregnancy is not recommended due to insufficient human data; animal reproductive toxicity studies are included in the prescribing information.

6. Preclinical Pharmacology

6.1 In vitro cardiac myosin inhibition

Aficamten inhibits cardiac myofibril ATPase activity with an IC₅₀ of 1.26 micromolar (95 percent confidence interval 1.20 to 1.33 micromolar) [1]. In isolated adult rat cardiomyocytes, 10 micromolar aficamten reduced fractional shortening to 12.0 plus or minus 2.0 percent of baseline ($p < 0.0001$) without altering calcium transients, confirming a direct sarcomeric mechanism independent of calcium handling [1].

6.2 In vivo contractility reduction

In healthy rats, aficamten produced dose-dependent reductions in fractional shortening with a pharmacodynamic IC₁₀ (the concentration producing a 10 percent reduction in contractility) of 0.8 micromolar and IC₅₀ of 7.9 micromolar, yielding a pharmacodynamic window of 10 [1].

In beagle dogs, the LVEF IC₁₀ was 0.18 micromolar and IC₅₀ was 1.3 micromolar, yielding a pharmacodynamic window of 7.2 [1].

6.3 HCM disease model

In the R403Q knock-in mouse model of HCM (carrying the missense mutation in MYH7 equivalent to a common human HCM-causing variant), aficamten produced dose-dependent fractional shortening reduction ($p < 0.01$ at therapeutic exposures) with complete return to baseline by 24 hours, no effect on heart rate, and a pharmacodynamic window of 7.1 to 7.5 [1]. The pharmacodynamic window was similar between wild-type and R403Q mutant mice, supporting the conclusion that the mechanism operates on both normal and mutant myosin.

6.4 Feline HCM model

A single-dose pharmacokinetic and pharmacodynamic study in the A31P MYBPC3 cat model of naturally occurring HCM demonstrated dose-dependent reduction in cardiac contractility consistent with the mechanism of action and predicted from allometric scaling [13].

6.5 Preclinical safety pharmacology

Preclinical cardiac safety studies demonstrated no QTc prolongation at clinically relevant concentrations. No clinically significant off-target pharmacology was identified in standard safety pharmacology panels (cardiovascular, respiratory, central nervous system).

7. Clinical Evidence Base

7.1 Phase 1: Dose-escalation in healthy participants

The Phase 1 study was a randomized, double-blind, placebo-controlled, ascending-dose study in 102 healthy adults, conducted from November 2018 through January 2020 [9]. The study comprised single-ascending-dose (SAD) cohorts (1, 3, 10, 25, 40, 50, and 75 mg), multiple-ascending-dose (MAD) cohorts (5, 7.5, and 10 mg once daily for 14 to 17 days), a CYP2D6 poor metabolizer cohort (10 mg single dose), and a food-effect cohort (10 mg single dose).

Pharmacokinetics were dose-proportional across the studied range. C_{max} ranged from 5.8 nanograms per milliliter at 1 mg to 359.4 nanograms per milliliter at 50 mg. At steady state (MAD cohorts), C_{max} ranged from 69.0 to 147.6 nanograms per milliliter and AUC_{tau} from 1,320 to 2,632 nanogram-hours per milliliter across 5 to 10 mg doses [9].

Pharmacodynamic effects on LVEF were dose-dependent. The maximum placebo-corrected LVEF reduction in the SAD cohorts was 5.5 percent at 50 mg (1.5 hours post-dose). LVEF below 50 percent was observed in 18 percent of 50 mg recipients and in the single 75 mg recipient; all reductions were reversible within 4 to 6 hours. In the MAD cohorts, the 10 mg daily dose produced a maximum mean LVEF reduction of 5.0 percent at day 14 [9].

No serious adverse events occurred. No study discontinuations were attributable to adverse events. The most common treatment-emergent adverse event was headache. No QTcF prolongation exceeding 30 milliseconds was observed in any aficamten-treated participant. The study supported progression to Phase 2 in HCM patients [9].

7.2 Phase 2: REDWOOD-HCM

REDWOOD-HCM was a Phase 2, multicenter, randomized, placebo-controlled, double-blind, dose-finding study conducted between January 2020 and May 2021 across 30 centers in Europe and North America [10]. The study enrolled adults with symp-

tomatic obstructive HCM (NYHA class II or III, resting or provoked LVOT gradient of 30 mmHg or greater).

