Long-term Safety and Effectiveness of Mavacamten in Symptomatic Obstructive Hypertrophic Cardiomyopathy Patients, PIONEER-Open Label Extension Study (PIONEER-OLE)

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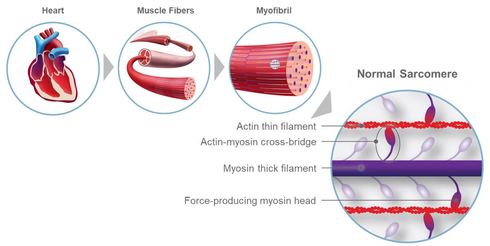
INTRODUCTION

- Obstructive hypertrophic cardiomyopathy (oHCM) comprises left ventricular (LV) hypertrophy, LV outflow tract obstruction (LVOTO), and impaired myocardial relaxation.[1]
- Disease pathogenesis is associated with sarcomeric gene mutations resulting in hypercontractility, reduced ventricular compliance, and inefficient energy utilization.[2]
- Symptom management is with either medications (eg, β-blockers, calcium channel blockers, or disopyramide) or septal reduction procedures (septal myectomy or alcohol septal ablation).
- Mavacamten is a first-in-class selective allosteric modulator of cardiac myosin that reversibly attenuates cardiac contractility—thus addressing the primary pathophysiologic mechanism of oHCM—and is proposed to have salutary clinical effects (**Figure 1**).
- In the completed phase 2 open-label PIONEER-HCM study (NCT02842242), safety and effectiveness of mavacamten were investigated in patients with symptomatic oHCM.[3]
- The open-label extension study (PIONEER-OLE) was initiated to examine the long-term safety and effectiveness of mavacamten in this patient population.

Figure 1. Mavacamten Mechanism of Action



Mavacamten targets proteins in the sarcomere to normalize cardiac contractility and restore the appropriate number of actin-myosin cross-bridges

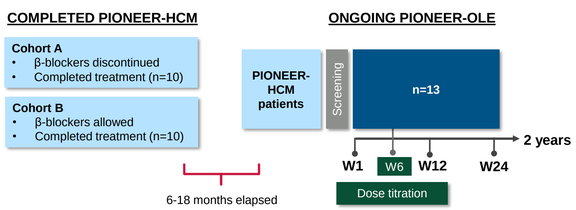
OBJECTIVE

- We report interim results from the first 24 weeks of the 2-year PIONEER-OLE study, which is an ongoing open-label extension study to examine the long-term safety and effectiveness of mavacamten using individualized dosing regimen.

METHODS

- PIONEER-OLE (NCT03496168) is a 2-year trial for patients who completed PIONEER-HCM (NCT02842242) (**Figure 2**).

Figure 2. PIONEER-OLE Study Design



Mavacamten PIONEER-OLE Overview	
Patients enrolled	• n=13 • From PIONEER-HCM cohort A (n=5) and cohort B (n=8)
Outcomes	• Safety, tolerability, and select measures of efficacy using individualized dosing • Key measurements include LVOT gradient, LVEF, NT-proBNP

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

- Starting dose of mavacamten is 5 mg per day followed by dose titration at Week 6 to an individualized therapeutic dose (5, 10, or 15 mg) based on individualized dosing to achieve predefined PK range based on data obtained from PIONEER-HCM.
- Evaluations occur at Weeks 0, 4, 8, and 12 and every 12 weeks thereafter.
- Primary assessments include LV ejection fraction (LVEF), left ventricular outflow tract (LVOT) gradient, New York Heart Association (NYHA) Class, N-terminal pro b-type natriuretic peptide (NT-proBNP), drug concentration, and safety. Exploratory assessments include ventricular filling.
- The same patients (n=13) are reported from PIONEER-HCM and PIONEER-OLE.

RESULTS

- Longest duration on mavacamten in the study as of March 1, 2019, is 42.5 weeks.
- 13 patients who completed PIONEER-HCM were enrolled in PIONEER-OLE (**Table 1**).

Table 1. Demographics and 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)	
Female	4 (30.8)	
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

