EXPLORER-HCM

Efficacy and Safety of Mavacamten in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy: Results of the EXPLORER-HCM Study

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On behalf of the EXPLORER-HCM investigators

Declaration of Interest

Presenting author:

- Grant/research support: Sanofi-Genzyme, Shire, Amicus, Bayer, MyoKardia
- Honoraria: Sanofi-Genzyme, Shire, Bayer
- Consultant: MyoKardia

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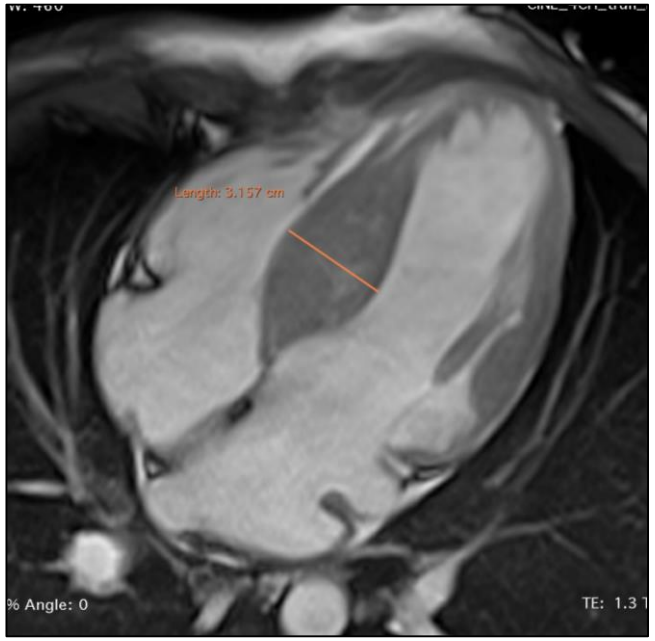
Introduction

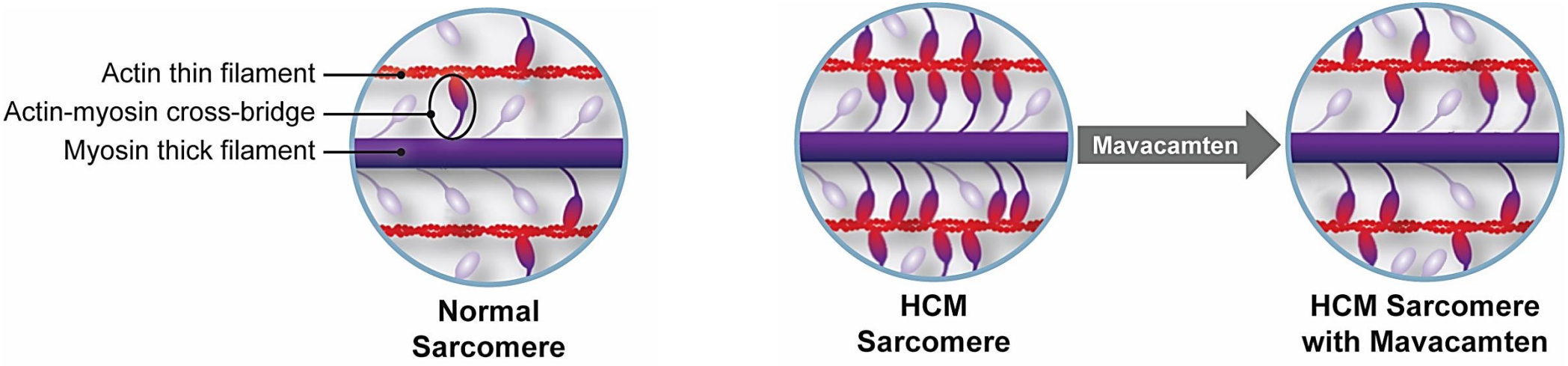
- Hypertrophic cardiomyopathy (HCM) is a myocardial disorder characterized by primary left ventricular (LV) hypertrophy
- Symptoms are often related to dynamic outflow obstruction
- Current medical management for obstructive HCM includes beta-blockers, non-dihydropyridine calcium channel blockers, or disopyramide[1-2]



Developing effective pharmacological therapy for obstructive HCM is an important unmet need

[1]Elliot PM, et al. *Eur Heart J.* 2014;35(39): 2733-2779.
[2]Gersh BJ, et al. *Circulation.* 2011;124(24):2761-2796.