Cohort 1 tested doses of 5, 10, and 15 mg and Cohort 2 tested doses of 10, 20, and 30 mg, with dose uptitration guided by echocardiographic LVOT gradient and LVEF assessments. Overall, 28 patients were randomized to aficamten and 13 to placebo [10].

Aficamten produced statistically significant reductions from baseline versus placebo in mean resting and post-Valsalva LVOT gradients. Target gradient reduction (resting gradient less than 30 mmHg and post-Valsalva gradient less than 50 mmHg) was achieved by 78.6 percent of Cohort 1 patients and 92.9 percent of Cohort 2 patients at week 10. Reductions occurred within 2 weeks of treatment initiation and were sustained through the 10-week treatment period. The medication was well tolerated, with no treatment discontinuations and only modest LVEF reduction [10].

Cohort 4 of REDWOOD-HCM evaluated aficamten in patients with symptomatic non-obstructive HCM. In this cohort, 55 percent of aficamten-treated patients showed at least 1 NYHA class improvement and 29 percent became asymptomatic, supporting expansion into the Phase 3 ACACIA-HCM trial [14].

7.3 Phase 3: SEQUOIA-HCM (pivotal trial)

SEQUOIA-HCM (NCT05186818) was the pivotal Phase 3, randomized, double-blind, placebo-controlled trial that served as the basis for FDA approval [4]. The trial randomized 282 patients with symptomatic obstructive HCM (NYHA class II or III, resting or provoked LVOT gradient of 30 mmHg or greater, LVEF of 60 percent or greater) in a 1:1 ratio to aficamten or placebo for 24 weeks. Doses were titrated from 5 mg to a maximum of 20 mg daily based on echocardiographic LVOT gradient and LVEF monitoring.

Primary endpoint: Change from baseline in peak oxygen uptake (pVO₂) at week 24. Aficamten produced a least-squares mean difference of 1.74 mL/kg/min over placebo (p = 0.000002) [4].

Key secondary endpoints (all statistically significant):

- Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS): significant improvement at weeks 12 and 24

- NYHA functional class improvement of at least 1 class: 34.2 percent treatment difference (95 percent confidence interval 23.4 to 45.0; $p < 0.001$)
- Post-Valsalva LVOT gradient: 49.3 percent of aficamten-treated patients achieved gradient below 30 mmHg versus 3.6 percent on placebo
- NT-proBNP: geometric mean ratio 0.2 ($p < 0.0001$)
- Cardiac troponin reduction: statistically significant [4]

Safety: Treatment-emergent adverse events occurred in 73.9 percent of aficamten patients versus 70.7 percent on placebo. Treatment-emergent serious adverse events occurred in 5.6 percent on aficamten versus 9.3 percent on placebo. Core echocardiographic LVEF below 50 percent was observed in 3.5 percent on aficamten versus 0.7 percent on placebo; all instances were reversible and not associated with clinical heart failure or treatment interruption [4].

7.4 Phase 3: MAPLE-HCM (comparison with metoprolol)

MAPLE-HCM (NCT05767346) was a Phase 3, randomized, double-blind trial comparing aficamten monotherapy to metoprolol succinate monotherapy in 175 patients with symptomatic obstructive HCM [5]. Results were presented at the European Society of Cardiology Congress 2025 and simultaneously published in The New England Journal of Medicine.

Primary endpoint: Change from baseline in pVO₂ at week 24. Aficamten improved pVO₂ by a mean of 1.1 mL/kg/min, while metoprolol declined by 1.2 mL/kg/min, yielding a least-squares mean difference of 2.3 mL/kg/min ($p < 0.0001$) [5].

Secondary endpoints: Superiority for aficamten over metoprolol was demonstrated in five of six prespecified secondary endpoints: NYHA class improvement (51 percent versus 26 percent, $p < 0.001$); KCCQ-CSS improvement (6.9 points, $p < 0.01$); resting and Valsalva LVOT gradient reductions (30 and 35 mmHg respectively, both $p < 0.0001$); NT-proBNP reduction (81 percent, $p < 0.0001$); and left atrial volume index improvement ($p < 0.0001$). Left ventricular mass index did not differ between groups ($p = 0.16$) [5].

