Updates in hypertrophic cardiomyopathy care: Bridging the current treatment gaps with emerging novel therapies

What are the current conventional pharmacological treatments for HCM and what unmet needs remain?

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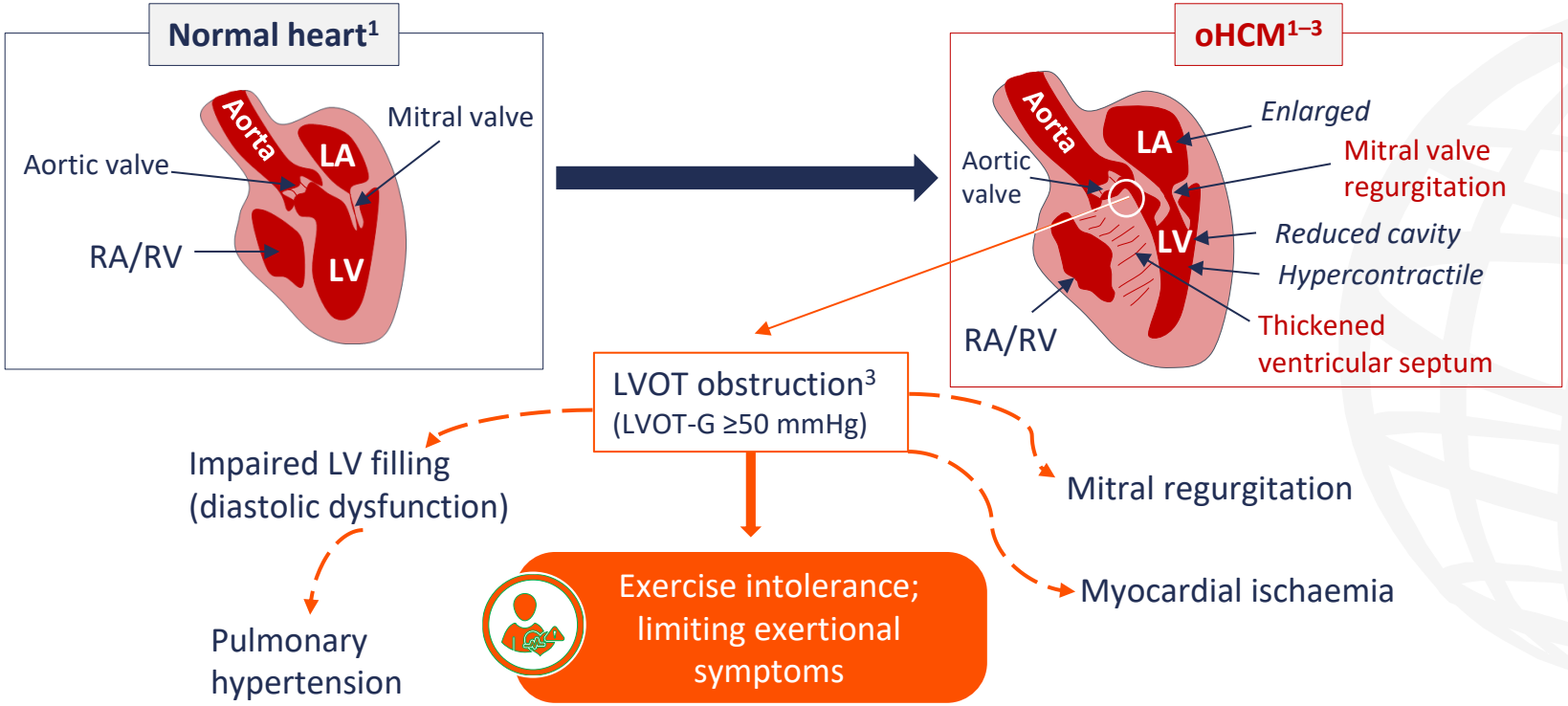
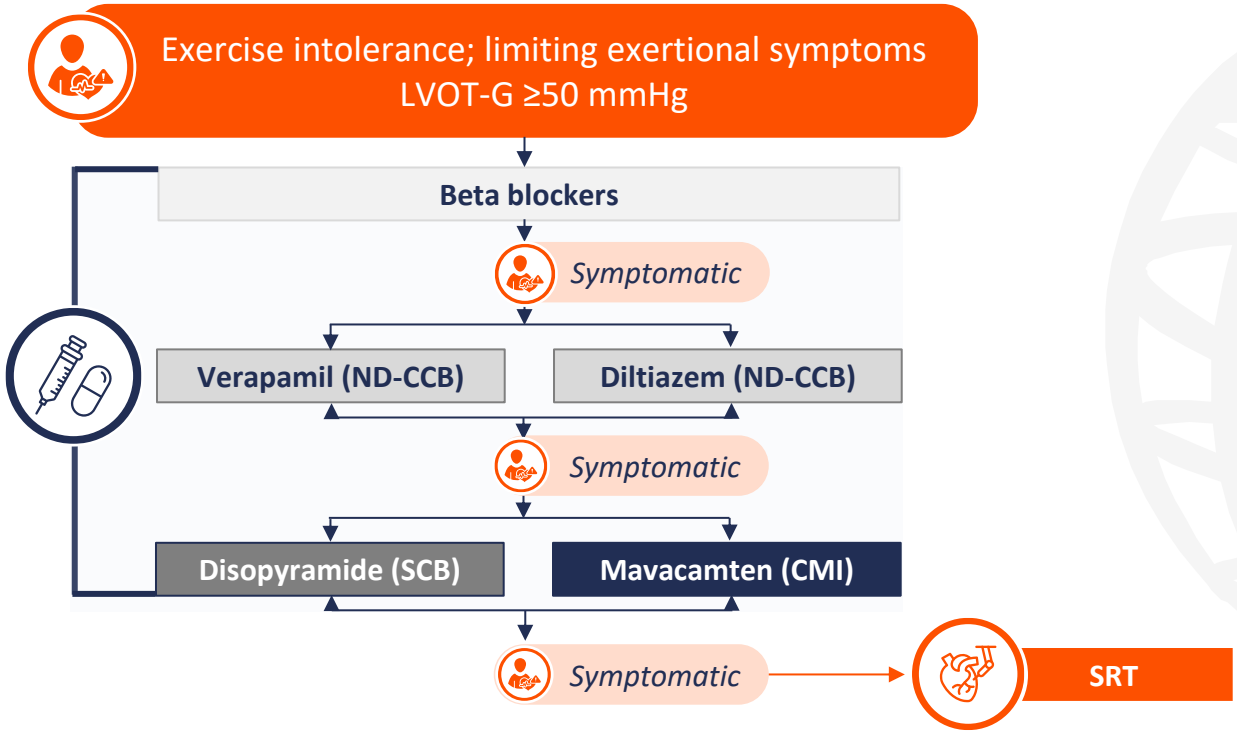
The pathobiology of obstructive HCM