Mavacamten: Mechanism of Action



Normal Sarcomere

Normal contractility
Effective relaxation

HCM Sarcomere

HCM Pathophysiology
Hypercontractility
Impaired relaxation
Altered myocardial energetics

HCM Sarcomere with Mavacamten

Attenuated hypercontractility
Improved compliance
Improved energetics

Mavacamten is a first-in-class, targeted inhibitor of cardiac myosin

→ It reduces the number of myosin-actin cross-bridges and thus decreases excessive contractility characteristic of HCM

EXPLORER-HCM Study Design

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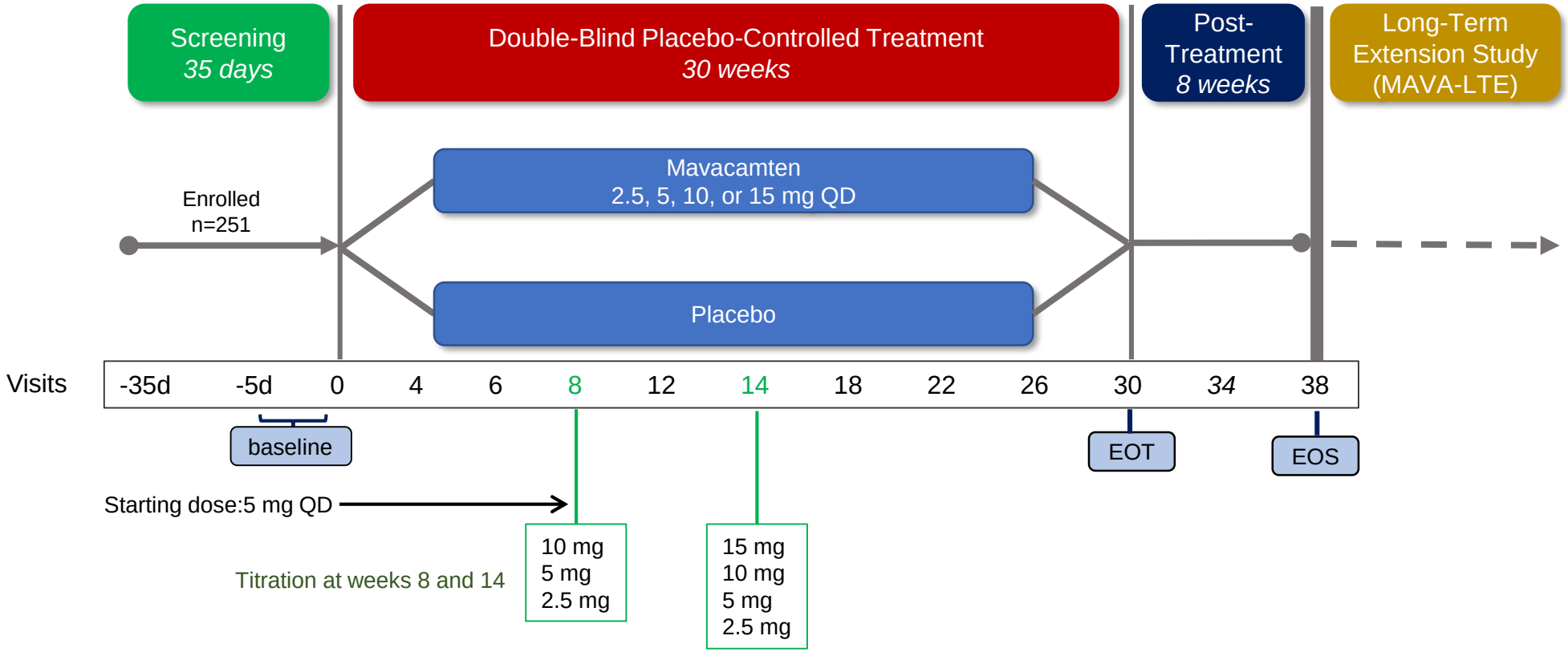
Pivotal Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial in Patients With Obstructive HCM[1]

Patients with LVOT gradient ≥50 mmHg and New York Heart Association (NYHA) class II-III symptoms were randomized 1:1 to receive once-daily oral mavacamten (starting dose of 5 mg with a 2-step dose titration) or placebo for 30 weeks