Safety: Aficamten demonstrated a favorable tolerability profile compared to metoprolol. Dose down-titration was required in 4.5 percent of aficamten patients versus 29.9 percent for metoprolol. Core-lab LVEF below 50 percent was observed in 1.1 percent of aficamten-treated patients [5].

7.5 Phase 3: ACACIA-HCM (non-obstructive HCM)

ACACIA-HCM was the first clinical trial to evaluate a cardiac myosin inhibitor in non-obstructive HCM, randomizing 516 patients 1:1 to aficamten or placebo [6]. The trial met both dual primary endpoints: KCCQ-CSS improvement (3.0 points greater than placebo, $p = 0.021$) and pVO2 improvement (0.67 mL/kg/min greater than placebo, $p = 0.003$). Statistically significant improvements were observed in key secondary endpoints including NYHA functional class, composite ventilatory efficiency and pVO2 z-score, NT-proBNP levels, and left atrial volume index [6].

LVEF below 50 percent occurred in 27 aficamten versus 2 placebo participants. Two serious heart failure events with LVEF below 50 percent occurred in the aficamten group. Three percent of aficamten-treated patients experienced treatment interruption due to LVEF below 40 percent [6]. The higher rate of LVEF reduction in non-obstructive HCM compared to obstructive HCM reflects the absence of the afterload-reducing effect of LVOT gradient relief and is a safety consideration specific to this population.

7.6 FOREST-HCM (long-term extension)

FOREST-HCM is the ongoing open-label long-term extension study evaluating the sustained efficacy and safety of aficamten in patients who completed REDWOOD-HCM, SEQUOIA-HCM, or ACACIA-HCM [15]. Data through 72 weeks have demonstrated sustained LVOT gradient reduction, stable functional improvement, and continued favorable remodeling including reductions in left ventricular wall thickness and left atrial volume. LVEF below 50 percent occurred in 4.3 percent at 48 weeks. One temporary treatment interruption (2.2 percent) for LVEF reduction has been reported in the oHCM cohort [15].

8. Sourcing and Quality Verification

Aficamten is a proprietary pharmaceutical compound manufactured by Cytokinetics, Inc. and available exclusively through the MYQORZO REMS program for clinical use.

Pharmaceutical grade: MYQORZO is supplied as immediate-release tablets in 5, 10, 15, and 20 mg strengths. Prescribing and dispensing require enrollment in the REMS program, which mandates prescriber certification, patient enrollment, and pharmacy participation [7].

Research grade: Research-grade aficamten is available from multiple chemical suppliers (MedChemExpress, Selleckchem, Cayman Chemical, MedKoo Biosciences) as the free base at greater than 98 percent purity by HPLC. Supply is in milligram to gram quantities. Pricing varies by supplier and quantity but is moderate at the time of monograph preparation.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ 338.16 for the protonated free base)
- Chiral HPLC or polarimetry to confirm enantiomeric purity of the (1R) configuration
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation
- Residual solvent analysis by gas chromatography

Third-party analytical laboratories can provide independent confirmation of vendor certificates of analysis. Given the stereochemical requirement for the (1R) enantiomer, chiral purity verification is essential for any investigation where pharmacological accuracy is required.

9. Reconstitution and Handling

Aficamten free base is a crystalline solid with limited aqueous solubility. For in vitro research applications, the compound is typically prepared as a concentrated stock solution in dimethyl sulfoxide (DMSO) at 10 to 50 millimolar, stored at minus 20 degrees Celsius in sealed aliquots, and diluted to working concentrations in assay buffer immediately before use. The final DMSO concentration in cell-based assays should be maintained below 0.1 percent to avoid solvent-related cytotoxicity.

For in vivo animal studies, the compound has been formulated in polyethylene glycol-based vehicles, hydroxypropyl methylcellulose suspensions, or cyclodextrin-based solutions for oral gavage administration.

The commercial pharmaceutical formulation (MYQORZO tablets) should be stored at controlled room temperature (20 to 25 degrees Celsius) with excursions permitted between 15 and 30 degrees Celsius. Tablets should be protected from moisture and stored in the original packaging.

For research-grade material, the solid compound should be stored desiccated at minus 20 degrees Celsius. DMSO stock solutions are stable through at least 5 freeze-thaw cycles without measurable potency loss but should be aliquoted for single-use to minimize degradation. Aqueous solutions at physiological pH are less stable and should be prepared fresh for each experiment.

