Long-term safety and effectiveness of mavacamten in symptomatic obstructive hypertrophic cardiomyopathy patients: update from PIONEER open-label extension (PIONEER-OLE) study

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Disclosure

- Presenting Author:
  - Andrew Wang: Consultant/Advisory Board- MyoKardia; Research grants- MyoKardia
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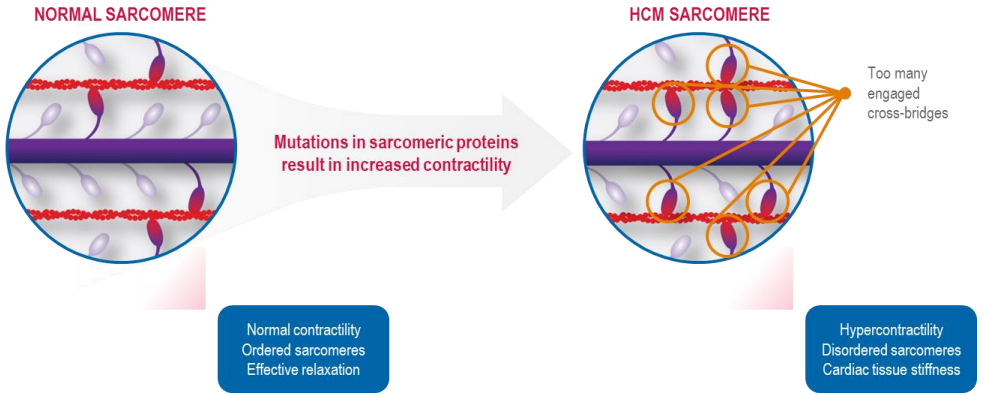
Introduction

- Hypertrophic cardiomyopathy (HCM) is a disease caused by dysfunction of cardiac sarcomeres
- Excess myosin-actin cross-bridging results in hypercontractility[1]



1. Ammirati E. *Eur J Heart Fail*. 2016;18(9):1106-18.

Introduction

- Mavacamten is a first-in-class selective allosteric inhibitor of cardiac myosin that **reduces excessive contractility** in HCM by reducing myosin-actin cross-bridges.
- In the completed 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.[1]
- The open-label extension study (**PIONEER-OLE**) was initiated to examine the long-term safety and effectiveness of mavacamten in this patient population.

1. Heitner SB, et al. *Ann Intern Med*. 2019;170(11):741-48.

PIONEER-OLE Study Design

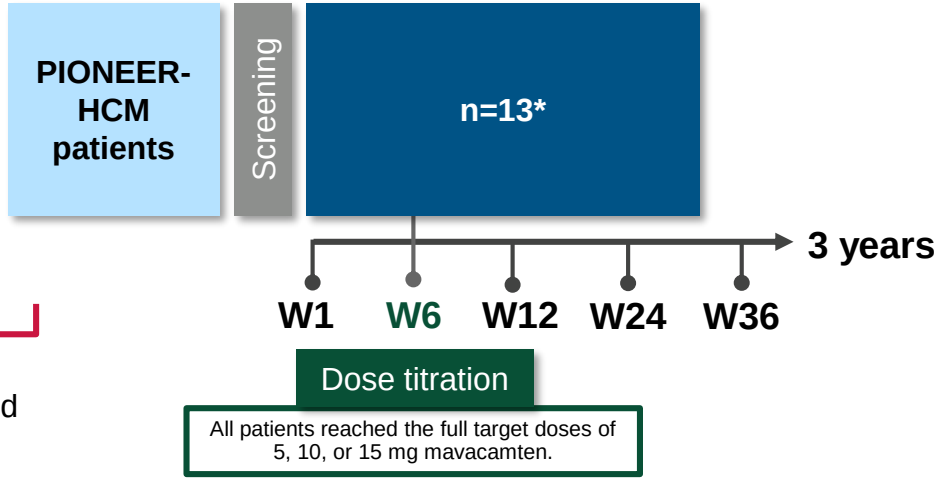
COMPLETED PIONEER-HCM

Cohort A
- β-blockers discontinued
- Completed treatment (n=10)

Cohort B
- β-blockers allowed
- Completed treatment (n=10)