[1]Ho CY et al. Circ Heart Fail. 2020; 13(6):e006853

EXPLORER-HCM Endpoints

Primary composite functional endpoint

Change from baseline to Week 30		pVO_2		NYHA Classification
EITHER	**Composite 1**	≥1.5 mL/kg/min	***and***	Reduction of ≥1 class
OR	**Composite 2**	≥3.0 mL/kg/min	***and***	No worsening

Secondary endpoints included change from baseline to Week 30 in:

- Post-exercise LVOT gradient
- pVO_2
- Proportion of patients with ≥1 NYHA class improvement
- Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS)
- HCM Symptom Questionnaire Shortness-of-Breath (HCMSQ-SoB) subscore

Only the primary and secondary endpoints are alpha-controlled

Baseline Demographics and Patient Characteristics

Characteristic	Mavacamten (N = 123)	Placebo (N = 128)
Age, years, mean ± SD	58.5 ± 12.2	58.5 ± 11.8
Female sex, n (%)	57 (46.3)	45 (35.2)
Background HCM therapy, n (%) Beta-blocker Calcium channel blocker	 94 (76.4) 25 (20.3)	 95 (74.2) 17 (13.3)
NYHA functional class, n (%) II III	 88 (71.5) 35 (28.5)	 95 (74.2) 33 (25.8)
History of atrial fibrillation, n (%)	12 (9.8)	23 (18.0)
pVO_2, ml/kg/min, mean ± SD	18.9 ± 4.9	19.9 ± 4.9
NT-proBNP, geometric mean (CV%), ng/L*	777 (136)	616 (108)
HCM genetic testing performed, n (%)	90 (73.2)	100 (78.1)
Pathogenic/likely pathogenic HCM gene variant — n/N tested (%)	28/90 (31.1)	22/100 (22.0)

*NT-proBNP: mavacamten, n = 120; placebo, n = 126.

HCM, hypertrophic cardiomyopathy; NYHA, New York Heart Association; NT-proBNP, N-terminal pro b-type natriuretic peptide; pVO_2, peak oxygen consumption.

Baseline Echo Parameters

Echocardiographic parameters, mean ± SD	Mavacamten (N = 123)	Placebo (N = 128)
LVEF, %	74 ± 6	74 ± 6
Maximum LV wall thickness, mm	20 ± 4	20 ± 3
LVOT gradient resting, mm Hg	52 ± 29	51 ± 32
LVOT gradient Valsalva, mm Hg	72 ± 32	74 ± 32
LVOT gradient post-exercise, mm Hg*	86 ± 34	84 ± 36
LA volume index, mL/m^2 ‡	40 ± 12	41 ± 14

*Post-exercise LVOT: mavacamten, n = 122; placebo, n = 127.
‡LA volume index: mavacamten, n = 123; placebo = 128.
LA, left atrial; LV, left ventricular; LVOT, left ventricular outflow tract

Primary Endpoint

	Mavacamten (N = 123) n (%)	Placebo (N = 128) n (%)	Difference (95% CI) P value
EITHER ≥1.5 ml/kg/min increase in pVO_2 with ≥1 NYHA class improvement **OR** ≥3.0 ml/kg/min increase in pVO_2 with no worsening of NYHA class	45 (36.6)	22 (17.2)	19.4 (8.7, 30.1) 0.0005
BOTH ≥3.0 ml/kg/min increase in pVO_2 **AND** ≥1 NYHA class improvement	25 (20.3)	10 (7.8)	12.5 (4.0, 21.0) 0.0005*

*P value not alpha-controlled

NYHA, New York Heart Association; pVO_2, peak oxygen consumption.

Secondary Endpoints

	Mavacamten	Placebo	Difference* (95% CI) P value
Post-exercise LVOT gradient, n†	117	122	
Change from baseline to week 30, mmHg, mean ± SD	–47 ± 40	–10 ± 30	–36 (–43.2, –28.1) <0.0001
pVO_2, n†	120	125	
Change from baseline to week 30, ml/kg/min, mean ± SD	1.40 ± 3.1	–0.05 ± 3.0	1.35 (0.58, 2.12) 0.0006
≥1 NYHA class improvement, n†	123	128	
Improvement from baseline to week 30, n (%)	80 (65.0)	40 (31.3)	34 (22.2, 45.4) <0.0001
KCCQ-CSS, n† (positive better)	92	88	
Change from baseline to week 30, mean ± SD	13.6 ± 14.4	4.2 ± 13.7	9.1 (5.5, 12.7) <0.0001
HCMSQ-SoB, n† (negative better)	85	86	
Change from baseline to week 30, mean ± SD	–2.8 ± 2.7	–0.9 ± 2.4	–1.8 (–2.4 to –1.2) <0.0001

*Model estimated least-square mean differences were reported for continuous variables.
†N = number analyzable for secondary end point based on N availability of both baseline and week 30 values.
HCM Symptom Questionnaire Shortness-of-Breath (HCMSQ-SoB) subscore; Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS); LVOT, left ventricular outflow tract; NYHA, New York Heart Association; pVO_2, peak oxygen consumption.

