Precision Pharmacological Treatment For Obstructive Hypertrophic Cardiomyopathy With Mavacamten: One-year Results From PIONEER-OLE

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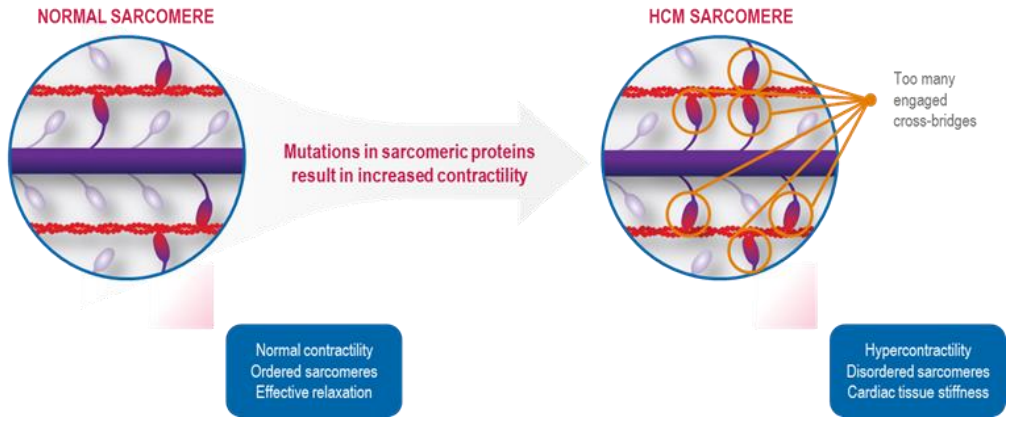
Introduction

- Hypertrophic cardiomyopathy (HCM) is a sarcomeric disease resulting from excess myosin-actin cross-bridging and is manifested as hypercontractility[1]
- Mavacamten is a first-in-class, selective allosteric inhibitor of cardiac myosin – reduces the excessive contractility at the level of the actin-myosin cross link
- In the phase 2, open-label PIONEER-HCM study, safety and effectiveness of mavacamten were demonstrated in patients with symptomatic obstructive HCM after 12 weeks of treatment[2]
- This open-label extension study (**PIONEER-OLE**) examines the long-term safety and effectiveness of mavacamten in this patient population