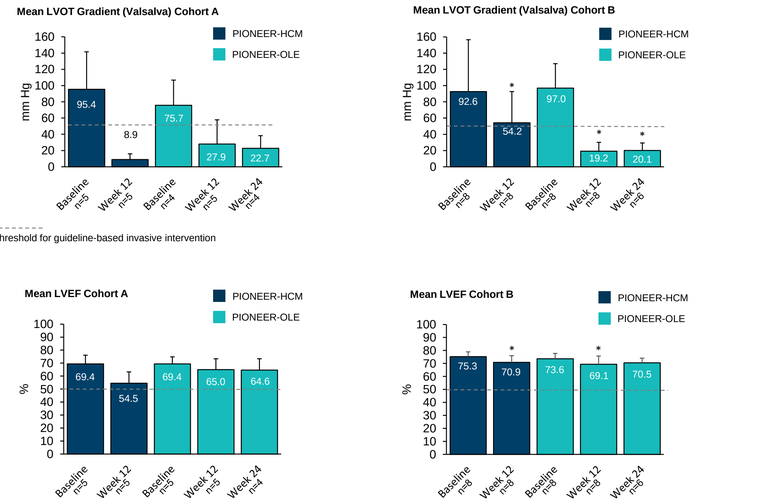
- Mean baseline LVOT peak instantaneous gradient and LVEF measures were similar between PIONEER-HCM and PIONEER-OLE (**Figure 3**).
- There were significant improvements in primary assessments of mavacamten effectiveness:
  - In the targeted therapeutic range, there were significant effects on LVOT gradient relief, without significant changes in LVEF.
    - Mavacamten significantly reduced resting (mean change at Week 12, -55.5 mm Hg; Week 24, -66.6 mm Hg) and provoked (**Figure 3**) LVOT gradients at Weeks 12 and 24 compared to baseline (all P<0.004).
    - LVEF was maintained above 50% for all patients at all timepoints (**Figure 3**).
  - Levels of NT-proBNP were significantly reduced at Weeks 12 and 24 (**Table 2**).
- For exploratory assessments, mavacamten improved markers related to ventricular filling at Weeks 12 and 24 (**Table 2**):
  - 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.

Table 2. NT-proBNP and Filling-related Parameters

Mean (SD)	PIONEER-HCM BL n=13	PIONEER-HCM Wk 12 n=13	PIONEER-HCM Δ BL to Wk 12	PIONEER-OLE BL n=13	PIONEER-OLE Wk 12 n=13	PIONEER-OLE Δ BL to Wk 12	PIONEER-OLE Wk 24 n=10	PIONEER-OLE Δ BL to Wk 24
e'_{lat} cm/s	6.2 (0.9)	7.2 (2.2)	0.9 (1.9)	6.4 (1.3)	8.4 (2.3)	2.0 (2.0)*	7.8 (2.2)	1.4 (2.0)*
E/e'_{lat}	13.1 (2.7)	10.5 (3.7)	-2.5 (3.4)*	12.8 (2.9)	9.8 (2.5)	-3.0 (3.4)*	10.3 (3.0)	-2.8 (3.1)*
LA vol index (mL/m^2)	39.0 (18.7)	35.1 (11.0)	-3.9 (11.8)	40.9 (16.4)	31.8 (8.4)	-9.2 (11.7)*	29.7 (8.0)	-13.6 (13.3)*
NT-proBNP	1601.3 (2782) n=12	684 (980) n=13	-1070 (2409)*	1836 (2886)	178 (202)	-1658 (2695)*	170 (225)	-2128 (3104)*

*P<0.05. LA, left atrial.

Figure 3. LVOT Valsalva Gradient and LVEF in PIONEER-HCM and PIONEER-OLE



*P<0.05 for change from baseline

- Eight (out of 10) patients reported significant improvements in NYHA Class at Week 24 (per-protocol evaluable timepoint) (**Figure 4**).

Figure 4. Change in NYHA Functional Class at Week 24

*Three patients did not reach evaluation timepoint.

Safety

- There were no cardiovascular adverse events (AEs); 6 AEs were possibly related to study drug (**Table 3**).
- There were no dose changes or dose interruptions due to AEs.

Table 3. Summary of Adverse Events

	PIONEER-OLE n=13
Number of patients with any AEs	12
Number of reported AEs[a]	34
Mild	25
Moderate	5
Severe[a]	3
Life-threatening and serious AEs[a]	1

[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

CONCLUSIONS

- Despite management with current therapies such as β-blockers, patients enrolled in PIONEER-OLE with similar levels of obstruction and hypercontractility after completing PIONEER-HCM 6-18 months prior.
- After 24 weeks of treatment patients experienced a significant reduction in LVOT peak instantaneous gradient, surrogate measures of left ventricular filling pressure, and improvement in clinical status:
  - There were significant reductions in LVOT gradient and levels of NT-proBNP, as well as in E/e'_{lat} and LA volume.
  - Eight out of 10 evaluable patients reported significant improvements in NYHA.
- Ejection fraction was maintained above 50% in all patients.
- Dose titration to the target therapeutic range reduced gradient without compromising contractility below normal levels.
- During this approximately 10-month treatment period, mavacamten was well tolerated; the majority of AEs were mild and unrelated to the study drug.

REFERENCES

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DISCLOSURES

SB Heitner, S Lester, A Wang: Consultant/Advisory Board MyoKardia. D Jacoby: Consultant/Advisory Board; MyoKardia, Abbott, Alnylam, Deerfield. Consultant/Advisory Board; Admera. L Fang, A Sehnert: Employment; MyoKardia.

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