LA, left atrium; LV, left ventricle; LVOT, left ventricular outflow tract; LVOT-G, LVOT-gradient; oHCM, obstructive hypertrophic cardiomyopathy; RA/RV, right atrium/right ventricle.

1. Mayo Clinic: Hypertrophic cardiomyopathy. Available at: http://bit.ly/4q3tJII (accessed 14 October 2025); 2. Ostrominski JW, et al. *JACC Heart Fail*. 2023;11:735–48; 3. Ommen SR, et al. *J Am Coll Cardiol*. 2024;83:2324–405.

Clinical guidelines for managing obstructive HCM[1,2]

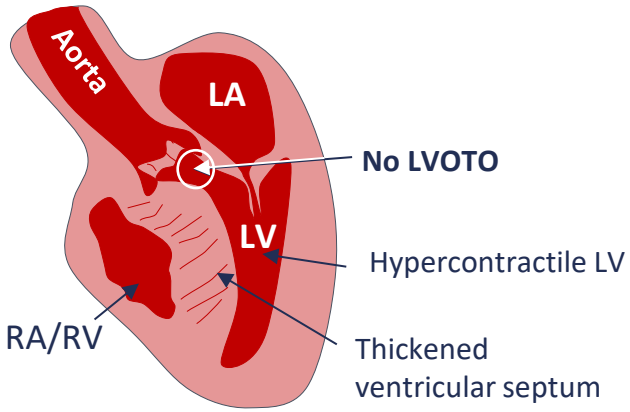


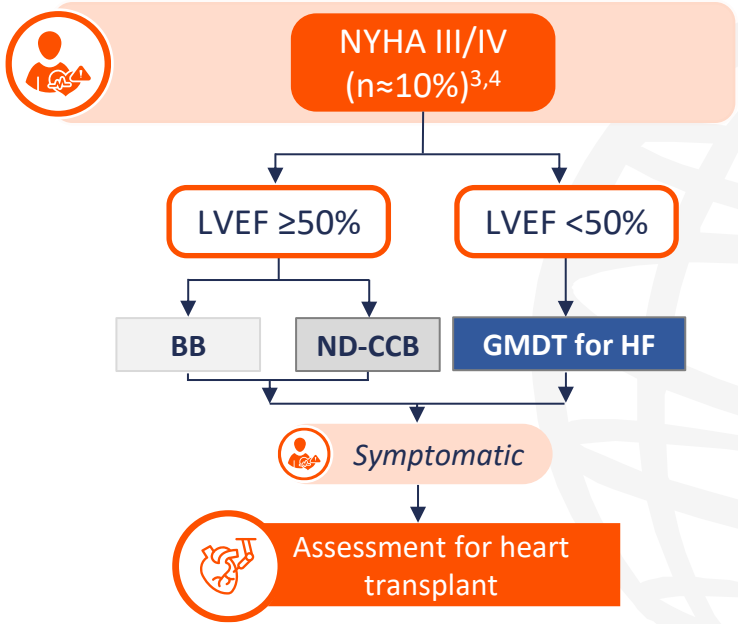
CMI, cardiac myosin inhibitor; HCM, hypertrophic cardiomyopathy; LVOT-G, left ventricular outflow tract-gradient; ND-CCB, non-dihydropyridine calcium channel blocker; SCB, sodium channel blocker; SRT, septal reduction therapy.

1. Arbelo E, et al. *Eur Heart J.* 2023;44:3503–626; 2. Ommen SR, et al. *J Am Coll Cardiol.* 2024;83:2324–405.

Management of symptomatic nonobstructive HCM

nHCM[1–3]





- Symptomatic nHCM is a diagnostic and therapeutic challenge
- BBs and ND-CCBs have only been evaluated in a few small trials that included patients with oHCM and nHCM

BB, beta blocker; GMDT, guideline-directed medical therapy; HCM, hypertrophic cardiomyopathy; HF, heart failure; LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction; ND-CCB, non-dihydropyridine calcium channel blocker; nHCM, nonobstructive HCM; NYHA, New York Heart Association; oHCM, obstructive HCM; RA/RV, right atrium/right ventricle.

1. Mayo Clinic: Hypertrophic cardiomyopathy. Available at: http://bit.ly/4q3tJII (accessed 14 October 2025); 2. Ostrominski JW, et al. *JACC Heart Fail*. 2023;11:735–48; 3. Ordine L, et al. *Heart Fail Rev*. doi: 10.1007/s10741-025-10535-w. Online ahead of print; 4. Ommen SR, et al. *J Am Coll Cardiol*. 2024;83:2324–405.

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What therapeutic classes are emerging for HCM and what is the latest evidence for their use?

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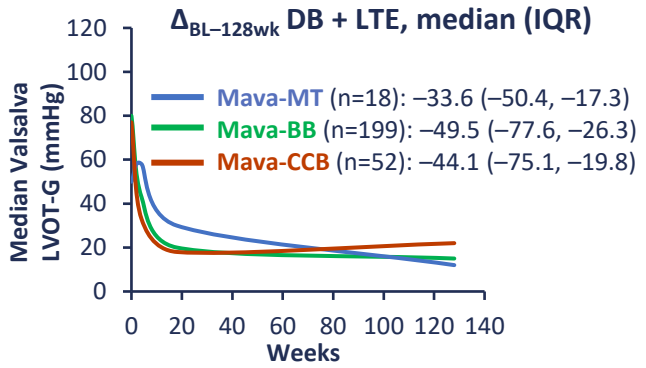
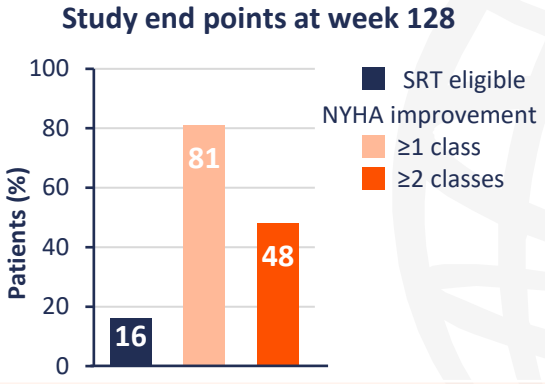
Recent data from trials with mavacamten in oHCM

