ValorHCM

Myosin Inhibition in Patients with Obstructive HCM Referred for Septal Reduction Therapy

Week 56 results of the VALOR-HCM Trial

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On behalf of the VALOR-HCM investigators

C5Research
Cleveland Clinic Coordinating Center for Clinical Research

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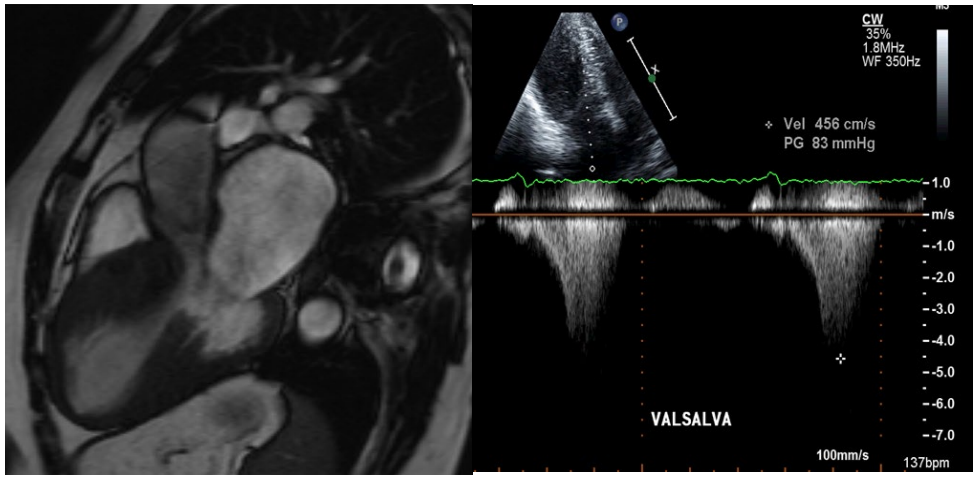
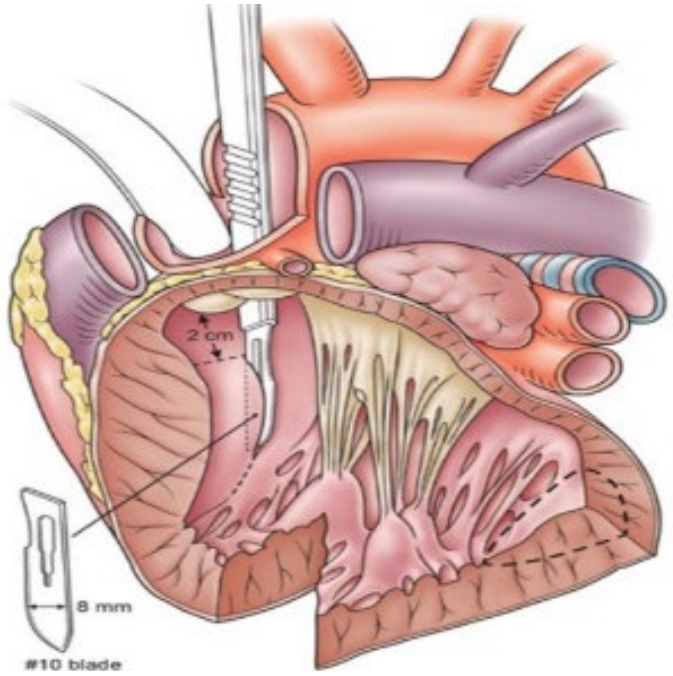
Obstructive Hypertrophic Cardiomyopathy

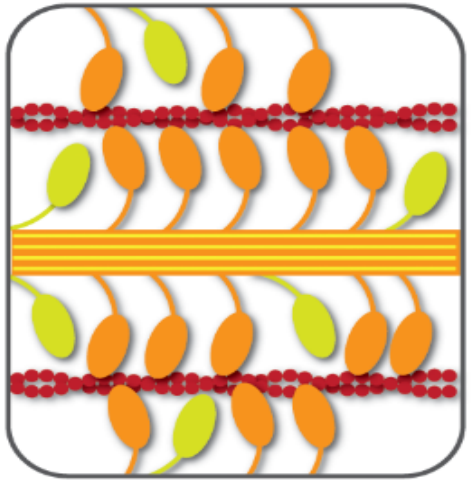
- Hypertrophic cardiomyopathy (HCM) is a myocardial disorder characterized by primary left ventricular (LV) hypertrophy
  - Two-thirds of patients have obstructive HCM
  - Current guideline-recommended medical therapies not developed specifically for HCM
- Septal reduction therapies (SRT), either surgical septal myectomy or alcohol ablation, recommended for intractable symptoms despite maximal medical therapy
  - Although SRT improves long-term survival, symptoms and quality of life, optimal results require specialized care not widely available
  - Unmet need for medical alternatives to SRT





Ommen S, Mital S et al. J Am Coll Cardiol. 2020 Dec 22;76(25):e159-e240, Maron B, Desai M et al. J Am Coll Cardiol. 2022 Feb 1;79(4):390-414, Desai M Smedira N et al. Circulation. 2013 Jul 16;128(3):209, Desai M, Smedira N et al. JAMA Network Open 2022, Olivotto et al. Lancet. 2020 Sep 12;396(10253):759-769 Desai MY et al. J Am Coll Cardiol. 2022 Jul 12;80(2):95-108

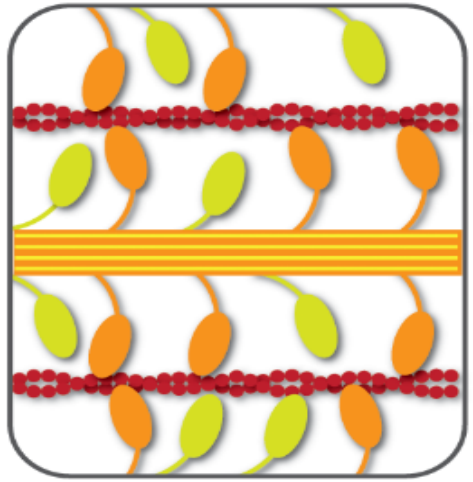
Mavacamten: First in Class Cardiac Myosin Inhibitor



HCM Sarcomere

- Hyper contractility
- Impaired relaxation
- Altered myocardial energetics

Mavacamten



HCM Sarcomere with Mavacamten

- Reduces myosin-actin cross bridges
- Attenuates hypercontractility and improve compliance and energetics