6-18 months elapsed

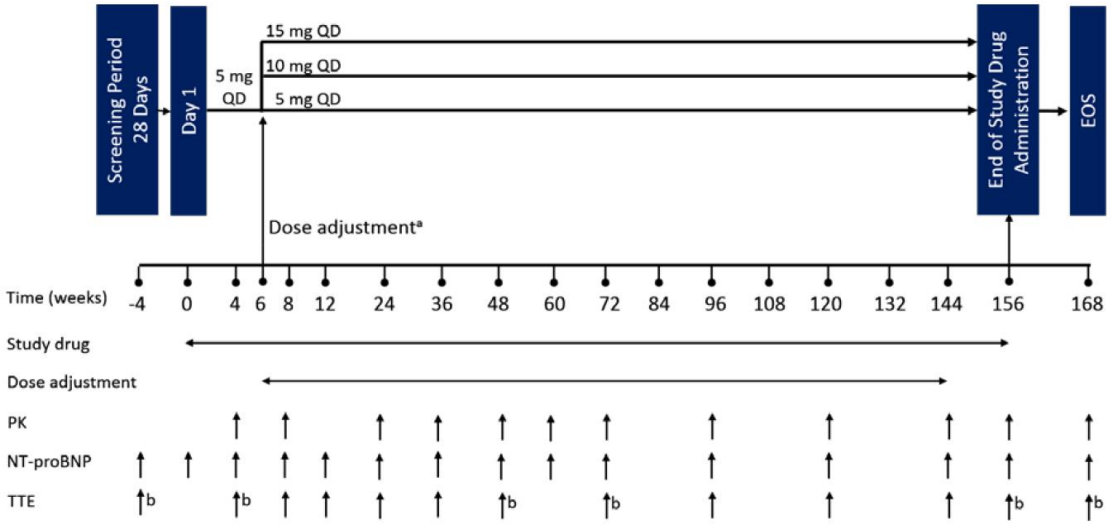
ONGOING PIONEER-OLE



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

* One patient discontinued the study before Week 36

PIONEER-OLE Study Schema



Phone contact on Weeks 18, 30, 42, 54, 66, 78, 90, 102, 114, 126, 148, and 150

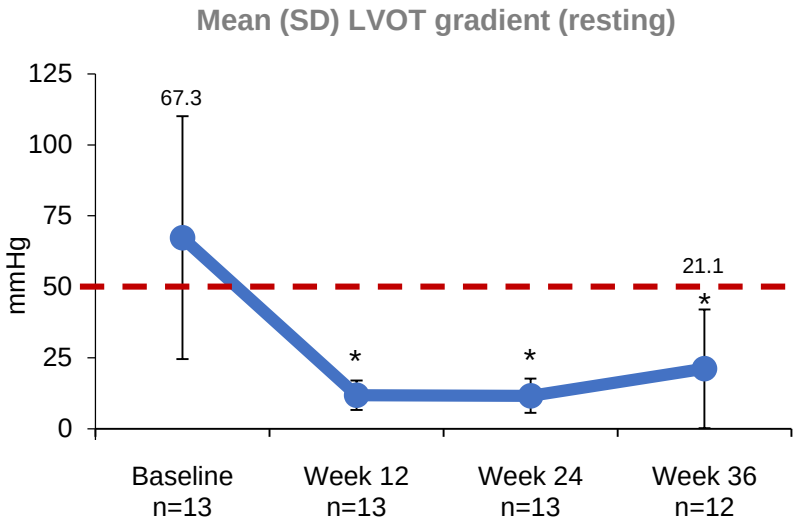
[a] Dose adjustment to individual targeted dose: dose calculated to achieve mavacamten plasma concentration of 250-500 ng/mL in each participant. Dose adjustment may also take place beyond Week 6 based on results of TTE/stress echocardiogram and PK evaluation and based upon the opinion of the Investigator in conjunction with the MyoKardia Medical Monitor. Dose adjustments beyond the previous Target Dose may only be exceeded for each given participant following discussion between the Investigator and the MyoKardia Medical Monitor. Lower doses are permissible.
[b] Includes a stress TTE at baseline, Weeks 4, 48, 72, 156/ET, and 168/EOS. These are in addition to resting and post-Valsalva TTEs at all visits indicated with a vertical arrow.