10. Stack Interactions and Combinations

Aficamten interacts with several drug classes through its pharmacological mechanism and CYP-mediated metabolism. The following interactions are relevant for clinical use and for research applications involving combination dosing.

CYP2C9 inhibitors: Strong CYP2C9 inhibitors (fluconazole, amiodarone) can increase aficamten exposure given the approximately 50 percent contribution of CYP2C9 to metabolism. However, the distribution across multiple CYP pathways mitigates the magnitude of single-pathway inhibition compared to mavacamten [12]. Dose monitoring and echocardiographic surveillance are appropriate during concurrent use.

CYP3A4 inhibitors and inducers: Strong CYP3A4 inhibitors (ketoconazole, itraconazole, clarithromycin, ritonavir) may modestly increase aficamten exposure. Rifampin, a strong CYP inducer affecting CYP2C9, CYP3A4, and CYP2C19, is contraindicated due to the risk of substantially reduced aficamten exposure and loss of efficacy [7].

Multiple CYP pathway inhibitors: Concurrent administration of drugs that inhibit more than one of the CYP pathways involved in aficamten metabolism (CYP2C9 plus CYP3A4, or CYP2C9 plus CYP2D6) may produce clinically significant increases in aficamten exposure and heart failure risk. The prescribing information specifically warns against combinations that inhibit multiple metabolic pathways [7].

Beta-adrenergic receptor antagonists: Concurrent beta-blockers are permitted and were used by the majority of patients in SEQUOIA-HCM. The combination produces additive negative inotropy through complementary mechanisms (reduced myosin cross-bridge formation plus reduced calcium-mediated contractility). LVEF monitoring is indicated to ensure the combined effect does not produce excessive contractility reduction [4].

Non-dihydropyridine calcium channel blockers: Verapamil and diltiazem produce additional negative inotropic and chronotropic effects when combined with aficamten. The combination should be approached with caution and echocardiographic monitoring [7].

Disopyramide: Disopyramide is a sodium channel blocker with negative inotropic properties used as second-line therapy for oHCM. Combination with aficamten may produce additive contractility reduction. Clinical data on the combination are limited.

QT-prolonging agents: Aficamten has not demonstrated QT-prolonging potential in clinical studies. However, patients with HCM are at baseline risk for arrhythmia, and concurrent QT-prolonging agents should be used with standard monitoring.

Other cardiac myosin inhibitors: Concurrent use with mavacamten is pharmacologically redundant and would produce excessive myosin inhibition with high risk of systolic dysfunction. The combination is contraindicated.

11. Adverse Events and Safety Signal

11.1 Common adverse events

The principal adverse events observed in the SEQUOIA-HCM pivotal trial at frequencies higher than placebo include [4, 7]:

- Hypertension: 8 percent versus 2 percent on placebo. This was the only adverse reaction exceeding 5 percent incidence above placebo in the pivotal trial. The mechanism may relate to baroreceptor-mediated sympathetic activation in response to reduced cardiac output.
- Dizziness: 4.2 percent (lower than rates observed with mavacamten)
- Headache: reported at low frequency similar to placebo
- Upper respiratory tract infection: similar to placebo

Overall treatment-emergent adverse event rates were comparable between aficamten (73.9 percent) and placebo (70.7 percent) in SEQUOIA-HCM [4].

11.2 Left ventricular ejection fraction reduction

LVEF reduction is the principal mechanism-related safety concern for all cardiac myosin inhibitors. In SEQUOIA-HCM, core echocardiographic LVEF below 50 percent occurred in 3.5 percent of aficamten-treated patients versus 0.7 percent on placebo [4]. In ACACIA-HCM (non-obstructive population), LVEF below 50 percent occurred more frequently (27 aficamten versus 2 placebo participants), with 3 percent requiring treatment interruption due to LVEF below 40 percent [6].

All LVEF reductions in the oHCM trials were mild, reversible with dose reduction or interruption, and not associated with clinical heart failure events, serious adverse events, or treatment discontinuation [4]. The reversibility within 24 to 48 hours (reflecting the 75- to 100-hour half-life) is a safety advantage over mavacamten, where LVEF reduction may persist for weeks following drug discontinuation due to the 7- to 9-day half-life.