In Phase III RCTs of symptomatic obstructive HCM patients (EXPLORER-HCM and VALOR-HCM), mavacamten reduces need for SRT, improves LVOT gradient, QOL and physical functioning

Currently, clinically approved in 5 continents for use in adult symptomatic obstructive HCM patients

EXPLORER-HCM (Clinicaltrials.gov NCT03470545) and VALOR-HCM (Clinicaltrials.gov NCT04349072)

Desai MY et al. J Am Coll Cardiol. 2022 Jul 12;80(2):95-108, Desai MY et al. Circulation 2023 Mar 14;147(11):850-863, Olivotto et al. Lancet. 2020 Sep 12;396(10253):759-769, Spertus J et al. Lancet. 2021 Jun 26;397(10293):2467-2475

VALOR-HCM

Phase III placebo-controlled RCT (for 16 weeks) with placebo to mavacamten cross over starting Week 16

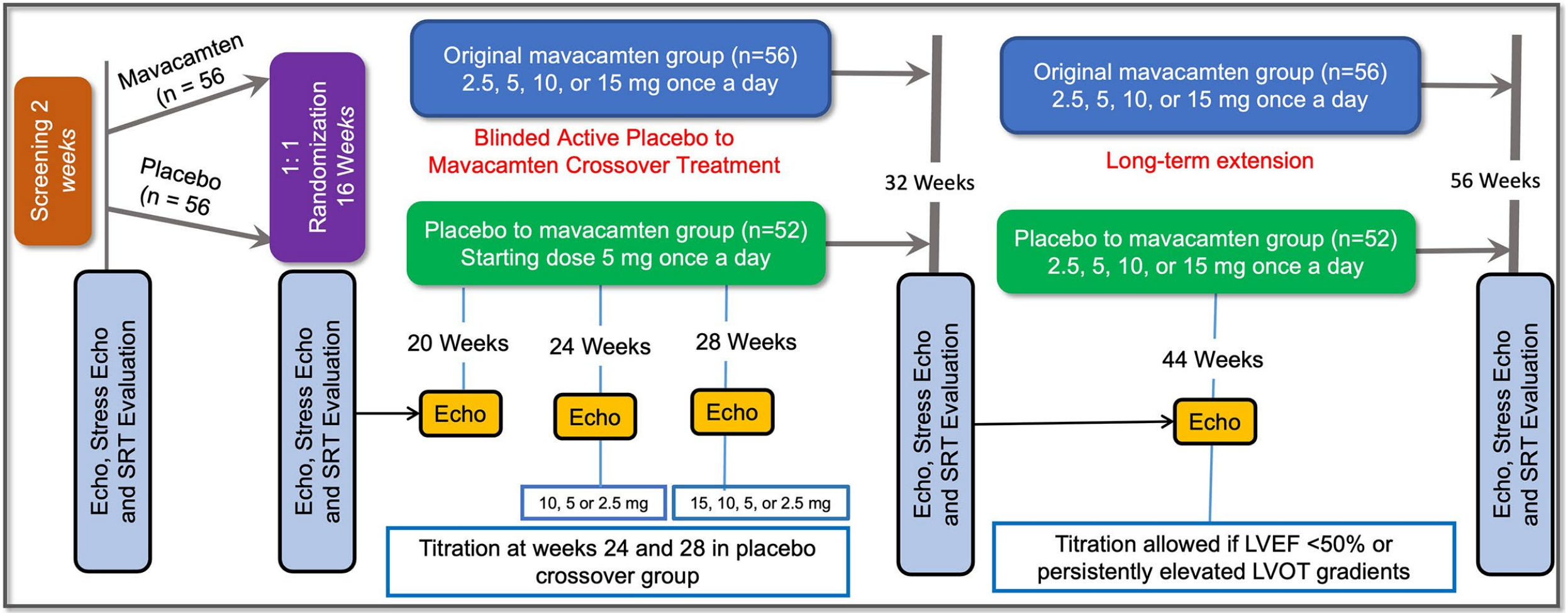
Sought to determine if addition of mavacamten to maximally-tolerated medical therapy would allow severely symptomatic oHCM patients to improve sufficiently that they no longer met guideline criteria for SRT or chose not to undergo SRT

Principal Objective of Week 56 VALOR-HCM

Report the safety and efficacy results through 56 weeks of dose-blinded treatment in patients initially randomized to mavacamten (Day 1 to Week 56) and patients initially randomized to placebo who crossed over to mavacamten for 40 weeks exposure (Week 16 to Week 56)

Desai MY et al. J Am Coll Cardiol. 2022 Jul 12;80(2):95-108
Desai MY et al. Circulation 2023 Mar 14;147(11):850-863

Study Design



Mavacamten titrated using core-lab measured ECHO LVEF and LVOT gradient at rest and Valsalva provocation

Mavacamten titrated using site measured ECHO LVEF and LVOT gradient at rest and Valsalva provocation

Key inclusion criteria

- Age ≥18 years
- Documented HCM with maximum septal wall thickness ≥15 mm or ≥13 mm with family history of HCM (determined by a core echo laboratory)
- Severe symptoms despite maximally-tolerated medical therapy
  - NYHA functional Class III/IV or Class II with exertional syncope or near syncope
  - Maximal medical HCM therapy could include disopyramide and/or combination therapy
- Dynamic LVOT gradient at rest or with provocation (Valsalva maneuver or exercise) ≥50 mmHg
- Documented LV ejection fraction ≥60%
- Must have been referred within the past 12 months for SRT and actively considering scheduling the procedure
  - Patients could elect to proceed to SRT at any time following randomization

Desai M et al. 2021 Sep;239:80-89
Desai MY et al. J Am Coll Cardiol. 2022 Jul 12;80(2):95-108.