Mava-MT: Integrated efficacy and safety analysis
Pooled analysis of four phase III studies
(EXPLORER-HCM, MAVA-LTE, VALOR-HCM, EXPLORER-CN)[1]

VALOR-HCM
(primary endpoint: patients eligible for SRT*)
Mava (n=56) and transitioned from pbo (n=52) at 128 weeks[2]





- Similar reductions in LVEF from BL to week 128 were observed for Mava-MT vs Mava-BB and Mava-CCB
- Comparable proportions of Mava-MT patients experienced safety events vs Mava-BB and Mava-CCB

- The most common AEs were fatigue (17%) and dizziness (15%)
- LVEF <50%: 14% (5.41/100 patient-years)†
- New-onset AF: 10.2% (4.55/100 patient-years)

*Eligibility for SRT according to the 2011 guidelines or deciding to proceed with SRT. †Two patients had LVEF ≤30% and there was one death.
AE, adverse event; AF, atrial fibrillation; BB, beta-blocker; BL, baseline: CCB, calcium channel blocker; CN, China; DB, double blind; HCM, hypertrophic cardiomyopathy; IQR, interquartile range; LTE, long-term extension; LVEF, left ventricular ejection fraction; LVOT-G, left ventricular outflow tract gradient; Mava, mavacamten; MT, monotherapy; NYHA, New York Heart Association; oHCM, obstructive HCM; pbo, placebo; SRT, septal reduction therapy; wk, week.
1. Olivotto I, et al. Integrated efficacy and safety analysis of mavacamten monotherapy in patients with oHCM. Presented at: ESC Congress 2025, Madrid Spain. 29 August–1 September 2025; 2. Desai MY, et al. *Circulation*. 2025;151:1378–90.

Clinical trials with mavacamten in symptomatic oHCM

Study	SCOUT-HCM (NCT06253221, ph III)[1,2]	MEMENTO (NCT06112743, ph IV)[3]	COLLIGO-HCM (NCT06372457)[4]	COMPASS-HCM (NCT06551129)[5]
Aim	• Efficacy, safety and PK	• Impact on myocardial structure	• Observational • Real-world effectiveness	• Observational • $\Delta_{BL-wk96}$ health status
Patients	• Adolescents (12–17 years; N=40)	• Adults (N=63) • LVOT-G: ≥30 mmHg and ≥50 mmHg after Valsalva/exercise • LVEF ≥55% • NYHA, II/III	• Adults ≥18 years (N=500) • ≥1 diagnosis of HCM during or after 2018* • Mava cohort received mava after the index data	• Adults ≥18 years (N=118)
Primary endpoint	• $\Delta_{BL-wk28}$, peak Valsalva LVOT-G	Composite at wk 48 of reduction in: • Max. $LAVI_{BL-wk48}$ ≥5 mL/m^2 • $LVMI_{BL-wk48}$ ≥5 g/m^2	• Echo: BL–33 months • NYHA: BL–33 months • Procedures: BL–33 months	• HCM symptoms:† BL–wk 96 • Procedures: BL–wk 96 • NYHA: BL–wk 96
Completion/ latest data	• March 2031	• September 2026	• Confirms clinical trial data with a diverse population of patients • Low incidence of LVEF ≤50%	• June 2027