11.3 Comparative safety versus mavacamten

Pooled analyses across clinical programs suggest a more favorable safety profile for aficamten compared to mavacamten on several parameters [16]:

- Atrial fibrillation: 4.1 per 100 patient-years (aficamten) versus 11.5 per 100 patient-years (mavacamten)
- Heart failure events: zero in aficamten oHCM trials versus 1.7 per 100 patient-years with mavacamten
- LVEF-related treatment discontinuation: 0.5 percent (aficamten) versus 8.7 percent (mavacamten) in oHCM
- QT prolongation-related discontinuation: zero (aficamten) versus 2.4 percent (mavacamten)
- Syncope: zero in SEQUOIA-HCM versus 5.7 percent in EXPLORER-HCM
- Deaths in oHCM trials: zero (aficamten) versus 6 across mavacamten programs (deemed unrelated)

These comparisons should be interpreted with caution given the shorter total exposure duration for aficamten and the absence of direct randomized head-to-head comparison between the two agents [16].

11.4 Boxed warning and REMS

The FDA approval includes a boxed warning stating that aficamten reduces LVEF and can cause heart failure due to systolic dysfunction [7]. Echocardiographic monitoring is mandatory before and during treatment. Aficamten is not recommended for initiation in patients with baseline LVEF below 55 percent. Dose reduction is required if LVEF drops below 50 percent but remains at or above 40 percent. Dosing must be interrupted if LVEF falls below 40 percent or if heart failure symptoms emerge. The MYQORZO REMS program requires prescriber certification, patient enrollment, and certified pharmacy dispensing [7].

11.5 Pregnancy and reproductive safety

Human data in pregnancy are insufficient. Animal reproductive toxicity data are included in the prescribing information. Given the mechanism of action (reduction of cardiac contractility), theoretical concerns exist regarding fetal cardiac development. Use during pregnancy is not recommended.

12. Comparative Assessment

This section presents a structured comparative assessment of five alternative agents against aficamten for the management of hypertrophic cardiomyopathy, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators represent the principal pharmacological approaches to HCM management, ranging from the first-in-class cardiac myosin inhibitor to the established standard-of-care agents.

12.1 Mavacamten (MYK-461, CAMZYOS)

Mechanism: Allosteric inhibitor of cardiac myosin ATPase that stabilizes the super-relaxed (SRX) state through binding at the mesa-converter interface. Reduces the proportion of force-generating myosin heads and decreases LVOT obstruction [8].

Development trajectory: Developed by MyoKardia (acquired by Bristol-Myers Squibb). FDA-approved April 2022 for symptomatic oHCM based on the EXPLORER-HCM and VALOR-HCM Phase 3 trials. EMA-approved subsequently. The most mature clinical program in the cardiac myosin inhibitor class [8].

Novelty: High at the time of approval. Mavacamten was the first-in-class cardiac myosin inhibitor and represented a fundamentally new approach to HCM management. Now moderate relative to aficamten, which shares the general mechanism but differs in binding site and pharmacokinetic profile.

Effect size: EXPLORER-HCM demonstrated pVO₂ improvement of 1.4 mL/kg/min LSMD versus placebo, with 37 percent achieving the composite primary endpoint versus 17 percent on placebo. VALOR-HCM demonstrated a 41.1 percent difference in the proportion of patients meeting guideline criteria for septal reduction therapy [16]. Compared to aficamten SEQUOIA-HCM (1.74 mL/kg/min pVO₂ improvement), the effect size is modestly smaller, although direct comparison is limited by differences in trial populations and design.

Promising potential: Moderate to high. The compound is FDA- and EMA-approved and commercially available for oHCM. Long-term extension data (MAVA-LTE, median 166 weeks) support sustained efficacy. The non-obstructive HCM pro-

gram (MAVERICK-HCM) has not produced clinical efficacy endpoints. Competition from aficamten and potential next-generation agents may limit future market position [16].

Side-effect profile: Mavacamten carries a higher rate of LVEF-related treatment interruptions (8.7 percent in oHCM versus 0.5 percent for aficamten), higher atrial fibrillation incidence (11.5 versus 4.1 per 100 patient-years), and higher dizziness rates (26.8 percent in EXPLORER-HCM versus 4.2 percent in SEQUOIA-HCM) [16]. The long half-life (7 to 9 days) means that LVEF reduction persists for weeks after discontinuation. CYP2C19 genotyping is required due to substantial pharmacokinetic variability in poor metabolizers. A REMS program with drug level monitoring is required [8].