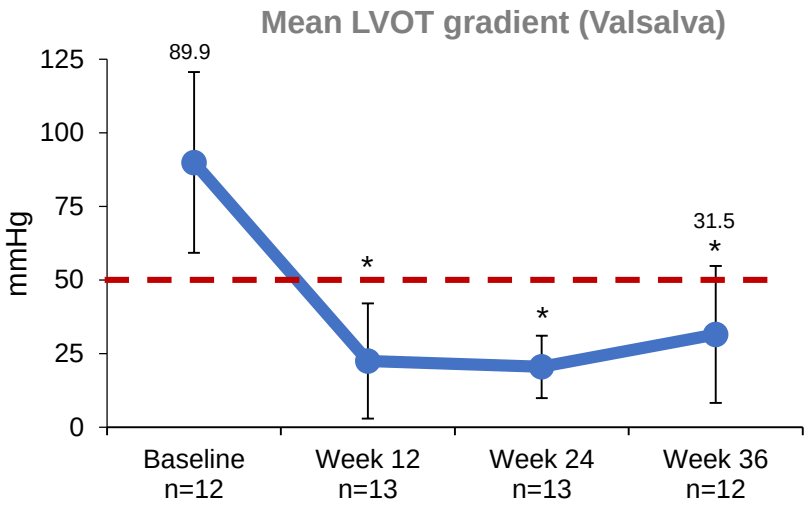
Results: Baseline Characteristics

Characteristic	PIONEER-HCM n=13	PIONEER-OLE n=13
Age, year, mean (SD)	56.5 (13.2)	57.8 (13.3)
Sex, n (%)		
Male	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	11
Bisoprolol	0	1
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;– NYHA, New York Heart Association; SD, standard deviation