1. Ammirati E. *Eur J Heart Fail*. 2016;18(9):1106-1118.
2. Heitner SB, et al. *Ann Intern Med*. 2019;170(11):741-748.

PIONEER-OLE Study Design

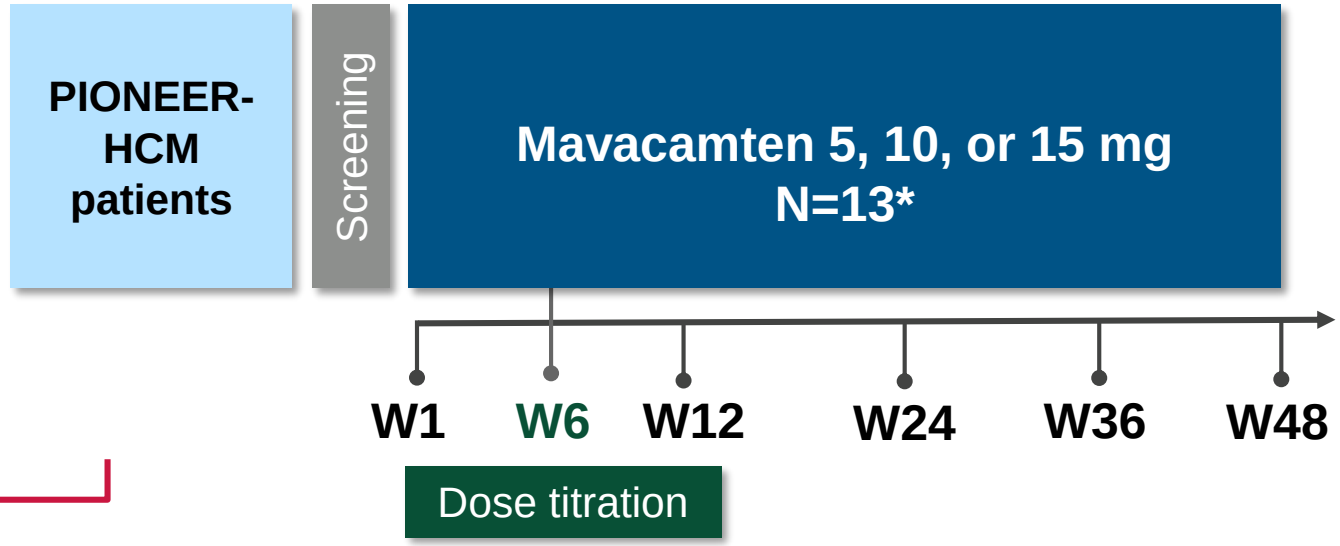
COMPLETED PIONEER-HCM

Cohort A
- β-blockers discontinued
- **Mavacamten 10 or 15 mg**
- Completed treatment (n=10)

Cohort B
- β-blockers allowed
- **Mavacamten 2 or 5 mg**
- Completed treatment (n=10)

6-18 months elapsed

ONGOING PIONEER-OLE



Study endpoints
- Safety, tolerability, and select measures of efficacy using individualized dosing
- Key measurements include LVOT gradient, LVEF, NT-proBNP

*One patient discontinued before Week 36.

LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro b-type natriuretic peptide; W, week.

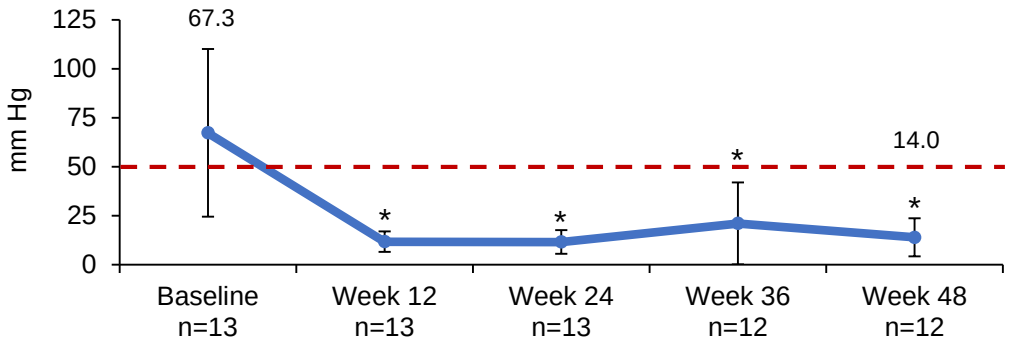
Results: Baseline Characteristics

Characteristic	PIONEER-HCM n=13	PIONEER-OLE N=13
Age, year, mean (SD)	56.5 (13.2)	57.8 (13.3)
Male, n (%)	9 (69.2)	
NYHA functional class, n (%)		
Class II	9 (69.2)	12 (92.3)
Class III	4 (30.8)	1 (7.7)
Background HCM therapy while on study drug, n		
Metoprolol	7 (53.8)	11 (84.6)
Bisoprolol	0	1 (7.7)
Echocardiography parameters		
Resting LVEF, %, mean (SD)	73.0 (5.6)	72.0 (4.9)
LVOT gradient, mm Hg, mean (SD)		
Resting	69.7 (53.9)	67.3 (42.8)
Valsalva	93.7 (55.6)	89.9 (30.7)
Post-exercise	94.5 (45.0)	127.5 (33.4)
NT-pro BNP, pg/mL, mean (SD)	1601 (2702)	1836 (2886)

HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

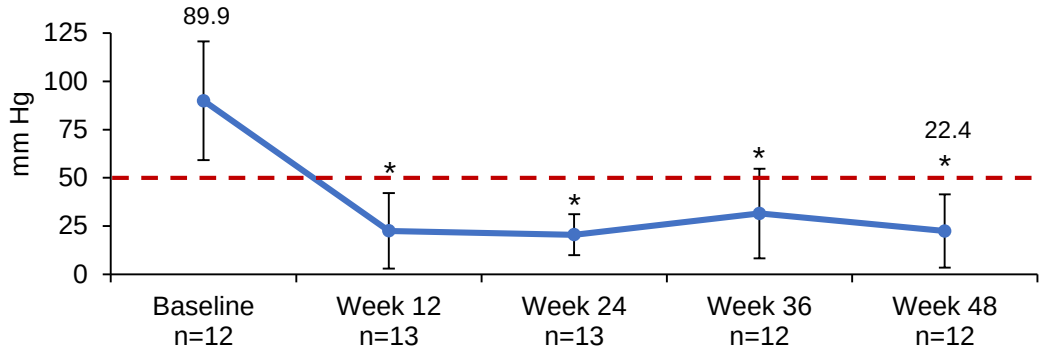
Results: LVOT Gradient and Ejection Fraction

Mean (SD) LVOT gradient (resting)



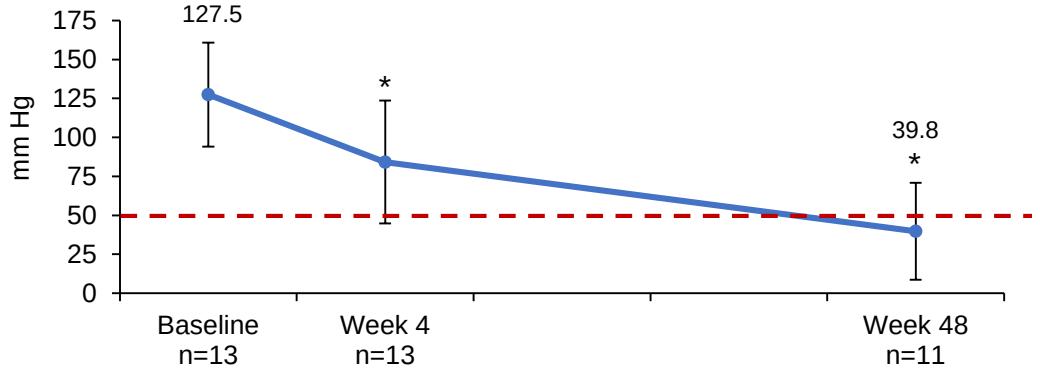
*P <0.01 for change from baseline.

Mean (SD) LVOT gradient (Valsalva)



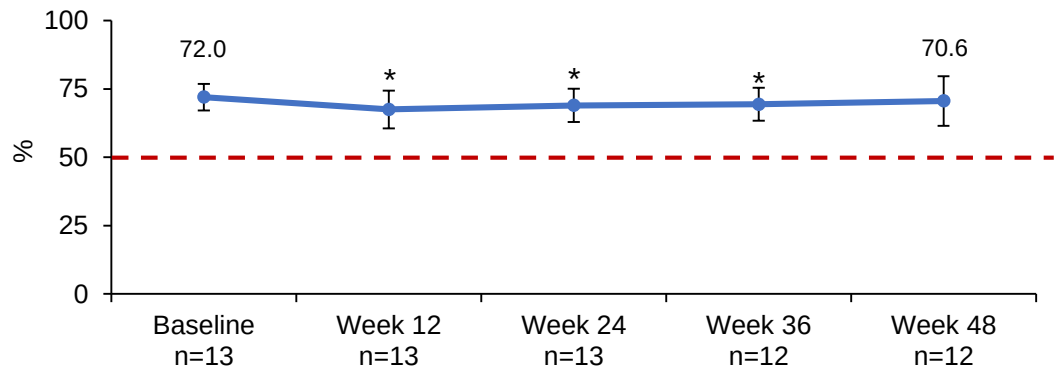
*P <0.01 for change from baseline.