Efficacy and Safety Endpoints

ValorHCM

- Composite principal endpoint
  - Patient decision to proceed with SRT
  - Eligibility for SRT according to the 2011 AHA/ACC guidelines
  - SRT status non-evaluable
- Change from baseline in clinical, laboratory and echocardiographic endpoints
  - Resting and provokable LVOT gradient
  - NYHA functional class
  - Kansas City Cardiomyopathy Questionnaire 23-item Clinical Summary Score (KCCQ-23 CCS)
  - N-terminal pro brain natriuretic peptide (NT-proBNP) and Cardiac troponin I
  - LV mass index, Left atrial volume index and Septal E/e'
- Safety endpoints
  - Death, LV ejection fraction <50%, hospitalization for heart failure, and atrial fibrillation or ventricular tachyarrhythmia

Gersh et al. HCM Guidelines. J Am Coll Cardiol. 2011 Dec 13;58(25):e212-60

Results: Baseline Characteristics

	Original Mavacamten Group (n=56)	Placebo to Mavacamten Crossover Group (n=52)
Age, mean(SD)	59.8 (14.2) years	60.9 (10.4) years
Female sex	27 (48.2%)	27 (51.9%)
Family history of HCM	17 (30.4%)	15 (28.9%)
NYHA Class III or higher	52 (92.9%)	50 (96.2%)
Type of SRT recommended Myectomy Alcohol septal ablation	 48 (85.7%) 8 (14.3%)	 47 (90.4%) 5 (9.6%)
Medical therapy n(%) Beta Blocker monotherapy Nondihydropyridine CCB monotherapy Combination therapy	 26 (46.43%) 7 (12.50%) 20 (35.7%)	 23 (44.2%) 10 (19.2%) 17 (32.7%)
Resting LVOT Gradient, mean(SD)	51.2 (31.4) mmHg	46.6 (29.1) mmHg
Post-exercise Gradient, mean(SD)	82.5 (34.7) mmHg	82.9 (36.7) mmHg
LV ejection fraction, %, mean(SD)	67.9 (3.7)	68.7 (3.1)
KCCQ-23 CSS -points, mean (SD)	69.5 (16.3)	67.6 (18.7)
NT-proBNP – ng/L, median (IQR)	724 (291, 1913)	706 (372, 1318)
Cardiac troponin I, ng/L , median (IQR)	17.3 (7.0, 31.6)	13.2 (6.6, 27.4)

22 (20%) were on disopyramide (mono or combination therapy)

Composite SRT endpoint at Week 56

	Patients initially treated with mavacamten (56 weeks exposure) N=56	Patients crossed over to mavacamten (40 weeks exposure) N=52
Principal SRT composite outcome – no. (%)	5 (8.9)	10 (19.2)
Patient decision to proceed with SRT	3 (5.4)	3 (5.08)
SRT-eligible based on guideline criteria	1 (1.8)	4 (7.7)
SRT status not evaluable (imputed as meeting SRT criteria or mavacamten failure)*	1 (1.8)	3 (5.8)

Between Week 32 and 56, a NET INCREASE of 3 patients in the placebo group and a NET DECREASE of 1 patient in the original mavacamten group meeting the composite SRT outcome

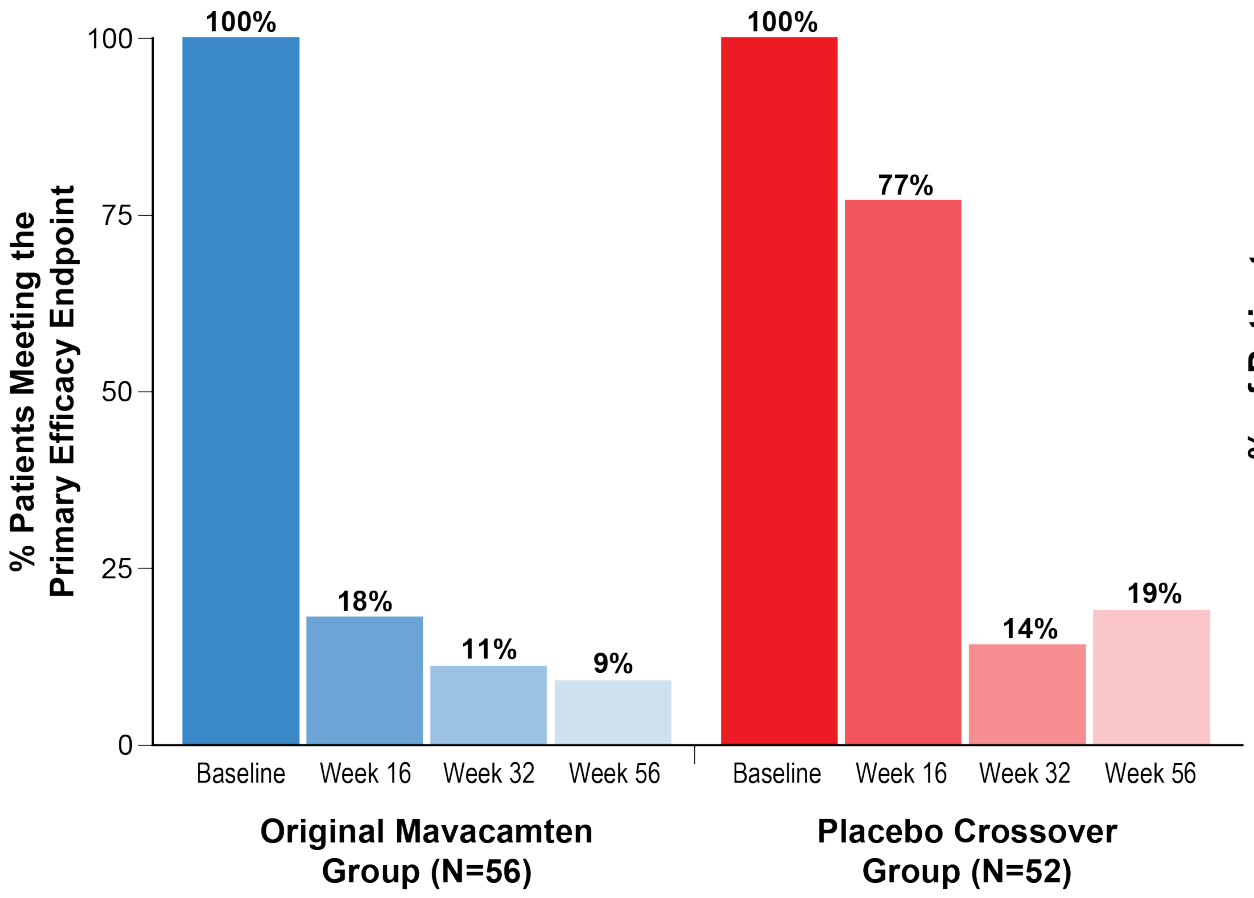
96/108 (89%) have continued in the long-term extension of this ongoing study without SRT

*2 withdrew consent, 1 withdrawn by PI due to noncompliance and 1 unable to complete week 56 exercise echo, so provoked LVOT gradient not assessed

