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

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Objectives: Mavacamten is a skeletal muscle selective and neurovascular inhibitor of cardiac myosin that orally abolishes systolic pressure and myocardial workload in a direct and dose-dependent manner.

Introduction

• Mavacamten has a low CV dose and a relatively administrable cardiomyopathic and hypertrophic cardiomyopathy (HCM; Dose Adjustment Algorithm, figure 1).

• Mavacamten reduces the percentage of LVH in human cardiac tissues from an HCM patient with the ECH20 modifier, as depicted in the left panel of figure 1.

• Similar effects are observed for other HCM intrinsic pathways.

Mavacamten

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Mavacamten Repopulates the Super-relaxed (SRX) "Off" State of Myosin

Study Design and Methods

• The study was a phase II PIONEER-HCM study as a dose-ranging study of mavacamten in symptomatic HCM.

• The study was conducted by two sites (figure 1B) in the United States (vanderbilt and University of Pennsylvania) and conducted in a class I study site, and echocardiography was read at the core laboratory (Northwell and Boston Children’s Hospital) (figure 2).

• Participants received mavacamten once daily for 12 weeks, either 10 mg (n=55) or 5 mg (n=55) (completed at 2-9 mg/m2, cohort A; figure 2). (See figure 3 and table 1)

• In cohort A, background imaging was discordant prior to treatment with mavacamten.

• In cohort B, 1 of 10 subjects continued background beta blocker therapy.

• All patients were analyzed according to allocated enrollment/randomization group, except the primary end point, treatment change from baseline to week 12 of rest echo.

Results

• Compared to baseline, mavacamten reduced hypertrophy, in a dose-dependent fashion, with relief of symptoms

• Mavacamten achieved significant echocardiographic improvements in end-systolic volume (ESV) compared to baseline (figure 3A). The change was significant at 12 weeks in opioid hypertrophic cardiomyopathy (OP; cohort A) and there were no changes in systolic A (P<0.05, cohort A). (See figure 4).

• Relationship between lateral E/e’ and LVEDV index for patients in cohort A.

• Dysfunction, dyspnea, and a novel rhythm atrial rate during stress NMS scores of Behath risk as an end point, improved in both cohort A and cohort B.

Conclusions

• Administration of mavacamten is associated with improvements in measures of systolic and diastolic function.

• These effects are consistent with preclinical findings reported in healthy dogs and a genetic minigene model of cardiomyopathy.

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Author Disclosure Information


References