Results: LVOT Gradient Resting and Valsalva

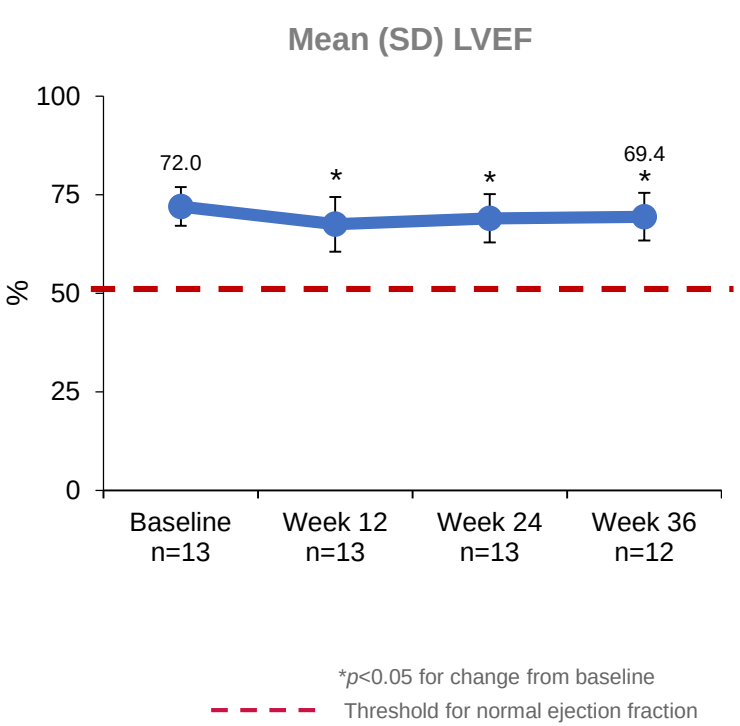


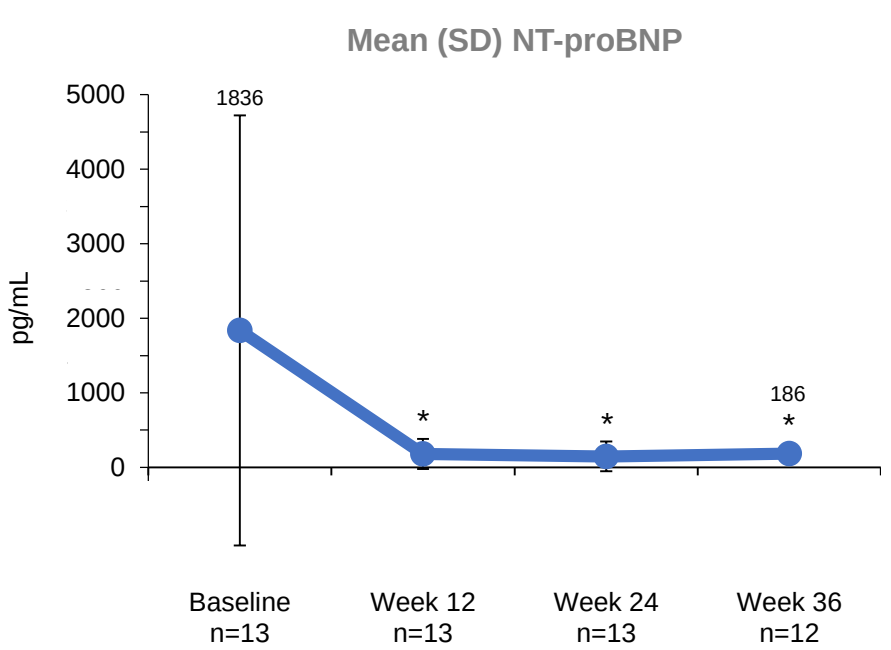


*p<0.01 for change from baseline

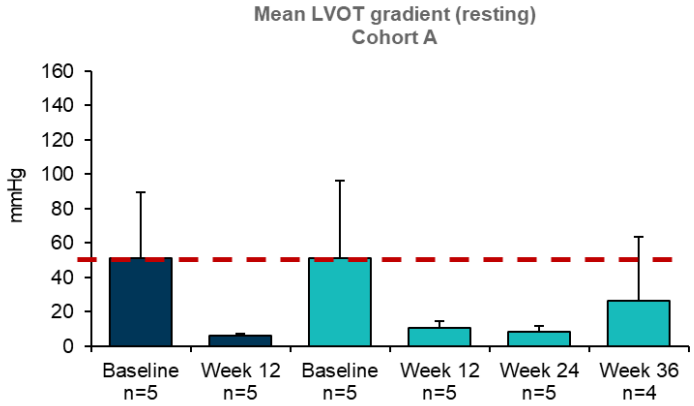
Threshold for guideline-based invasive intervention

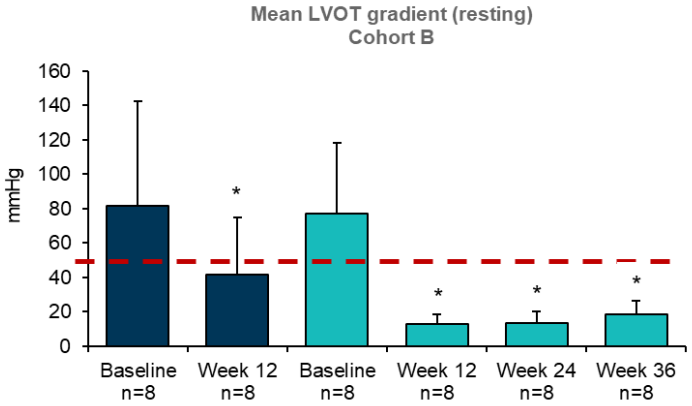
Results: Ejection Fraction and NT-proBNP