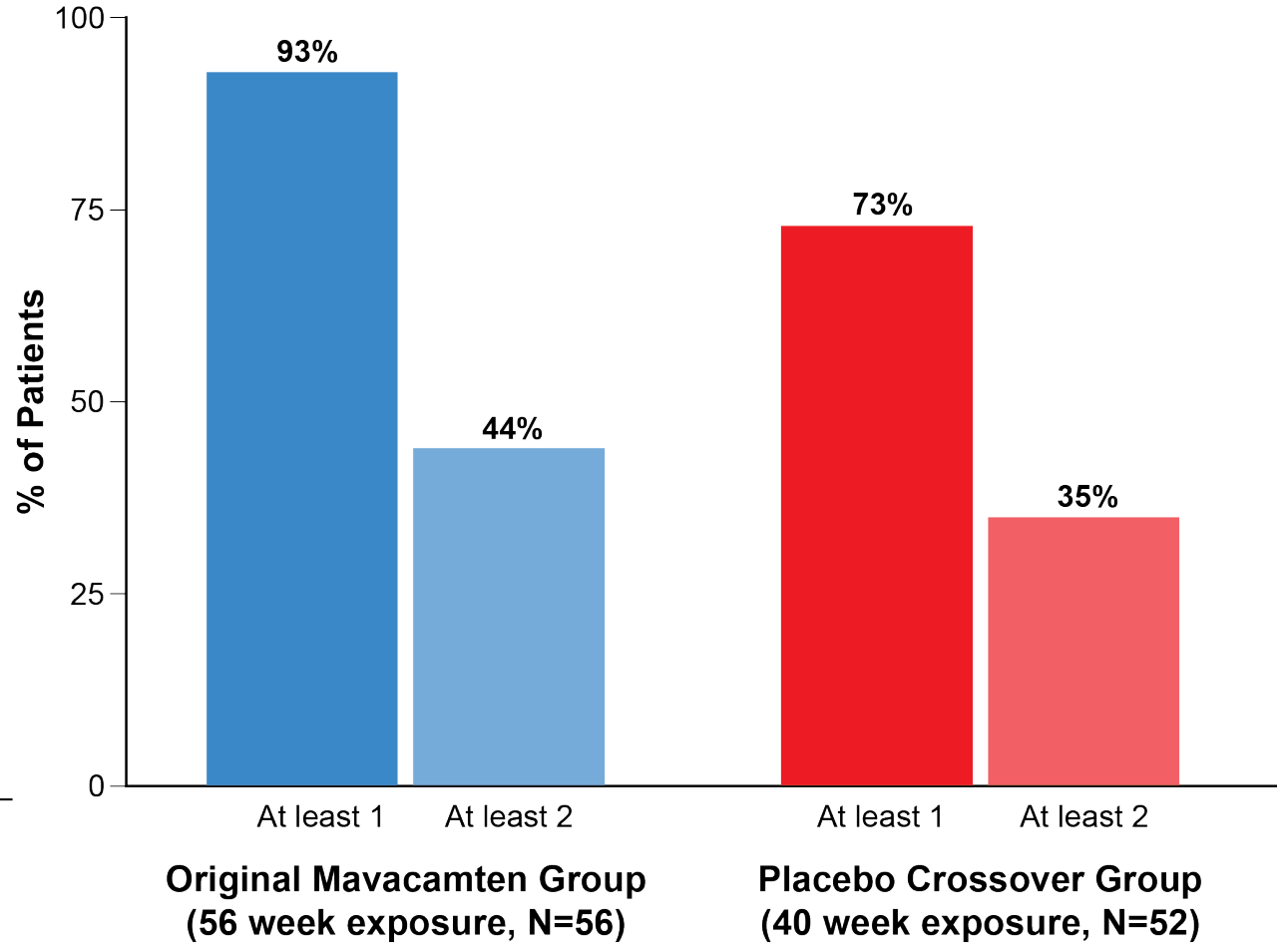
Gersh et al. HCM Guidelines. J Am Coll Cardiol. 2011 Dec 13;58(25):e212-60

Sustained Improvement in Principal Endpoint and NYHA Class

Principal Composite Endpoint



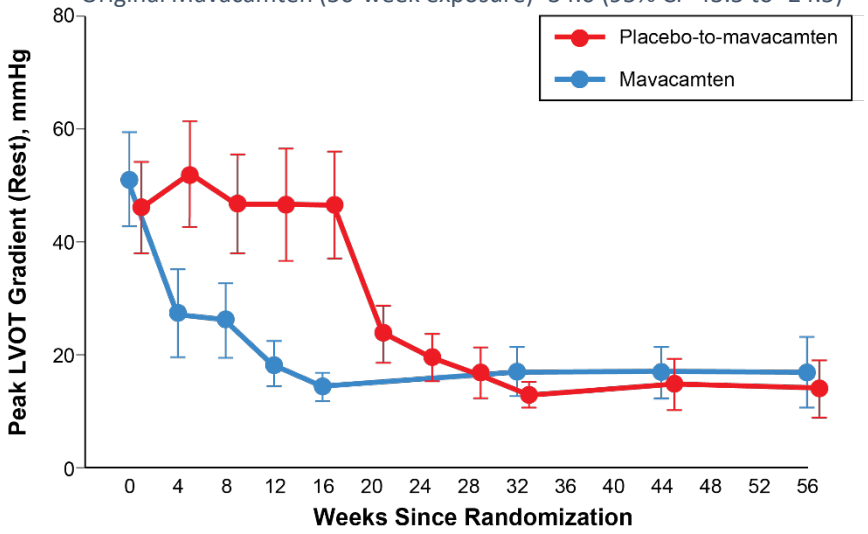
NYHA Class Improvement At Week 56



Sustained Improvement in Efficacy Endpoints

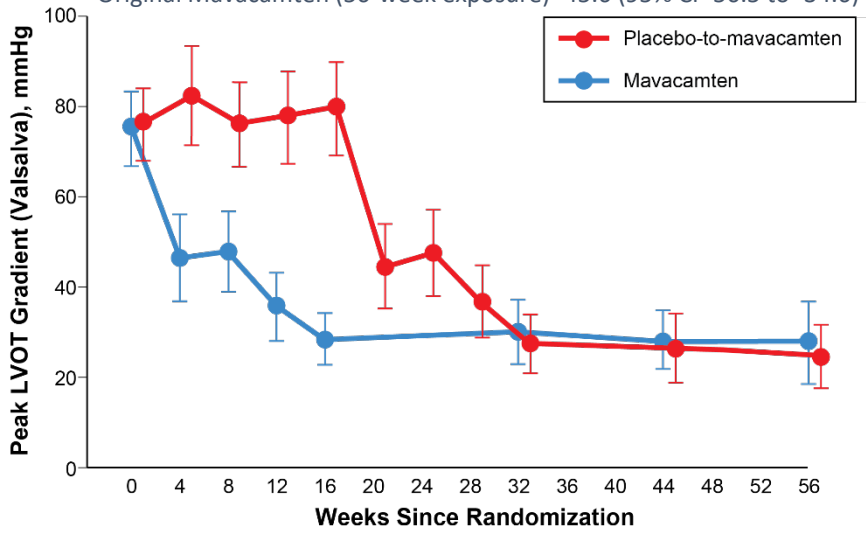
Resting LVOT Gradient

Original Placebo (40-week exposure) -33.2 (95% CI -41.9 to -24.5)
Original Mavacamten (56-week exposure) -34.0 (95% CI -43.5 to -24.5)