Mean (SD) LVOT gradient (post-exercise)



*P <0.01 for change from baseline.
One patient could not complete a stress echocardiogram at Week 48 due to a serious adverse event.

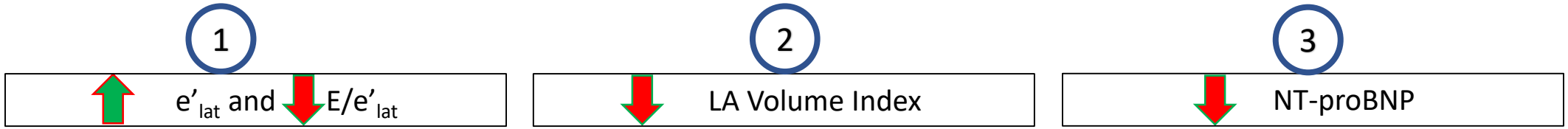
Mean (SD) LVEF



*P <0.05 for change from baseline.

- - - - Threshold for guideline-based invasive intervention (LVOT) or threshold for normal ejection fraction (LVEF). LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; SD, standard deviation.

Results: Measures of Left Ventricular Filling



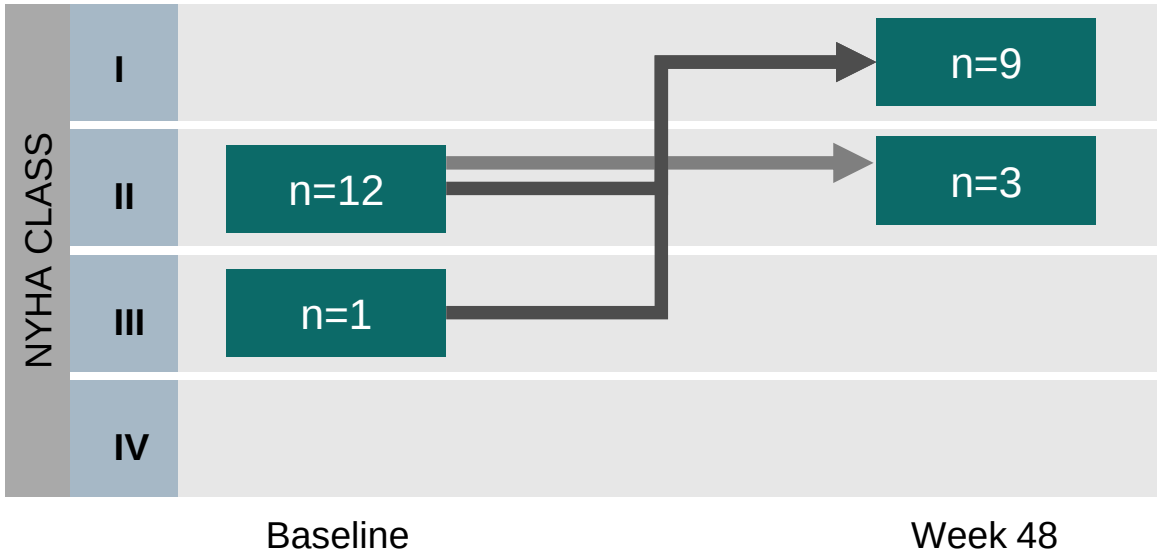
Parameter	Normal ranges	BL n=13	Wk 24 n=13	Δ BL to Wk 24	Wk 36 n=12	Δ BL to Wk 36	Wk 48 n=12	Δ BL to Wk 48
e'_{lat}, cm/s, mean (SD)	>10	6.4 (1.3)	7.9 (2.2)	**1.5 (1.8)****	8.7 (2.8)	**2.3 (2.2)****	8.0 (1.6) n=11	**1.6 (1.1)****
E/e'_{lat}, mean (SD)	<13	12.8 (2.9)	10.2 (2.7)	**−2.5 (2.8)****	8.5 (2.3)	**−4.1 (3.0)****	9.1 (2.0) n=11	**−3.4 (3.4)****
LA vol index, mL/m², mean (SD)	16-34	40.9 (16.4)	30.8 (8.0)	**−10.1 (13.3)***	30.4 (8.7)	**−10.9 (12.8)****	31.5 (6.9)	**−9.8 (13.5)***
NT-proBNP, pg/mL, median (IQR)	<125	594	93	**−494 (−1047, −216)****	168	**−451 (−2381, −71)****	137	**−472 (−2467, −157)****