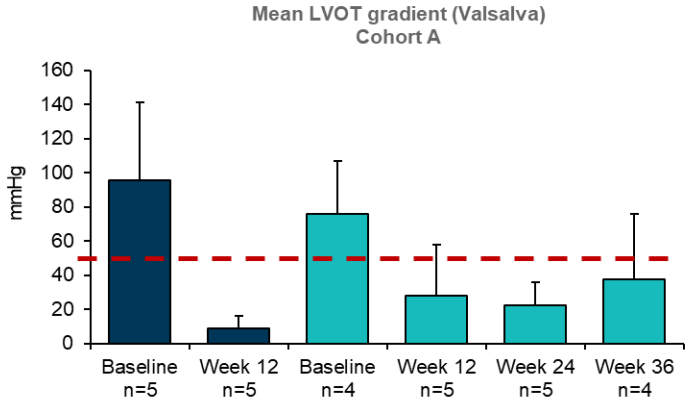


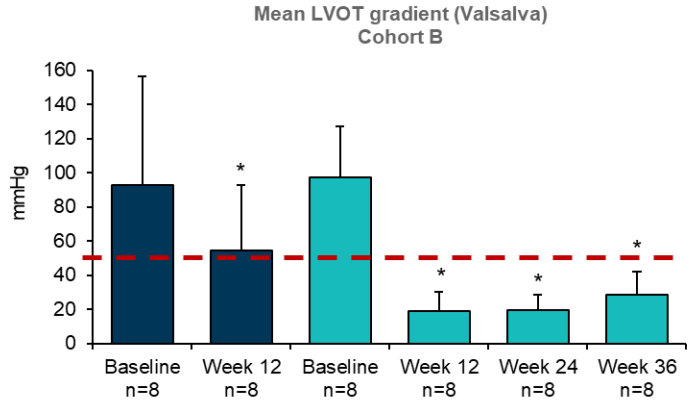


Results: Cohorts A and B in PIONEER-HCM and -OLE









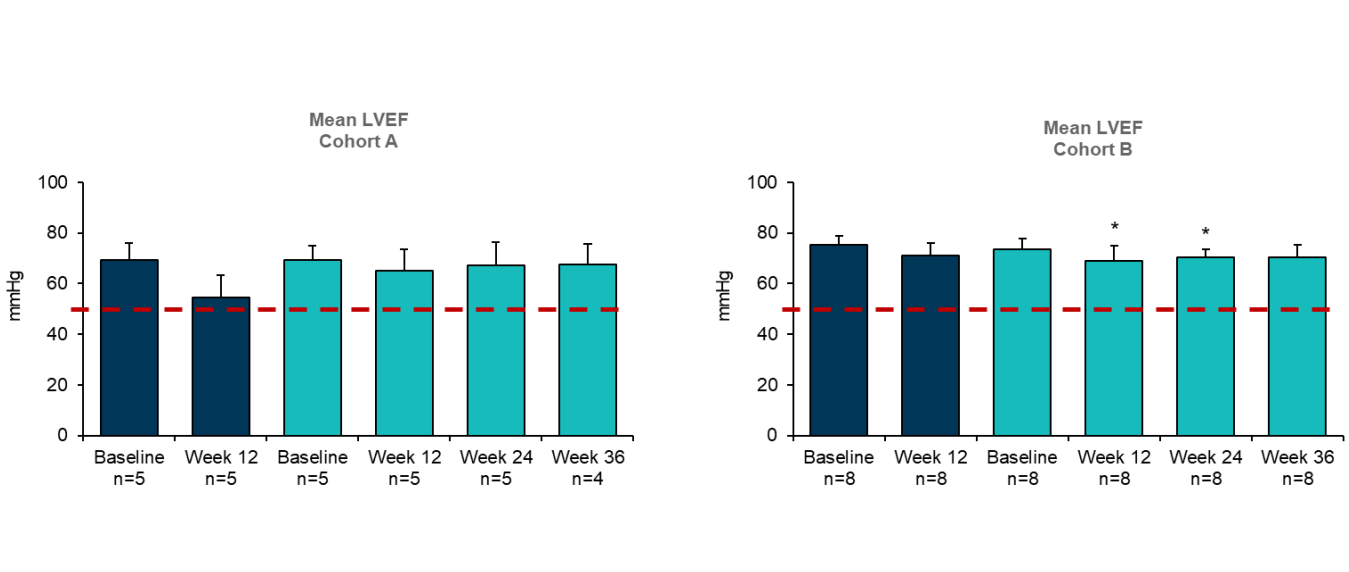
PIONEER-HCM

PIONEER-OLE

*$p<0.05$ for change from baseline

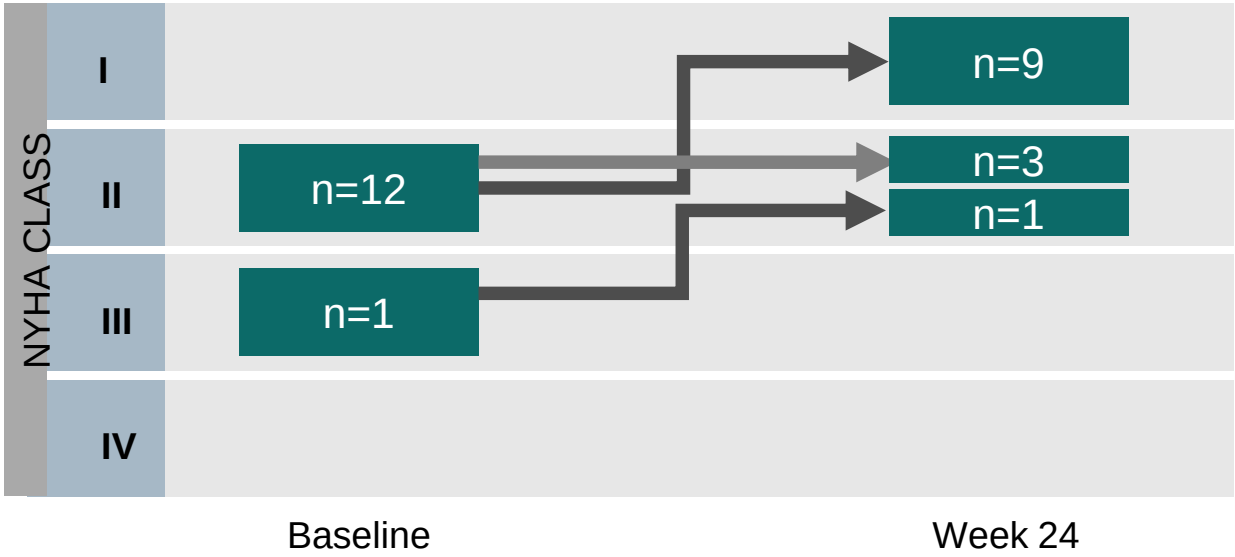
Threshold for guideline-based invasive intervention

Results: Cohorts A and B in PIONEER-HCM and -OLE



Results: NYHA Functional Class

- Per protocol, NYHA assessments were performed at Week 24 and will be performed again at Week 48
- For patients at Week 24, 10 reported improvement in NYHA class and 3 remained Class II



Safety and Tolerability

- The longest duration of mavacamten therapy is 66 weeks (1.3 years)
- There were no dose changes or dose interruptions due to AEs
- There was one cardiovascular AE (NSVT) not related to study drug
- Of 61 AEs, most were mild or moderate, and transient
  - 7 AEs in 3 patients were considered potentially related to study drug (fatigue, dyspnea, dizziness, lethargy); 6 were mild and 1 was moderate

Summary of AEs and SAEs	
Number of patients with any AEs	13
Number of reported AEs[a]	61
Number of AEs related to study drug	7
SAEs[a]	4
Number of SAEs related to study drug	0

[a]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 (>5X ULN), and biliary obstruction; subsequently diagnosed with Klatskin type cholangiocarcinoma at hepatic hilum (11/7) and underwent surgery; the patient discontinued study drug dosing and had an early study termination. AEs, adverse events; AST, aspartate aminotransferase; ULN, upper limit of normal.