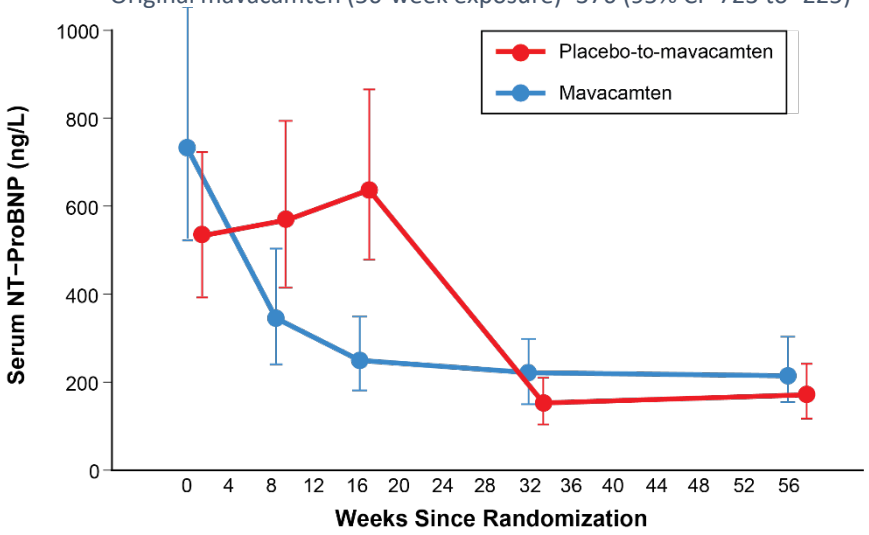
Valsalva LVOT Gradient

Original Placebo (40-week exposure) -54.6 (95% CI -66.0 to -43.3)
Original Mavacamten (56-week exposure) -45.6 (95% CI -56.5 to -34.6)



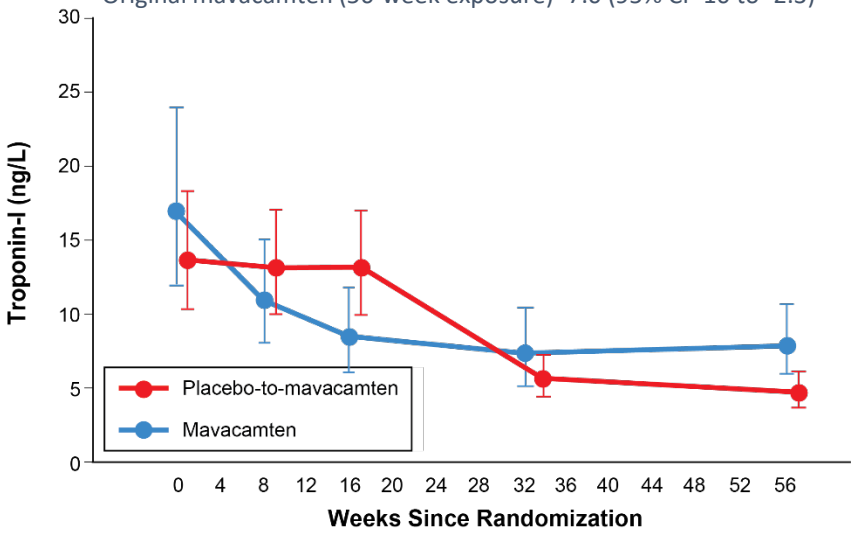
NT-ProBNP

Original placebo (40-week exposure) -423 (95% CI -624 to -252)
Original mavacamten (56-week exposure) -376 (95% CI -723 to -225)



Troponin I

Original placebo (40-week exposure) -6.2 (95% CI -11.5 to -3.3)
Original mavacamten (56-week exposure) -7.0 (95% CI -10 to -2.3)