**P* <0.03; ***P* <0.01.

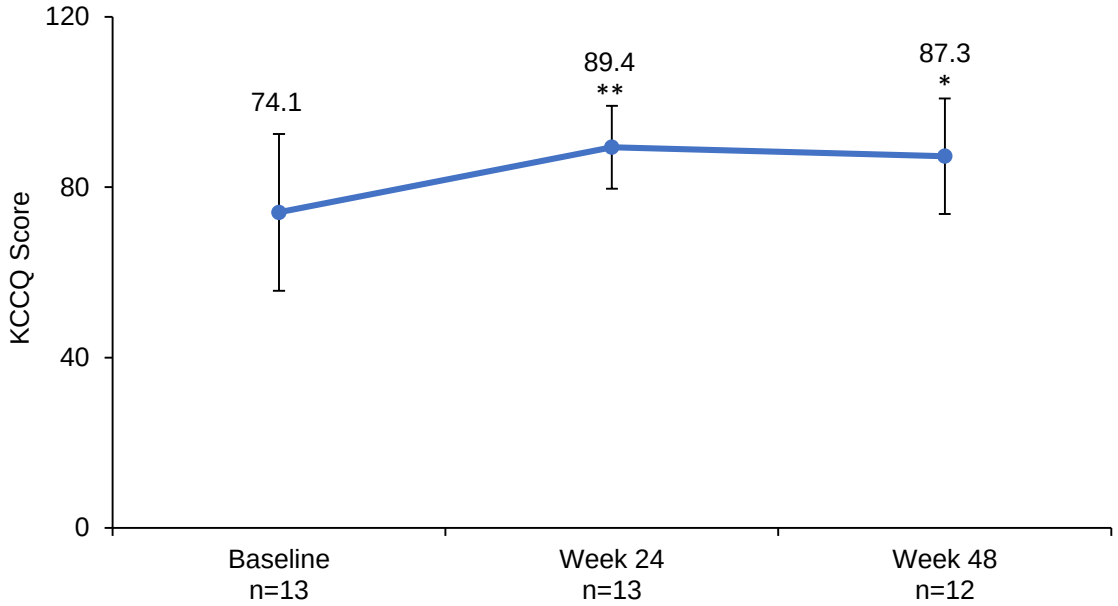
BL, baseline; e'_{lat}, lateral mitral annular velocity during early diastole; E/e'_{lat}, ratio between early mitral inflow velocity and mitral annular early diastolic velocity; IQR, interquartile range; LA vol, left atrial volume; NT-proBNP, N-terminal pro b-type natriuretic peptide; SD, standard deviation; Wk, week.

Results: Symptoms and Function

NYHA functional class



KCCQ Overall Summary Score



Scores range from 0 to 100; higher score reflects better health status.

A clinically significant change is defined as ≥5.

*P <0.03 for change from baseline.

