Mavacamten Improves Left Ventricular Relaxation and Compliance in Obstructive Hypertrophic Cardiomyopathy Through Direct Myosin Modulation

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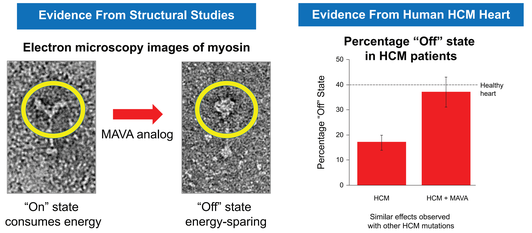
Introduction

- Obstructive hypertrophic cardiomyopathy (oHCM) consists of left ventricular (LV) hypertrophy, LV outflow tract obstruction (LVOTO), and impaired relaxation
- This constellation of abnormalities often results in dyspnea and reduced exercise capacity
- Pathogenesis of disease is associated with sarcomeric gene mutations resulting in hypercontractility, reduced compliance, and inefficient energy utilization
- In the phase 2 open-label PIONEER-HCM study (NCT02842242), 12 weeks of treatment with mavacamten in subjects with symptomatic oHCM resulted in improvements in post-exercise LVOT gradient, exercise capacity, and symptoms

Mavacamten

- Mavacamten is a first-in-class small molecule and selective allosteric modulator of cardiac myosin that inhibits cardiac myosin ATPase, thereby reversibly attenuating cardiac contractility and obstructive physiology
- Mavacamten re-populates the super-relaxed (SRX) "Off" state of myosin
- Electron microscopy images of myosin bound to a mavacamten analog are shown in the left panel of **Figure 1**
  - Both open "On" and "Off" states are shown
- Mavacamten restores the percentage of SRX in human cardiac fibers from an HCM patient with the R663H mutation, as depicted in the right panel of **Figure 1**
  - Similar effects are observed for other HCM mutations

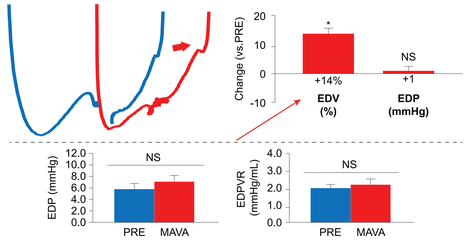
Figure 1. Mavacamten Repopulates the Super-relaxed "Off" State of Myosin



HCM, hypertrophic cardiomyopathy; MAVA, mavacamten.
Adapted with permission from Anderson RL, et al. *Proc Natl Acad Sci U S A.* 2018;115:E8143-E8152.

- In preclinical models (healthy dogs [**Figure 2**] and a genetic mini-pig model of non-obstructive HCM [nHCM] [del Rio CL, et al, AHA 2018, Session DD.AOS.01-196]), novel myosin modulators mavacamten and MYK-581 limit residual cross-bridges during diastole and improve LV compliance and relaxation

Figure 2. Mavacamten Improves LV Compliance in Healthy Dogs (N=8)

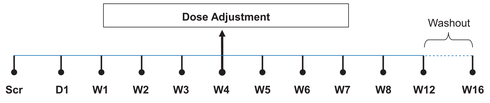


*P<0.05 vs. PRE.
Acute mavacamten administration in healthy dogs causes a rightward shift in the pressure-volume loop consistent with improved compliance/distensibility. There was a statistically significant increase of +14% EDV with MAVA vs. predose conditions and no significant change in EDP.
EDP, end diastolic pressure; EDPVR, end diastolic pressure volume relationship; EDV, end diastolic volume; MAVA, mavacamten; NS, not significant; PRE, predose.
Del Rio CL, et al. Presented at the Scientific Sessions of the American Heart Association; November 11-15, 2017, Anaheim, CA.