*The first diagnosis in this period is defined as the index. †Assessed by a range of different questionnaires.
BL, baseline; echo, echocardiogram; HCM, hypertrophic cardiomyopathy; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVOT-G, left ventricular outflow tract gradient; mava, mavacamten; max., maximum; NYHA, New York Heart Association; oHCM, obstructive hypertrophic cardiomyopathy; ph, phase; PK, pharmacokinetics; wk, week.
1. Rossano J, et al. *Circulation*. 2024:150(Suppl. 1):A4132223; 2. ClinicalTrials.gov. NCT06253221; 3. ClinicalTrials.gov. NCT06112743; 4. Adler A, et al. Real-world outcomes of mavacamten for symptomatic oHCM: Global evidence from COLLIGO-HCM. Presented at: ESC Congress 2025, Madrid Spain. 29 August–1 September 2025; 5. ClinicalTrials.gov. NCT06551129. **All clinical trials are available according to their study number at: www.clinicaltrials.gov/ (accessed 14 October 2025).**

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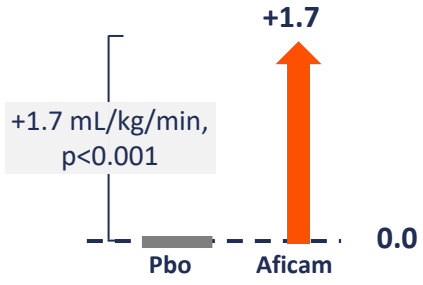
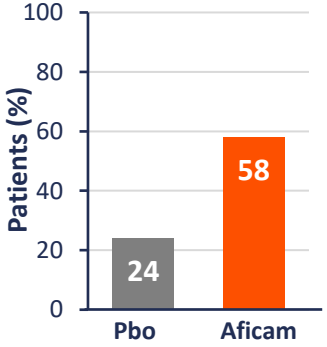
Phase III aficamten trials: recent data

SEQUOIA-HCM (NCT05186818)[1]
Aficamten (n=142) vs Pbo (n=140)

Primary endpoint:
$\Delta_{BL–wk24}$ pVO_2 (LSM)



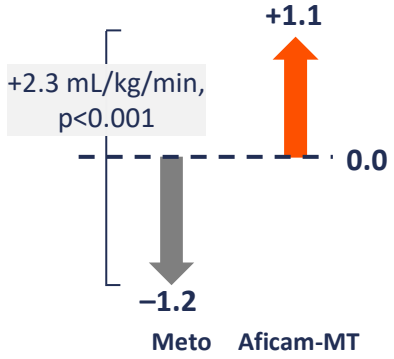
NYHA improvement, ≥1 class



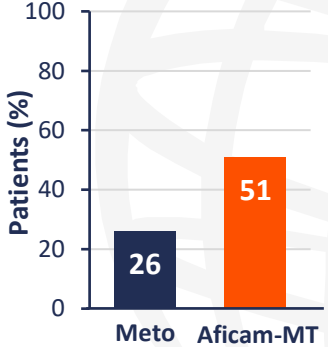
- A comparable proportion of patients in both groups experienced ≥1 AE (74% vs 71%) or SAE (6% vs 9%)
  - Palpitations were more common in the aficam group
- LVEF reduction vs pbo at week 24, LSM (95% CI): –4.8 (–6.3, –3.2)*

MAPLE-HCM (NCT05767346)[2]
Aficam-MT (n=88) vs Meto (n=87)

Primary endpoint:
$\Delta_{BL–wk24}$ pVO_2 (LSM)



NYHA improvement, ≥1 class



- A comparable proportion of patients in both groups experienced ≥1 AE (74% vs 76%) or SAE (8% vs 7%)
- LVEF reduction vs meto at week 24, LSM (95% CI): –4.2 (–5.3, –3.1)

*4% of patients treated with aficamten vs 1% of patient treated with pbo experienced a transient reduction of LVEF <50%.
AE, adverse event; aficam, aficamten; BL, baseline; CI, confidence interval; LSM, least-squares mean; LVEF, left ventricular ejection fraction; meto, metoprolol; MT, monotherapy; NYHA, New York Heart Association; pbo, placebo; pVO_2, peak oxygen uptake; SAE, serious adverse event; wk, week.