LVOT Gradients and LVEF Over Time

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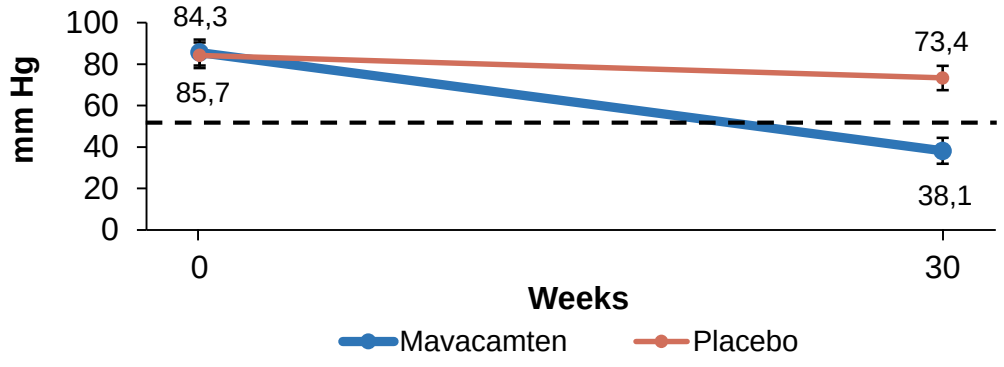
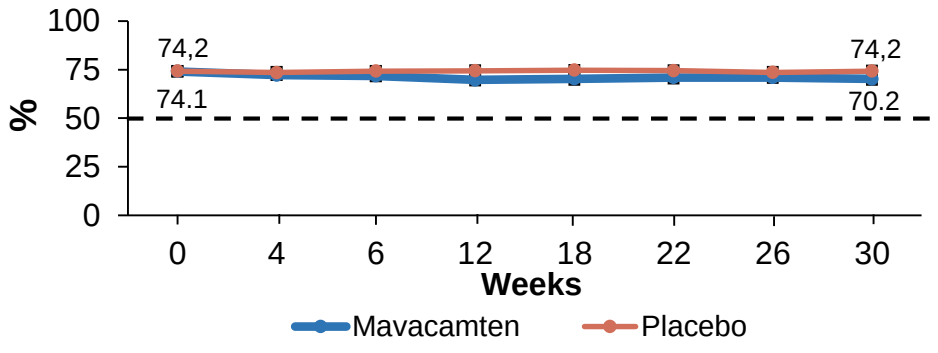
Mean (95% CI) post-exercise LVOT gradient



Number of patients at visit

Mavacamten	122							118
Placebo	127							123

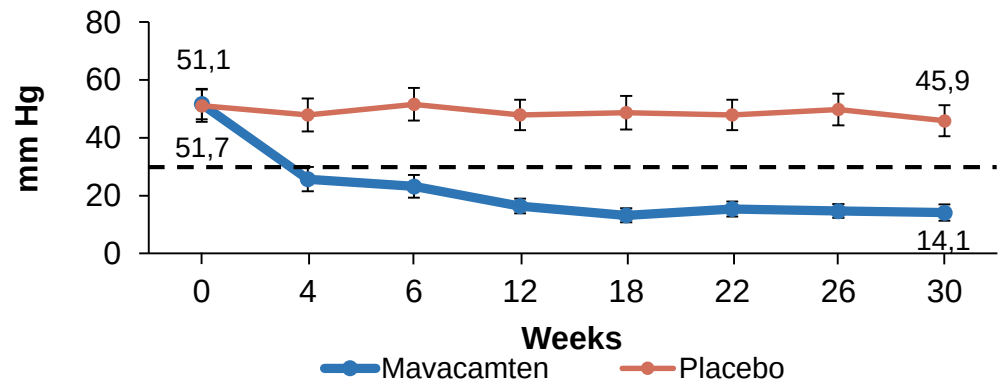
Mean (95% CI) LVEF



Number of patients at visit

Mavacamten	123	116	115	111	111	107	113	114
Placebo	128	115	117	120	119	121	121	119