Study Design and Methods

- The prospective, multi-site, phase 2 PIONEER-HCM study was a dose-ranging study of mavacamten in symptomatic oHCM
- The current study evaluated the effects of mavacamten on diastolic indices
- Analyses of Echo-Doppler indices of LV filling and relaxation were performed at study sites and echocardiograms were read at the core laboratory (Brigham & Women's Hospital) (**Figure 3**)
- Participants received mavacamten once daily for 12 weeks, either 10-20 mg (n=11, cohort A; 10 completed) or 2-5 mg (n=10, cohort B) (**Figure 3** and **Table 1**)
- In cohort A, background HCM therapy was discontinued prior to treatment with mavacamten
- In cohort B, 9 of 10 subjects continued background beta blocker therapy
- *P* values were derived from Wilcoxon signed rank tests, evaluating the distribution of within-subject 12-week changes from baseline around a null of zero

Figure 3. PIONEER-HCM: Study Design



	Scr	D1	W1	W2	W3	W4	W5	W6	W7	W8	W12	W16
Stress echo	x					x					x	x
CPET		x									x	
Rest echo	x	x	x	x	x	x	x	x	x	x	x	x

	Starting Dose	Dose Adjustment Algorithm	Doses in Study
Cohort A (n=11)	10 mg ≤ 60 kg 15 mg > 60 kg	Based on % decrease from baseline in LVEF	10 mg, 15 mg, 20 mg
Cohort B (n=10)	2 mg	Based on % decrease from baseline in resting LVOT peak gradient	2 mg, 5 mg

CPET, cardiopulmonary exercise testing; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline

Characteristic	Cohort A (n=11)	Cohort B (n=10)
Age (years)		
Mean (min-max)	56 (22–70)	58 (26–67)
Sex, n (%)		
Male	7 (64)	5 (50)
Female	4 (36)	5 (50)
BMI (kg/m^2), mean ± SD	29.7 ± 4.1	32.3 ± 5.4
Heart rate (beats/min), mean ± SD	76 ± 10	62 ± 8
Blood pressure (mmHg), mean ± SD		
Systolic	124 ± 10	125 ± 17
Diastolic	70 ± 11	74 ± 11
NYHA functional class (%)		
Class II	64	50
Class III	36	50
Background HCM therapy, n (%)*		
Beta blocker	9	9
Calcium channel blocker	1	0
Disopyramide	5	0
Echocardiography parameters		
Interventricular septum thickness, mean ± SD	1.7 ± 0.2	1.5 ± 0.2
Resting LVEF (%), mean ± SD	70 ± 7	75 ± 5
Peak LVOT gradient (mmHg), mean ± SD		
Resting	60 ± 28	86 ± 63
Valsalva	97 ± 32	100 ± 65
Post-exercise	103 ± 50**	86 ± 43**
Systolic anterior motion of mitral valve, n (%)	11 (100)	9 (90)
LA volume index (mL/m^2)	30 ± 10	41 ± 20
Mitral regurgitation present, n (%)	11 (100)	10 (100)
Peak VO_2 (mL/kg/min), mean ± SD	20.7 ± 7.4	19.4 ± 4.6
NT-pro BNP (pg/mL), mean ± SD	930 ± 647	1834 ± 3209**
Patient-reported symptoms, mean ± SD		
NRS dyspnea score	4.9 ± 1.6	4.0 ± 2.6
KCCQ OSS	64.9 ± 16.2	60.9 ± 26.3

There were 11 patients in cohort A and 10 patients in cohort B. BMI, body mass index; HCM, hypertrophic cardiomyopathy; KCCQ OSS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score; LA, left atrial; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NT-pro BNP, N-terminal pro-B-type-natriuretic peptide; NRS, numerical rating scale; NYHA, New York Heart Association; VO_2, oxygen consumption.
*Patients in cohort A discontinued background HCM therapy at least 14 days prior to starting mavacamten.
**Values measurable for N=9 patients.