Results: Filling-related Parameters

- For exploratory assessments, mavacamten improved markers related to ventricular filling at Weeks 12, 24 and 36
  - There was a significant increase in mitral annular velocity during early diastole (e'_{lat}) and concomitant reduction in E/e'_{lat}
  - There was a significant decrease in left atrial (LA) volume

	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
e'_{lat} cm/s	>12	6.4 (1.3)	8.4 (2.3)	**2.0 (2.0)***	7.9 (2.2)	**1.5 (1.8)***	8.7 (2.8)	**2.3 (2.2)***
E/e'_{lat}	<8	12.8 (2.9)	9.8 (2.5)	**-3.0 (3.4)***	10.2 (2.7)	**-2.5 (2.8)***	8.5 (2.3)	**-4.1 (3.0)***
LA vol index (mL/m^2)	16-34	40.9 (16.4)	31.8 (8.4)	**-9.2 (11.7)***	30.8 (8.0)	**-10.1 (13.3)***	30.4 (8.7)	**-10.9 (12.8)***

***P*<0.01**. LA, left atrial.

Summary

- After 36 weeks of treatment with mavacamten, patients with symptomatic obstructive HCM experienced persistent improvements in clinical status, LVOT gradients, and surrogate measures of LV filling pressure:
  - There were significant reductions in LVOT gradients and levels of NT-proBNP, as well as in E/e'$_{lat}$ and LA volume
  - 10/12 patients (83%) reported improvements in NYHA Class
- Ejection fraction (LVEF) was maintained above 50% in all patients.
- Dose titration to the target therapeutic range reduced gradient without compromising contractility below normal levels.
- With the longest duration of therapy to date (1.3 years), mavacamten was well tolerated:
  - The majority of AEs were mild and unrelated to the study drug