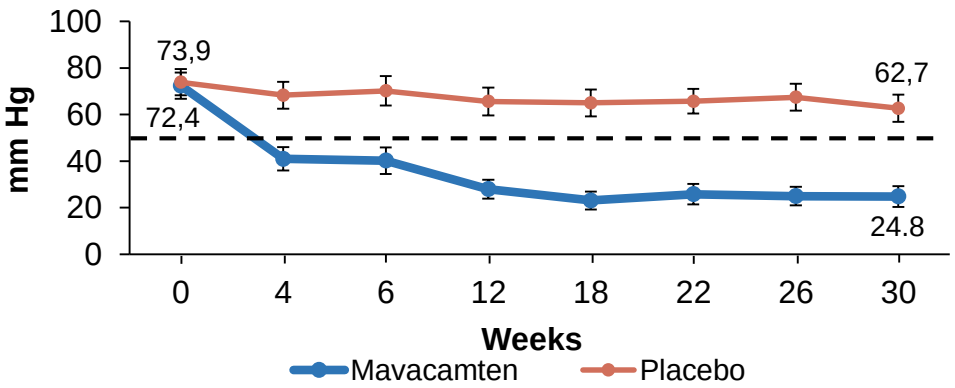
Mean (95% CI) resting LVOT gradient



Number of patients at visit

Mavacamten	123	119	119	118	116	118	120	117
Placebo	128	121	122	125	122	125	125	123