Results

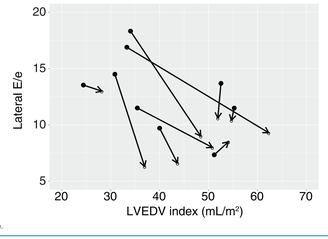
- Compared to baseline, mavacamten reduced hypercontractility in a dose-dependent fashion, with relief of LVOTO in all subjects achieving plasma mavacamten concentration >350 ng/ml (data previously reported)
- As shown in **Table 2** and **Figure 4**:
  - There was an increase in mitral annular velocity during early diastole (e'_{lat}) and concomitant reduction in E/e'_{lat} (P<0.05, cohort A)
  - LV end-diastolic volume (LVEDV) increased (P<0.05, cohort A), and there was no change in left atrial (LA) volume from baseline to week 12
  - Relationship between lateral E/e' vs. LVEDV index for patients in cohort A
  - Dyspnea score, as rated on a numerical rating scale where 0=no shortness of breath and 10=shortness of breath as bad as can be, improved in both cohorts A and B (P<0.05)
  - Levels of N-terminal pro b-type natriuretic peptide (NT-proBNP) were reduced

Table 2. Results of Echocardiographic Parameters, NRS Dyspnea Score, and NT-proBNP

	Cohort A (MAVA dose 10-20 mg/d) Background HCM Therapy Discontinued for Study					Cohort B (MAVA dose 2-5 mg/d) 9 of 10 on Background Beta Blocker Therapy				
	Baseline	WK12	Delta	n	*P*-value	Baseline	WK12	Delta	n	*P*-value
LVEF (%)	70±7	55±10	-15±12	10	0.004	75±5	69±6	-5.5±6	10	0.002
LVOT gradient, resting (mmHg)	60±28	14±25	-48±34	10	0.006	86±63	38±32	-49±48	10	0.004
Lateral e' (cm/s)	6.9±1.9	8.8±1.6	1.8±1.9	10	0.014	5.9±0.9	6.1±2.1	0.3±2.2	10	0.719
Septal e' (cm/s)	5.4±1.6	6.3±1.5	0.4±1.3	8	0.297	4.7±1.4	4.0±0.7	-0.7±1.4	10	0.242
E/e'_{lat} ratio (%)	12.9±3.3	9.1±2.2	-4.0±3.7	9	0.024	13.9±3.3	12.6±4.1	-1.3±4.6	10	0.432
E/e'_{sep} ratio (%)	17±6.9	12±2.6	-2.3±3.9	8	0.055	19±6.6	18±4.4	-0.4±5.4	10	0.999
LVEDV (mL)	82±24	97±24	16±21	11	0.027	95±15	101±25	6±18	10	0.492
LA vol (index) (mL/m^2)	30±10	31±8	1±7	10	0.476	41±20	35±12	-6±12	10	0.322
NRS dyspnea score	4.9±1.6	1.7±1.8	-3.1±1.4	10	0.002	4.0±2.6	1.0±0.7	-3.0±2.8	10	0.008
NT-proBNP (pg/mL), median (Q1, Q3)	789 (336, 1551)	202 (41, 679)	-425 (-748, -68)	10	0.084	461 (99, 835)	346 (50, 1199)	-81 (-637, -16)	9	0.074

HCM, hypertrophic cardiomyopathy; LA vol, left atrial volume; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MAVA, mavacamten; NRS, numerical rating scale; NT-proBNP, N-terminal pro b-type natriuretic peptide; WK, week.

Figure 4. E/e' versus Left Ventricular End-Diastolic Volume Index at Baseline (●) and After 12 Weeks of Mavacamten Treatment (→) in PIONEER Cohort A Patients (n=9)



LVEDV, left ventricular end-diastolic volume.

Conclusions

- Administration of mavacamten is associated with improvement in measures of myocardial relaxation and compliance in parallel with reduction in LVOT gradient
- These findings are consistent with preclinical findings reported in healthy dogs and a genetic mini-pig model of nHCM
- Based on these findings, additional evaluation of mavacamten in patients with oHCM or nHCM is warranted; further analyses are planned in the phase 2 MAVERICK-HCM and phase 3 EXPLORER-HCM studies

Author Disclosure Information

S.B. Heitner, S. Lester, A. Wang: Consultant/Advisory Board; Modest; MyoKardia. **D. Jacoby:** Consultant/Advisory Board; Modest; MyoKardia, Abbott, Alnylam, Deerfield. Consultant/Advisory Board; Significant; Admera. **A.T. Owens, A. Shah, S. Hegde:** None. **L. Fang, A. Sehnert, M. Semigran:** Employment; Significant; MyoKardia.

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