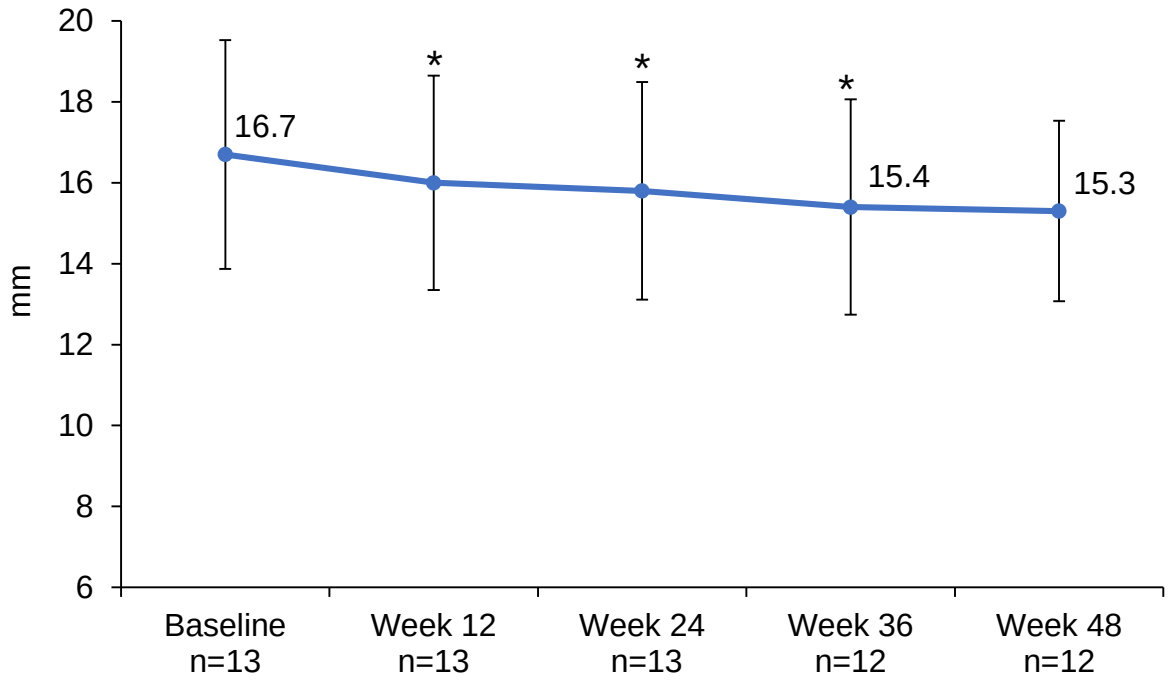
**P <0.01 for change from baseline.

KCCQ, Kansas City Cardiomyopathy Questionnaire.

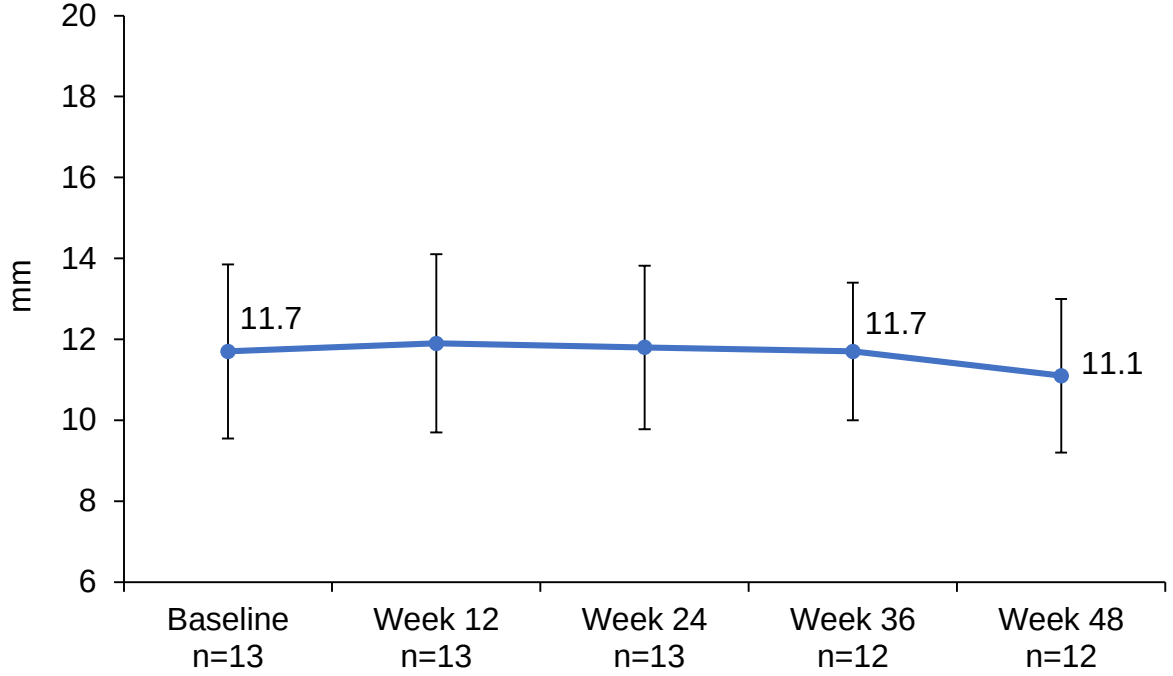
NYHA, New York Heart Association.