Overall validation: High. The compound has the longest clinical track record, the largest cumulative exposure database, and the most comprehensive long-term safety data. Real-world experience continues to accumulate. The pharmacokinetic limitations (long half-life, CYP2C19 dependence, narrow therapeutic window) are well characterized and managed through the REMS program.

Comparison to aficamten: Aficamten demonstrates comparable or modestly greater efficacy in exercise capacity improvement, with substantially improved pharmacokinetic properties (shorter half-life, faster steady-state, faster washout, reduced CYP interaction burden) and a more favorable short-term safety profile. Mavacamten has the advantage of longer clinical experience and established long-term safety data. The two agents bind different sites on cardiac myosin and produce distinct biochemical phenotypes. For clinical practice, aficamten may offer operational advantages for patients who require dose flexibility, who are on concurrent CYP2C19-interacting medications, or who require rapid reversibility.

12.2 Metoprolol succinate (standard-of-care beta-blocker)

Mechanism: Selective beta-1 adrenergic receptor antagonist that reduces heart rate, myocardial oxygen demand, and contractility through inhibition of sympathetic stimulation. Does not directly address the fundamental sarcomeric dysfunction in HCM [17].

Novelty: Low. Beta-blockers have been used for HCM management since the 1960s. The mechanism addresses symptoms through rate control and reduced catecholamine-driven contractility but does not target the underlying molecular

pathology.

Effect size: In MAPLE-HCM, metoprolol monotherapy produced a decline in pVO₂ of 1.2 mL/kg/min over 24 weeks, compared to a 1.1 mL/kg/min improvement with aficamten (total difference 2.3 mL/kg/min favoring aficamten, $p < 0.0001$) [5]. NYHA class improvement occurred in 26 percent versus 51 percent for aficamten. NT-proBNP and LVOT gradient endpoints were markedly inferior to aficamten.

Promising potential: Low as a definitive therapy. Beta-blockers remain the most commonly prescribed initial therapy for symptomatic HCM due to widespread availability, low cost, and physician familiarity. However, MAPLE-HCM demonstrates that metoprolol monotherapy is inferior to aficamten monotherapy across functional, symptomatic, hemodynamic, and biomarker endpoints [5]. Beta-blockers are likely to transition to a complementary role alongside cardiac myosin inhibitors.

Side-effect profile: Beta-blocker adverse effects include fatigue, exercise intolerance (paradoxically), bradycardia, hypotension, depression, and sexual dysfunction. In MAPLE-HCM, 29.9 percent of metoprolol patients required dose down-titration compared to 4.5 percent for aficamten [5].

Overall validation: High for historical standard-of-care status; moderate for clinical efficacy. Decades of clinical use support safety and familiarity, but the evidence base for efficacy in HCM is limited to observational studies and expert consensus rather than large placebo-controlled trials. MAPLE-HCM provides the first randomized evidence comparing a beta-blocker to a cardiac myosin inhibitor, with results clearly favoring aficamten.

12.3 Verapamil (non-dihydropyridine calcium channel blocker)

Mechanism: L-type calcium channel blockade producing negative inotropic, negative chronotropic, and vasodilatory effects. Reduces LVOT gradient through contractility reduction and improved diastolic filling [17].

Novelty: Low. Verapamil has been used for HCM management since the 1980s as an alternative to beta-blockers, particularly in patients intolerant of beta-blockade.

Effect size: Observational data and small randomized studies suggest modest symptomatic improvement and LVOT gradient reduction, but no large placebo-controlled trials exist. Effect size is considered modest and inferior to cardiac myosin inhibitors based on available data and on the indirect comparison with SEQUOIA-HCM and MAPLE-HCM results.

Promising potential: Low. The compound is a generic medication with no active development program for HCM-specific indications. Its role is as a second-line alternative to beta-blockers.

Side-effect profile: Adverse effects include constipation, hypotension, bradycardia, peripheral edema, and conduction abnormalities. Verapamil is contraindicated in patients with severe LVOT obstruction (resting gradient greater than 100 mmHg) due to risk of hemodynamic collapse from vasodilation-induced reflex sympathetic activation and worsened obstruction [17].

Overall validation: Low. Clinical use is based on expert consensus, small trials, and decades of observational experience rather than rigorous Phase 3 evidence.