Mean (95% CI) Valsalva LVOT gradient

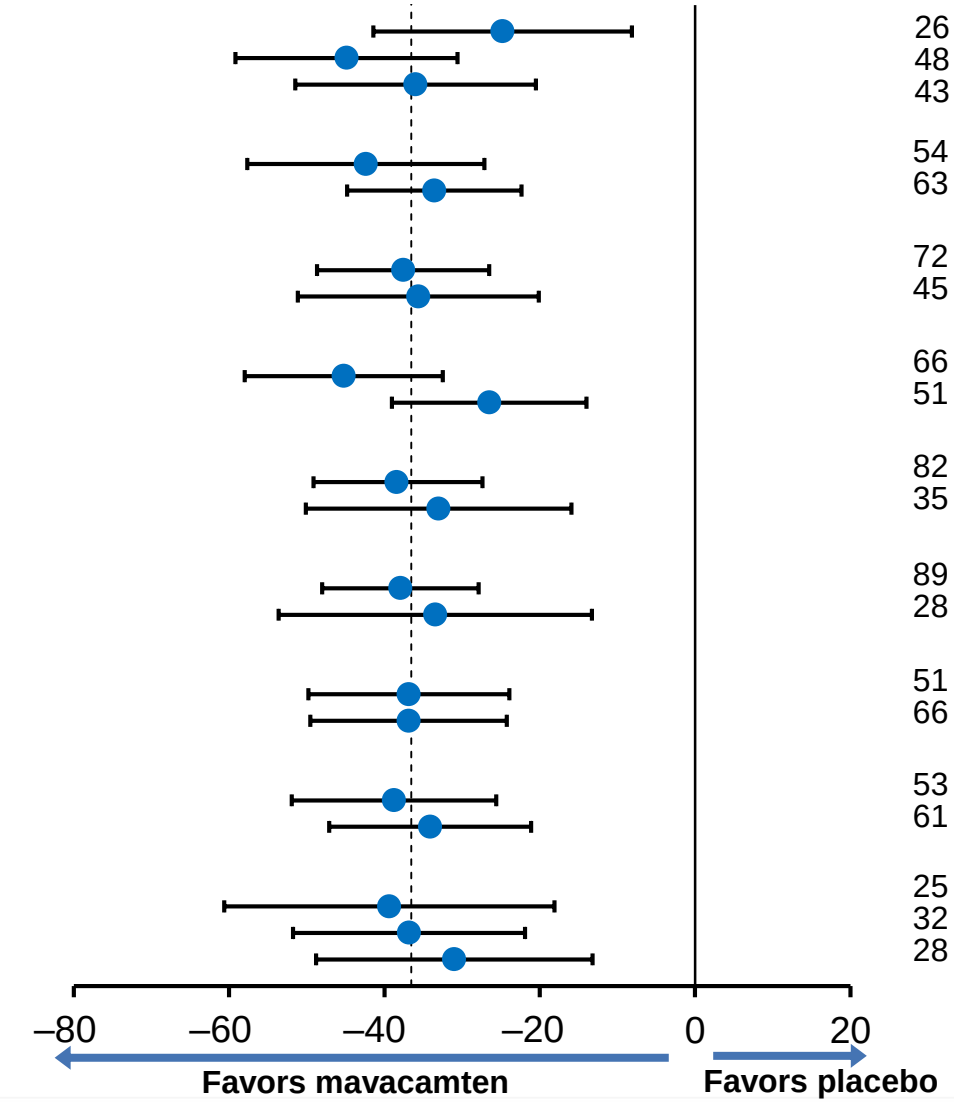


Number of patients at visit

Mavacamten	123	117	118	118	116	118	120	117
Placebo	128	119	119	125	122	125	124	124

The dashed lines represent the threshold for guideline-based invasive intervention (post-exercise and Valsalva LVOT gradient >50 mm Hg), the threshold for guideline-based diagnosis of obstruction (resting LVOT gradient <30 mm Hg), or the protocol threshold for temporary discontinuation (LVEF <50%).
LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract.

Treatment Effect on Post-Exercise LVOT Gradient by Subgroup



Subgroup	Mean difference, mm Hg (95% CI)	Mavacamten N (mean)	Placebo N (mean)	Difference, mm Hg (95% CI)
Age, years				
≤49		26 (–37.0)	23 (–12.2)	–24.8 (–41.4, –8.1)
50-64		48 (–57.1)	61 (–12.2)	–44.9 (–59.2, –30.6)
≥65		43 (–42.5)	38 (–6.5)	–36.0 (–51.5, –20.5)
Sex				
Female		54 (–47.9)	43 (–5.5)	–42.4 (–57.7, –27.1)
Male		63 (–46.7)	79 (–13.1)	–33.6 (–44.8, –22.4)
BMI, kg/m^2				
<30		72 (–47.5)	74 (–9.9)	–37.6 (–48.7, –26.5)
≥30		45 (–46.9)	48 (–11.3)	–35.6 (–51.1, –20.1)
LVEF at baseline, %				
<75		66 (–52.8)	64 (–7.6)	–45.2 (–58.0, –32.5)
≥75		51 (–40.1)	58 (–13.6)	–26.5 (–39.0, –14.0)
NYHA class at baseline				
Class II		82 (–48.7)	90 (–10.3)	–38.4 (–49.1, –27.7)
Class III		35 (–43.9)	32 (–10.9)	–33.0 (–50.1, –15.9)
Beta-blocker usage at baseline				
Yes		89 (–47.1)	92 (–9.1)	–37.9 (–48.0, –27.9)
No		28 (–47.9)	30 (–14.4)	–33.5 (–53.6, –13.3)
Type of exercise testing				
Bicycle		51 (–48.2)	57 (–11.4)	–36.9 (–49.8, –23.9)
Treadmill		66 (–46.5)	65 (–9.6)	–36.9 (–49.5, –24.2)
NT-proBNP at baseline, ng/L				–38.8 (–51.9, –25.6)
≤Median		53 (–48.8)	64 (–10.0)	–34.1 (–47.1, –21.1)
>Median		61 (–45.7)	56 (–11.6)	
HCM genetic testing result				
Pathogenic or likely pathogenic		25 (–49.8)	21 (–10.5)	–39.4 (–60.6, –18.1)
VUS		32 (–49.5)	40 (–12.7)	–36.8 (–51.8, –21.9)
Negative		28 (–38.9)	34 (–7.9)	–31.0 (–48.8, –13.2)

HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; NT-proBNP, N-terminal pro b-type natriuretic peptide; VUS, variant of uncertain significance.