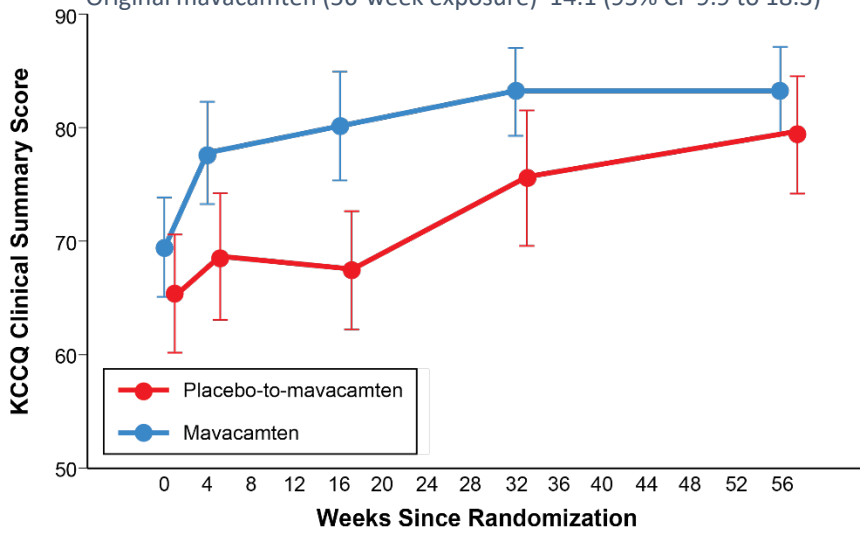


Sustained Improvement in QOL and Favorable Cardiac Remodeling

Valor HCM

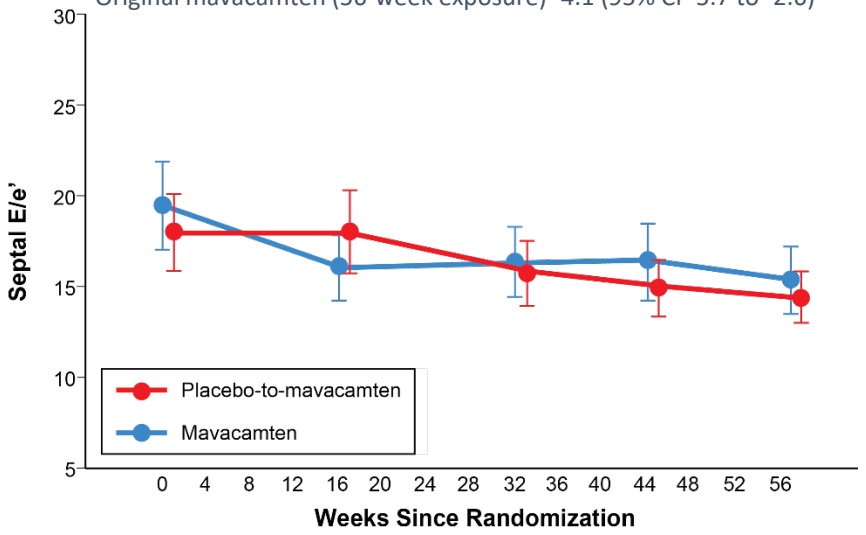
KCCQ Score

Original placebo (40-week exposure) 11.7 (95% CI 6.9 to 16.4)
Original mavacamten (56-week exposure) 14.1 (95% CI 9.9 to 18.3)



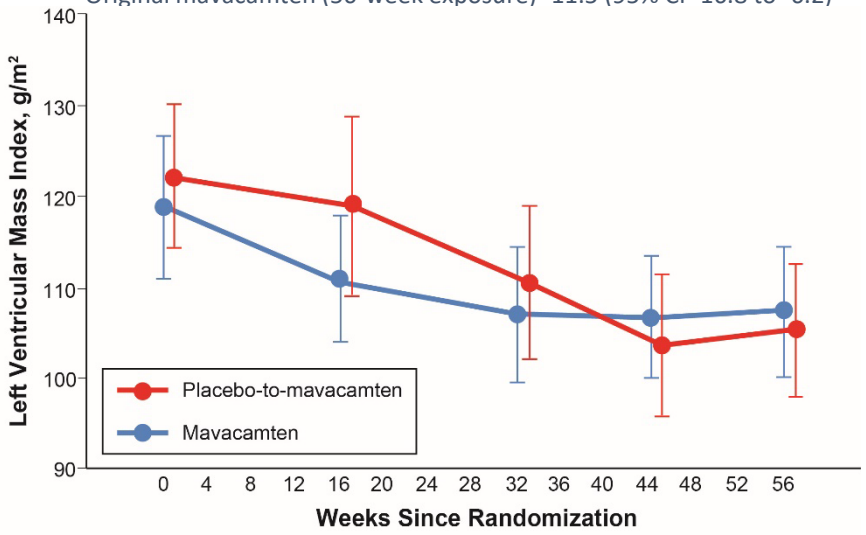
Septal E/e'

Original placebo (40-week exposure) -3.6 (95% CI -5.8 to -1.5)
Original mavacamten (56-week exposure) -4.1 (95% CI -5.7 to -2.6)



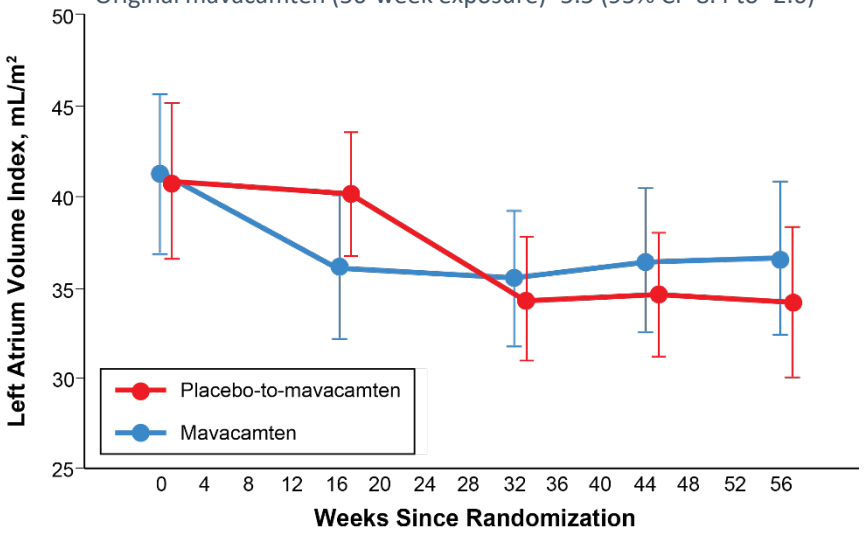
LV-Mass Index

Original placebo (40-week exposure) -14.5 (95% CI -20.8 to -8.3)
Original mavacamten (56-week exposure) -11.5 (95% CI -16.8 to -6.2)



LA Volume Index

Original placebo (40-week exposure) -5.3 (95% CI -7.6 to -2.9)
Original mavacamten (56-week exposure) -5.5 (95% CI -8.4 to -2.6)