12.4 Disopyramide

Mechanism: Class Ia antiarrhythmic (sodium channel blocker) with prominent negative inotropic effects that reduce LVOT gradient. The negative inotropy, typically considered an adverse effect in other contexts, is the therapeutic mechanism in oHCM [17].

Novelty: Low. Disopyramide has been used as an adjunctive therapy for oHCM since the 1980s, typically added to a beta-blocker or calcium channel blocker in patients with persistent symptoms.

Effect size: Observational studies and small randomized trials demonstrate meaningful LVOT gradient reduction (30 to 50 percent gradient reduction in responders) and symptomatic improvement. The evidence is limited by small sample sizes and the absence of large Phase 3 trials.

Promising potential: Low. The compound is a generic medication with no active development program. Its role has been as a third-line agent added to beta-blockers or calcium channel blockers before referral for septal reduction therapy. The availability of cardiac myosin inhibitors may reduce the need for disopyramide in clinical practice.

Side-effect profile: Anticholinergic adverse effects (dry mouth, urinary retention, constipation, blurred vision) are common and dose-limiting. QT prolongation and proarrhythmic potential are significant concerns, particularly in HCM patients who are already at elevated arrhythmic risk. The anticholinergic burden and proarrhythmic risk are substantially greater than the adverse-event profile of aficamten [17].

Overall validation: Low to moderate. Decades of clinical use in HCM support its role as an effective LVOT gradient-reducing agent, but the evidence base is limited by the absence of large controlled trials and the significant adverse-event burden limits broad applicability.

12.5 Septal reduction therapy (surgical myectomy and alcohol septal ablation)

Mechanism: Mechanical reduction of septal myocardial mass by surgical excision (myectomy) or controlled septal infarction (alcohol ablation), reducing LVOT obstruction by widening the outflow tract [17].

Novelty: Moderate. Surgical myectomy (Morrow procedure) has been performed since the 1960s; alcohol septal ablation was introduced in the 1990s. Both remain the definitive interventions for medically refractory oHCM.

Effect size: Large. Surgical myectomy at experienced centers produces immediate and durable LVOT gradient elimination in greater than 90 percent of patients, with sustained symptomatic improvement, functional class improvement, and exercise capacity improvement over decades of follow-up. Alcohol septal ablation produces similar LVOT gradient reduction but with a higher need for permanent pacemaker implantation (10 to 20 percent) and a modestly higher rate of residual obstruction [17].

Promising potential: Moderate. Septal reduction therapy will remain the definitive treatment for severely symptomatic patients who do not respond adequately to pharmacotherapy (including cardiac myosin inhibitors). However, the availability of effective pharmacotherapy with aficamten and mavacamten may reduce the number of patients referred for invasive procedures. In VALOR-HCM, mavacamten reduced the proportion of patients meeting guideline criteria for septal reduction therapy, and similar effects are expected with aficamten.

Side-effect profile: Surgical myectomy carries the risks of open-heart surgery, including mortality (less than 1 percent at experienced centers, higher at low-volume centers), complete heart block requiring pacemaker (2 to 5 percent), ventricular septal defect, aortic regurgitation, and stroke. Alcohol septal ablation carries risks of complete heart block (10 to 20 percent), coronary artery dissection, and ventricular arrhythmia. Both procedures are irreversible [17].

Overall validation: High. Septal reduction therapy has the longest track record and the most durable outcomes data in oHCM management. Surgical myectomy at high-volume centers is considered the gold standard intervention for refractory disease.

Comparison to aficamten: Aficamten and septal reduction therapy address the same hemodynamic target (LVOT gradient reduction) through fundamentally different approaches: reversible pharmacological myosin inhibition versus irreversible mechanical septal reduction. Aficamten offers the advantages of non-invasiveness, reversibility, systemic availability, and applicability to patients who are not surgical candidates. Septal reduction therapy offers the advantages of a single definitive intervention with decades of durability data. The two approaches are complementary rather than competitive; aficamten may reduce the need for septal reduction therapy in some patients while serving as a bridge to intervention in others.

12.6 Comparator summary

The five comparators occupy distinct positions in the HCM management landscape. **Mavacamten** is the direct mechanistic comparator with longer clinical experience but less favorable pharmacokinetic properties and a higher short-term adverse-event burden. **Metoprolol** is the most commonly prescribed initial therapy but has been demonstrated inferior to aficamten monotherapy in the randomized MAPLE-HCM trial. **Verapamil** and **disopyramide** are established adjunctive agents with limited evidence bases and significant adverse-event profiles relative to cardiac myosin inhibitors. **Septal reduction therapy** remains the gold standard for medically refractory disease but is invasive and irreversible.