Key Exploratory Efficacy Endpoints

	Mavacamten	Placebo	Difference (95% CI) P value*
Post-exercise LVOT peak gradient <50 mm Hg, n/N (%) †	75/101 (74.3)	22/106 (20.8)	53.5 (42.0, 65.0) <0.0001
Post-exercise LVOT peak gradient <30 mm Hg, n/N (%) ‡	64/113 (56.6)	8/114 (7.0)	49.6 (39.3, 59.9) <0.0001
Complete response, n/N (%) *Defined as NYHA class I and all LVOT gradients <30 mm Hg*	32/117 (27.4)	1/126 (0.8)	26.6 (18.3, 34.8) <0.0001

*P values not alpha controlled

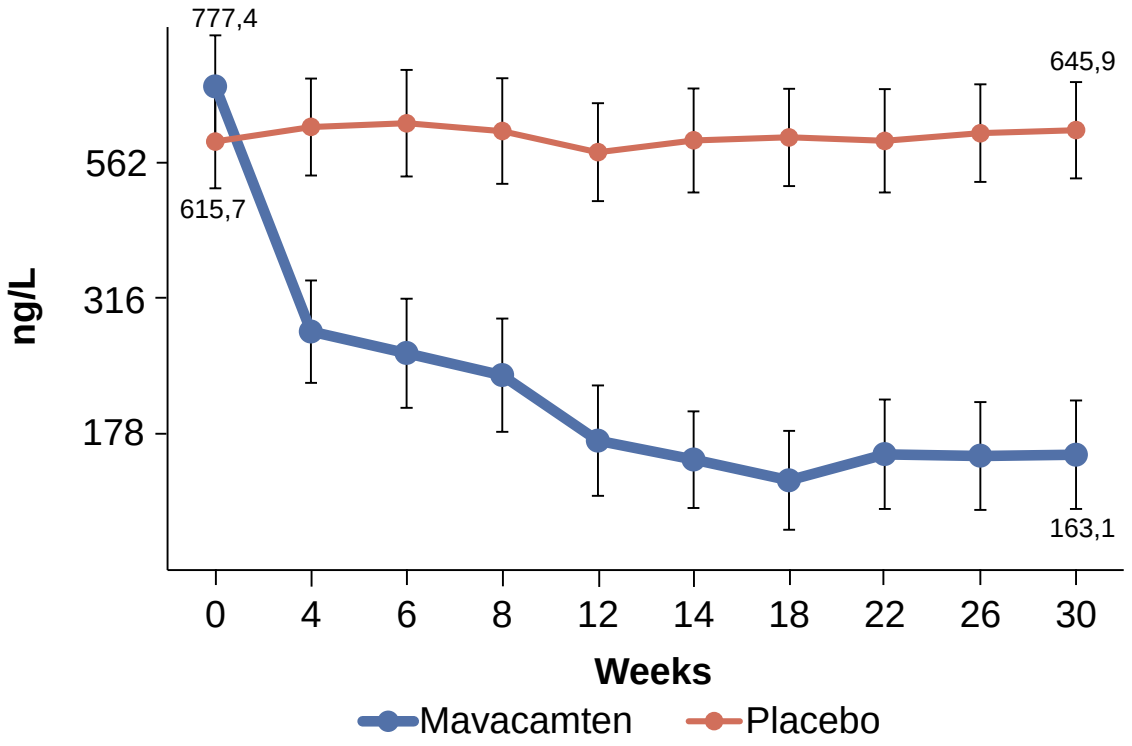
†Threshold for guideline-based invasive intervention. Only patients with baseline post-exercise LVOT peak gradient ≥50 mm Hg were assessed.

‡Threshold for guideline-based diagnosis of obstruction. Only patients with baseline post-exercise LVOT peak gradient ≥30 mm Hg were assessed.

LVOT, left ventricular outflow tract; NYHA, New York Heart Association.