Key efficacy findings, separated by sex

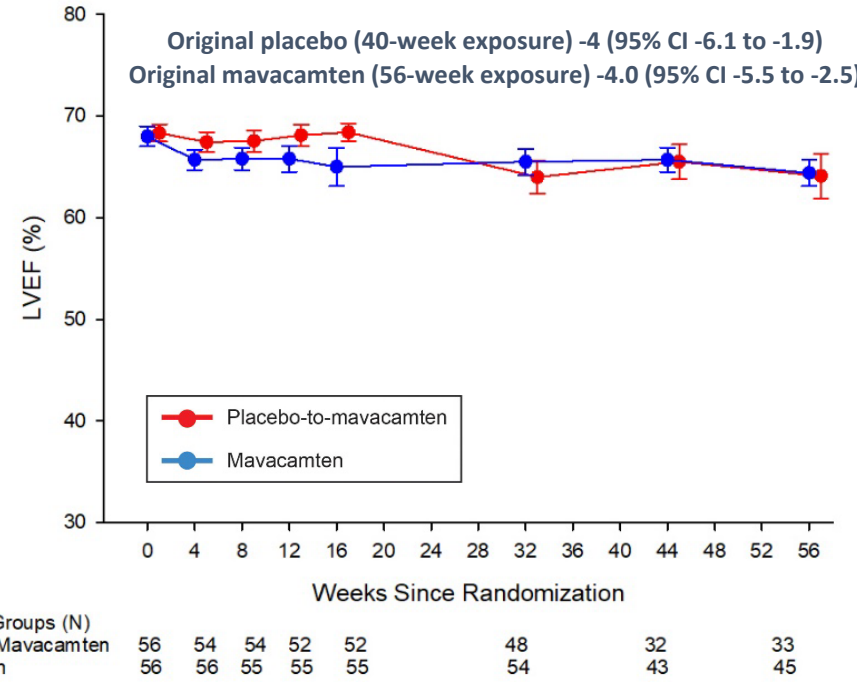
	Mavacamten exposure			
	Original Placebo (40 weeks)		Original Mavacamten (56 weeks)	
	Men (N=25)	Women (N=27)	Men (N=29)	Women (N=27)
Principal endpoint	4 (16.0)	6 (22.2)	2 (6.9)	3 (11.1)
At least 1 class of NYHA improvement	20 (80.0)	17 (65.4)	25 (89.3)	26 (96.3)
At least 2 class of NYHA improvement	9 (36.0)	9 (34.6)	14 (50.0)	10 (37.0)
Change in KCCQ-23-CSS, mean (95% CI)	10.2 (4.4 to 16.1)	13.0 (5.1 to 20.9)	12.1 (5.0 to 19.2)	16.2 (11.3 to 21.1)
Change in resting LVOT gradient (mmHg)	-35.2 (-47.4 to -23.0)	-31.2 (-44.3 to -18.0)	-29.8 (-40.9 to -18.8)	-38.7 (-55.2 to -22.2)
Change in Valsalva LVOT gradient (mmHg)	-58.1 (-74.6 to -41.5)	-51.1 (-67.8 to -34.5)	-34.8 (-50.5 to -19.1)	-57.7 (-72.4 to -42.9)
Change in NT-proBNP – ng/L, median (95% CI)	-442 (-815 to -175)	-423 (-659 to -154)	-196 (-413 to -109)	-723 (-1427 to -273)
Change in cardiac troponin I – ng/L, median (95% CI)	-10 (-17.7 to -3.1)	-4.2 (-10.0 to -2.8)	-6.4 (-14.2 to 0.3)	-7.4 (-15.9 to -2.8)
Change in LV filling pressures (E/'e' ratio)	-5.7 (-9.9 to -1.6)	-1.7 (-3.3 to -0.06)	-3.4 (-5.7 to -1.1)	-5.0 (-7.3 to -2.7)
Change in left atrial volume index – ml/m^2	-3.4 (-6.2 to -0.6)	-7.0 (-10.7 to -3.2)	-4.8 (-9.7 to 0.09)	-6.2 (-9.6 to -2.8)

Similar efficacy across both sexes

Selected safety endpoints at Week 56

Characteristic	Placebo-to-mavacamten (40 weeks exposure) N=52	Original mavacamten (56 weeks exposure) N=56	Total mavacamten N=108
Safety endpoints			
Permanent study drug discontinuation a) LVEF <30% b) Two consecutive LVEF measurements of < 50% despite dose reduction to 2.5 mg	 2 (3.8) 1 (1.9)	 0 0	3 (2.8)
One Temporary Interruption for LVEF (>30% to <50%)	2 (3.8)	7 (12.5)	9 (8.3)
Total with ANY LV EF (<50%)	5 (9.6)	7 (12.5)	12 (11.1)
Cardiac death	1 (1.9)*	0	
Heart failure hospitalization	1 (1.9)¥	0	
Selected serious treatment-emergent adverse events			
At least one serious treatment-emergent adverse event	6 (11.5)	4 (7.1)	10 (9.3)
Atrial fibrillation	0	3 (5.4)	3 (2.8)
Congestive heart failure	1 (1.9)	0	1 (0.9)
Ventricular arrhythmia	1 (1.9)	0	1 (0.9)
Drug administration site reaction	2 (3.8)	0	2 (1.9)
COVID-19	0	1 (1.8)	1 (0.9)

LV Ejection fraction



9/12 (75%) patients with LVEF < 50% were asymptomatic and able to resume mavacamten at a lower dose, after temporary interruption

* This patient had a site-reported LV ejection fraction of 30% and mavacamten was discontinued.

¥ This patient was admitted for congestive heart failure with concomitant atrial fibrillation and had a core-lab reported LV ejection fraction < 30%. Mavacamten was permanently discontinued.

Strengths and Limitations

- Composite efficacy endpoint driven by reduction in guideline eligibility for SRT
  - At Week 56, 9 out of 10 patients chose to remain on medical therapy vs. going for SRT
  - Efficacy findings similar in both sexes
  - Echo evidence of sustained disease modification
- Drug efficacy and safety monitored by echo-based LVEF and LVOT gradients, not drug concentrations
  - Successful utilization of site-based echo measurements (after Week 44)
- Need to ascertain long-term safety
  - Effect of mavacamten on long-term arrhythmias and sudden death not assessed
- Current study included predominantly white patients treated at high-volume HCM centers with established SRT programs

Conclusions

Valor HCM

- In obstructive HCM patients with intractable symptoms, referred for SRT, administration of mavacamten, titrated using echocardiography:
  - Significantly reduced eligibility for invasive SRT at 56 weeks
  - Showed treatment benefits for all efficacy endpoints
    - Resting and provoked LVOT gradient, NYHA Class, KCCQ-CSS
    - Reduction in biomarkers (NT ProBNP and troponin I) and significant improvement in echo indices (LV mass index, LA volume index, E/e')
- Given the potential for LV systolic dysfunction, safety and efficacy require continued monitoring

Provides an alternative for medically refractory patients with obstructive HCM, which may obviate the need for SRT in many patients

Longer-term studies evaluating the effect of mavacamten on outcomes are needed

Simultaneous publication in JAMA Cardiology

Research

JAMA Cardiology | Original Investigation

Mavacamten in Patients With Hypertrophic Cardiomyopathy Referred for Septal Reduction

Week 56 Results from the VALOR-HCM Randomized Clinical Trial

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IMPORTANCE There is an unmet need for novel medical therapies before recommending invasive therapies for patients with severely symptomatic obstructive hypertrophic