Aficamten occupies a strong position in this landscape: it is the second FDA-approved cardiac myosin inhibitor with improved pharmacokinetic properties relative to the first-in-class agent, the first cardiac myosin inhibitor to demonstrate superiority over standard-of-care beta-blocker monotherapy in a randomized trial,

and the first to demonstrate efficacy in non-obstructive HCM. The shorter half-life, distributed CYP metabolism, and more favorable short-term safety profile offer practical advantages for clinical use, although longer-term safety data (comparable to the multi-year mavacamten experience) are still accruing.

13. References

1. Hartman JJ, Hegde S, Engber TM, et al. Aficamten is a small-molecule cardiac myosin inhibitor designed to treat hypertrophic cardiomyopathy. *Nat Cardiovasc Res*. 2024;3(9):1005-1022.
2. Vander Zanden CM, Bhatt PN, Hegde S, et al. Discovery of aficamten (CK-274), a next-generation cardiac myosin inhibitor for the treatment of hypertrophic cardiomyopathy. *J Med Chem*. 2022;65(8):5949-5969.
3. Maron BJ, Maron MS. Hypertrophic cardiomyopathy. *Lancet*. 2013;381(9862):242-255.
4. Cytokinetics, Inc. Positive results from SEQUOIA-HCM, the pivotal Phase 3 clinical trial of aficamten in patients with obstructive hypertrophic cardiomyopathy. 2024.
5. Cytokinetics, Inc. Primary results from MAPLE-HCM presented at the European Society of Cardiology Congress 2025 and published in *The New England Journal of Medicine*. 2025.
6. Cytokinetics, Inc. Positive topline results from ACACIA-HCM, the pivotal Phase 3 clinical trial of aficamten in patients with non-obstructive hypertrophic cardiomyopathy. May 2026.
7. Cytokinetics, Inc. FDA approval of MYQORZO (aficamten) for the treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy to improve functional capacity and symptoms. December 19, 2025.
8. Olivotto I, Oreziak A, Barriales-Villa R, et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2020;396(10253):759-769.
9. Grillo MP, Bhatt PN, Gaffney M, et al. A Phase 1 dose-escalation study of the cardiac myosin inhibitor aficamten in healthy participants. *JACC Basic Transl Sci*. 2022;7(8):763-775.

10. Maron MS, Masri A, Choudhury L, et al. Phase 2 study of aficamten in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2023;81(1):34-45.
11. Xu RA, Grillo MP, Gaffney M, et al. Pharmacokinetics, disposition, and bio-transformation of the cardiac myosin inhibitor aficamten in humans. *Pharmacol Res Perspect*. 2024;12(5):e70006.
12. Mazzanti A, Vittori C, Cartella I, et al. CYP450 activity, drug interactions, and genetic polymorphisms: clinical relevance for the new selective cardiac myosin inhibitors. *Expert Opin Drug Saf*. 2025.
13. Stern JA, Markova S, Ueda Y, et al. Pharmacokinetics of a single dose of aficamten (CK-274) on cardiac contractility in a A31P MYBPC3 hypertrophic cardiomyopathy cat model. *J Vet Intern Med*. 2023;37(2):456-463.
14. Choudhury L, Masri A, Maron MS, et al. Efficacy and safety of aficamten in symptomatic nonobstructive hypertrophic cardiomyopathy: results from the REDWOOD-HCM trial, cohort 4. *J Card Fail*. 2024;30(6):750-759.
15. Cytokinetics, Inc. FOREST-HCM long-term extension study interim data. Presented at the American College of Cardiology Annual Scientific Session, 2025.
16. Shah SJ, Colan SD, Desai MY, et al. Safety and efficacy of mavacamten and aficamten in patients with hypertrophic cardiomyopathy. *J Am Heart Assoc*. 2025;14(12):e038758.
17. Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy. *Circulation*. 2020;142(25):e558-e631.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Aficamten (MYQORZO) is approved by the United States Food and Drug Administration for the treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy. Prescribing requires enrollment in the MYQORZO REMS program. Investigators using research-grade material should obtain analytical confirmation of identity, purity, and stereochemical integrity on every lot.