Results: LV Wall Thickness

Septal Wall Thickness



Posterior Wall Thickness



Normal range: 6 to 10 mm.
*P <0.05 for change from baseline.

Results: LV Wall Thickness

- Interventricular septal thickness was reduced at Weeks 12, 24, 36, and 48, without changes in posterior wall thickness

Parameter, mean (SD)	Normal ranges	BL n=13	Wk 12 n=13	Δ BL to Wk 12	Wk 24 n=13	Δ BL to Wk 24	Wk 36 n=12	Δ BL to Wk 36	Wk 48 n=12	Δ BL to Wk 48
Interventricular septal thickness, mm	6-10	16.7 (2.8)	16.0 (2.7)	**−0.7 (0.6)†**	15.8 (2.7)	**−0.9 (1.1)†**	15.4 (2.7)	**−1.3 (1.7)†**	15.3 (2.2)	−1.5 (2.6)
Posterior wall thickness, mm	6-10	11.7 (2.2)	11.9 (2.2)	0.2 (0.8)	11.8 (2.0)	0.2 (0.9)	11.7 (1.7)	0.0 (1.5)	11.1 (1.9)	-0.6 (2.0)

†*P* <0.05.

BL, baseline; SD, standard deviation; Wk, week.

Results: Safety and Tolerability

Summary of AEs and SAEs	
Number of patients with any AEs	13
Number of reported AEs*	64
Number of AEs related to study drug	8
SAEs*	4
Number of SAEs related to study drug	0

- The longest duration of mavacamten therapy is 1.5 years.
- There were no dose changes due to AEs
- There were 4 SAEs in 3 patients; not cardiovascular and not related to study drug.
- There was one cardiovascular AE (NSVT) not related to study drug
- Of 64 AEs, most were mild or moderate, and transient
  - 8 AEs in 3 patients were considered potentially related to study drug (fatigue, dyspnea, dizziness, lethargy); 7 were mild and 1 was moderate

*One patient had 3 severe AEs and 1 serious AE that were unrelated—male with history of ulcerative colitis presented 4 days after Week 24 visit with epigastric pain, elevated AST (>5× ULN), and biliary obstruction; subsequently diagnosed with Klatskin type cholangiocarcinoma; the patient discontinued study drug dosing and had an early study termination.

AEs, adverse events; AST, aspartate aminotransferase; NSVT, nonsustained ventricular tachycardia; SAEs, serious adverse events; ULN, upper limit of normal.

Summary

48 weeks of treatment with mavacamten resulted in persistent and durable improvements in LVOT obstruction, functional class, NT-proBNP, and symptoms

The LVEF was maintained within the normal limit for all patients using a personalized dosing strategy

The data from this study suggests that mavacamten has favorable impact on cardiac structure, which will be further explored in ongoing studies

Mavacamten therapy has been well tolerated in patients for up to 1.5 years with most AEs being unrelated to mavacamten