Exploratory Endpoints: Cardiac Biomarkers

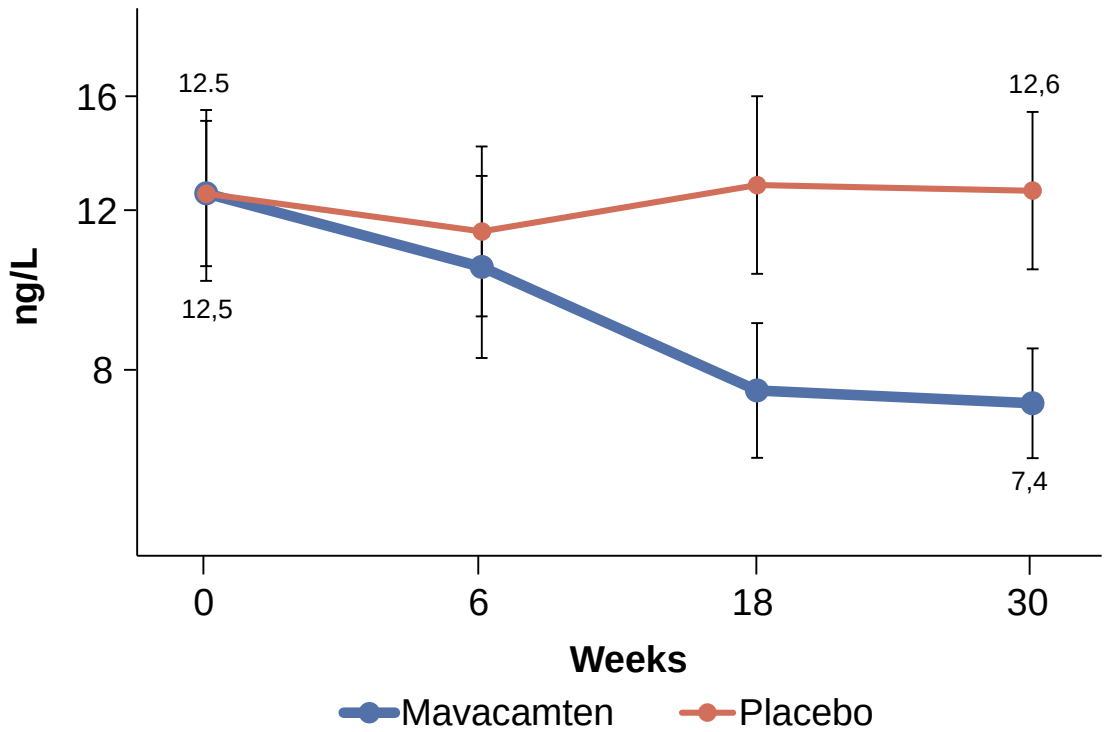
Geometric mean (95% CI) NT-proBNP



Number of patients at visit

Mavacamten	120	115	114	115	114	109	115	115	117	119
Placebo	126	118	112	119	116	117	124	121	120	123

Geometric mean (95% CI) hs-cTnI



Number of patients at visit

Mavacamten	120	86	102	115
Placebo	119	84	104	115

hs-cTnI, high-sensitivity cardiac troponin; NYHA, New York Heart Association; NT-proBNP, N-terminal pro b-type natriuretic peptide.

Summary of Safety through Week 30 (Treatment Period)

Adverse events Preferred term	Mavacamten (N = 123)	Placebo (N = 128)
Patients with ≥1 TEAEs, n (%)	108 (87.8)	101 (78.9)
Total number of SAEs	11	20
Patients with ≥1 SAE, n (%)	10 (8.1)	11 (8.6)
Atrial fibrillation	2 (1.6)	4 (3.1)
Syncope	2 (1.6)	1 (0.8)
Stress cardiomyopathy	2 (1.6)	0
Cardiac failure congestive	0	1 (0.8)
Sudden death	0	1 (0.8)

- There was a 97% completion rate through 30 weeks of treatment
- 3 patients discontinued due to AEs: 2 on mavacamten, 1 on placebo
  - No patients withdrew due to reduced LVEF or symptoms of heart failure

SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Protocol-Driven Temporary Discontinuations

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- Temporary discontinuation for LVEF <50% occurred in 5 patients in the treatment period (3 on mavacamten, 2 on placebo)
- 4 additional patients on mavacamten had LVEF <50% at week 30 (end-of-treatment)
  - LVEF recovered to baseline in 3 patients by the end of the 8-week washout
  - The fourth patient experienced a procedural complication and severe LVEF drop following an ablation for atrial fibrillation during the washout period

- Temporary discontinuation for changes in QTcF occurred in 6 patients (3 on mavacamten, 3 on placebo)

All patients resumed treatment and completed the study

LVEF, left ventricular ejection fraction; QTcF, QT interval corrected using Fridericia's formula

Conclusions

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EXPLORER-HCM trial demonstrated efficacy of mavacamten in obstructive HCM. Primary and all secondary endpoints were met with high statistical significance.

Mavacamten demonstrated clinically important effects on post-exercise LVOT gradients. Nearly 75% of patients saw a reduction below guideline-defined thresholds for invasive SRT and 56% showed complete relief of obstruction.

Mavacamten demonstrated marked improvements in NYHA class, exercise performance, and key aspects of health status, and were accompanied by reductions in serum NT-proBNP and troponin I levels.

Mavacamten was well tolerated with a safety profile comparable to placebo.

By virtue of these data, the FDA has granted breakthrough therapy designation.

I would like to thank:

Fellow co-authors:

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