1. Maron M, et al. *N Engl J Med.* 2024;390:1849–61; 2. Garcia-Pavia P, et al. *N Engl J Med*. 2025;393:949–60.

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Clinical trials with aficamten in symptomatic oHCM

Study	CEDAR-HCM (phase II/III, NCT06412666, N≈40)[1]	FOREST-HCM (OLE, NCT04848506, N≈900)[2,3]
Aim	• Efficacy, safety and PK of aficamten in a paediatric population	• Assess the long-term safety and tolerability of aficamten

Patients	• Adolescents (12–17 years)
	• Children (6–11 years)
	• LV end-diastolic wall thickness meeting a threshold of:
	  ○ Z-score >2.5 in the absence of family history **OR**
	  ○ Z-score >2.0 with positive family history/genetic test
	• LVEF ≥60% **AND** Valsalva LVOT-G ≥50 mmHg
	• NYHA class ≥II at screening
		• Adults (18–85 years) who had completed a trial investigating aficamten

Primary endpoint	• $\Delta_{BL-wk12}$ Valsalva LVOT-G	• Incidence of TEAEs, SAEs and LVEF <50%
Completion/ latest data	• January 2030	• Well-tolerated • LVEF <50%: 4% • No new-onset AF following 48 weeks of treatment

AF, atrial fibrillation; BL, baseline; LV, left ventricular; LVEF, LV ejection fraction; LVOT-G, LV outflow tract gradient; NYHA, New York Heart Association; oHCM, obstructive hypertrophic cardiomyopathy; OLE open-label extension; PK, pharmacokinetics; SAE, serious adverse events; TEAE, treatment-emergent adverse event; wk, week.

1. ClinicalTrials.gov. NCT06412666; 2. Saberi S, et al. *JACC: Heart Fail.* 2025;13:102496; 3. ClinicalTrials.gov. NCT04848506.

All clinical trials are available according to their study number at: www.clinicaltrials.gov/ (accessed 14 October 2025).

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CMIs in symptomatic nHCM

Study	ODYSSEY-HCM[1] Mavacamten (n=289) vs pbo (n=291)	FOREST-HCM (NCT04219826, phase II)[2] Aficamten (N=34)
Aim	• Change in exercise capacity and patient-reported health status	• Safety and efficacy of over 36 weeks
Patients	• pLVOT: <30 mmHg (rest); <50 mmHg (provocation) • NYHA class: II/III; KCCQ-23 CSS ≤85	• Adult patients from REDWOOD-HCM Cohort 4
Primary endpoint	• $\Delta_{BL-wk48}$ pVO_2 (CPET) • $\Delta_{BL-wk48}$ KCCQ-23 CSS	• Safety, LVEF • NYHA class, KCCQ-23 CSS • Cardiac biomarkers: NT-proBNP, hs-cTnI
Completion/ latest data	$\Delta_{BL-48wk}$ pVO_2, LSM (95% CI): 0.47 (–0.03–0.98), p=0.066 $\Delta_{BL-48wk}$ KCCQ-23 CSS, LSM (95% CI): 2.70 (–0.08–5.60), p=0.056 LVEF <50%, n (%): 62 (21) Total SAEs, n (%): 55 (19) vs 44 (15)	LVEF <50%, n (%): 2 (6)* SAEs: 8 in 5 patients; 1 treatment related $\Delta_{BL-36wk}$ KCCQ-23 CSS: 13.5 ± 12.5 points NHYA class: 79% improved by ≥1 class NT-proBNP, median (range): −665.5 pg/mL (−1244.0 to −232.0), p<0.0001

*One SAE occurred following pulmonary vein isolation and the other was associated with atrial fibrillation.
BL, baseline; CI, confidence interval; CMI, cardiac myosin inhibitor; CPET, cardiopulmonary Exercise Test; hs-cTnI, high-sensitivity cardiac troponin I; KCCQ-23 CSS, Kansas City Cardiomyopathy Questionnaire (23-item) Clinical Summary Score; LSM, least squares mean; LVEF, left ventricular ejection fraction; nHCM, nonobstructive hypertrophic cardiomyopathy; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; pbo, placebo; pLVOT, peak left ventricular outflow tract; pVO_2, peak oxygen uptake; SAE, serious adverse event; wk, week.
1. Desai MY, et al. Mavacamten in symptomatic nHCM. Presented at: ESC Congress 2025, Madrid Spain. 29 August–1 September 2025; 2. Masri A, et al. *Eur J Heart Fail*. 2024;26:1993–8.

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