Editor's Note

Supplemental content

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- **VALOR HCM Trial Leadership**
  - **Cleveland Clinic Coordinating Center for Clinical Research (C5Research):** Steven E. Nissen MD (Executive Committee Chairman), Milind Y. Desai MD (Study Principal Investigator), Kathy Wolski MPH (Lead Statistician), Christina Sewell BSN (Lead Project Manager), Ellen McErlean MSN (Manager, Project and Site Management), , Tammy Gamble (Project Specialist)
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- **VALOR HCM Site Investigators**
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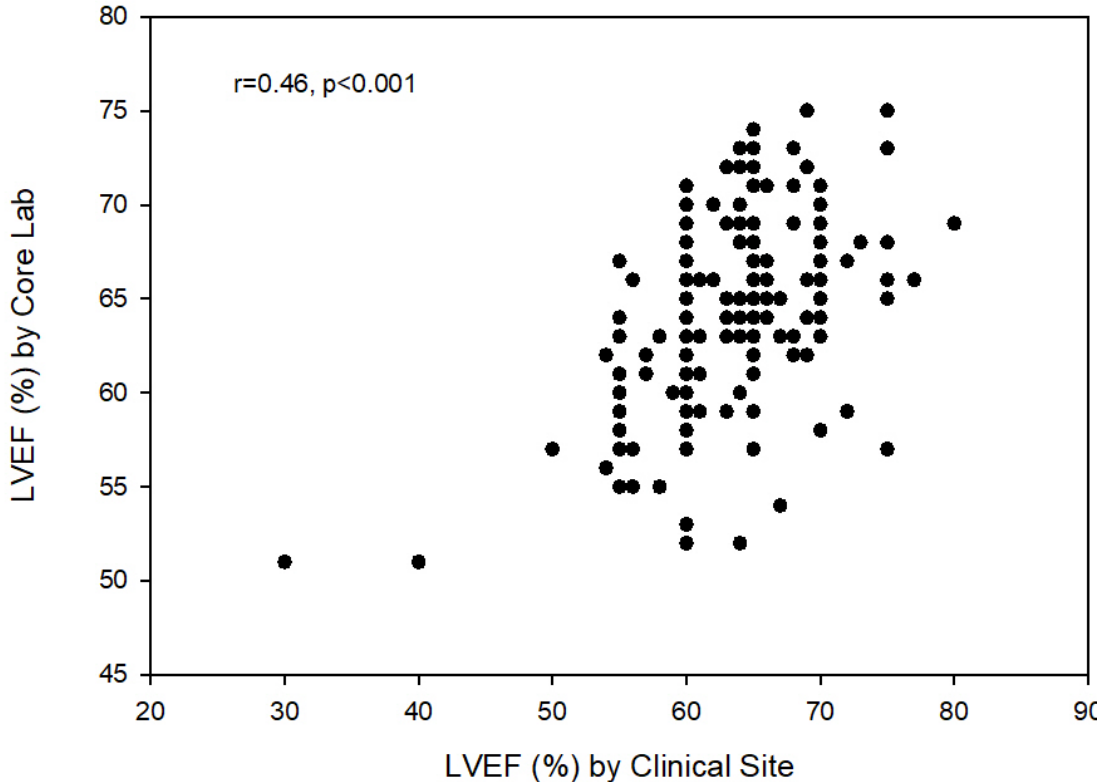
Back-up slides

Correlation between site-read and core-lab read echocardiograms

	Core laboratory read echo	Site-read echo	Correlation, r	p-value
LV ejection fraction	64.8 ± 4.9	64.0 ± 6.1	0.46	<0.001
Valsalva LVOT gradient, mmHg	26.1 ± 26.6	24.3 ± 29.7	0.86	<0.001
Resting LVOT gradient, mmHg	15.2 ± 16.9	12.5 ± 17.7	0.90	<0.001



Data on 8 patients undergoing SRT

ValorHCM

Subject	Original treatment arm	Age	Sex	Mavacamten dose before SRT	LV ejection fraction at end of treatment prior to SRT	SRT type	End of treatment	Valsalva LVOT gradient (mm Hg) at end of treatment (pre-SRT)	Valsalva LVOT gradient (mm Hg) 24 weeks post-SRT	NYHA Class at 24 weeks post-SRT	Complications
1	Placebo*	55	male	0	70%	Myectomy	Week 8	75	13	I	None
2	Placebo*	45	male	0	68%	ASA	Week 8	10	8	I	None
3	Placebo to mavacamten crossover	57	male	5 mg	70%	ASA	Week 20	43	49	III	Needed a 2nd ASA
4	Placebo to mavacamten crossover	36	Female	15 mg	72%	Myectomy	Week 32	53	24	I	Wound cellulitis
5	Placebo to mavacamten crossover	62	Female	10 mg	67%	Myectomy	Week 56	102	8	I	Post-operative hypotension, thrombocytopenia, pneumothorax, hallucinations
6	Mavacamten	22	male	5 mg	68%	Myectomy	Week 28	73	18	I	None
7	Mavacamten	66	female	15 mg	71%	Myectomy	Week 16	46	12	II	Postoperative respiratory failure(COVID-19) and atrial fibrillation
8	Mavacamten	41	Female	5 mg	60%	Myectomy	Week 4	51	71	II	None

Final drug dosing

Final Dosing	Original mavacamten group N=56	Placebo crossover group N=52
Final dosing at Week 56		
2.5 mg	11 (19.6%)	6 (11.5%)
5 mg	17 (30.4%)	14 (26.9%)
10 mg	16 (28.6%)	23 (44.2%)
15 mg	12 (21.4%)	9 (17.3%)

Background therapy reduction table

	Placebo-to-mavacamten N=52	Original mavacamten N=56	Total N=108
Beta blocker (n=83 at baseline)			
Increased dose	3 (5.8)	2 (3.6)	5 (4.6)
Decreased dose	3 (5.8)	10 (17.9)	13 (12.0)
Maintained dose	32 (61.5)	33 (58.9)	65 (60.2)
Calcium channel blocker (n=38 at baseline)			
Increased dose	1 (1.9)	0	1 (0.9)
Decreased dose	2 (3.8)	3 (5.4)	5 (4.6)
Maintained dose	19 (36.5)	13 (23.2)	32 (29.6)
Disopyramide (n=19 at baseline)			
Increased dose	1 (1.9)	0	1 (0.9)
Decreased dose	0	2 (3.6)	2 (1.9)
Maintained dose	7 (13.5)	9 (16.1)	16 (14.8)

20 background HCM therapy dose reductions