The Impact of Mavacamten on the Pathophysiology of Hypertrophic Cardiomyopathy: A Narrative Review

Jay M. Edelberg[1] · Amy J. Sehnert[1] · Matthew E. Mealiffe[2] · Carlos L. del Rio[1] · Robert McDowell[3]

[1]Clinical Development, Cardiovascular Global Drug Development, MyoKardia, Inc., a wholly owned subsidiary of Bristol Myers Squibb, Brisbane, CA, USA; [2]Early Clinical Development, MyoKardia, Inc., a wholly owned subsidiary of Bristol Myers Squibb, Brisbane, CA, USA; [3]Research & Early Development, MyoKardia, Inc., a wholly owned subsidiary of Bristol Myers Squibb, Brisbane, CA, USA

Running title: Mavacamten and the Pathophysiology of HCM

Journal: *American Journal of Cardiovascular Drugs*

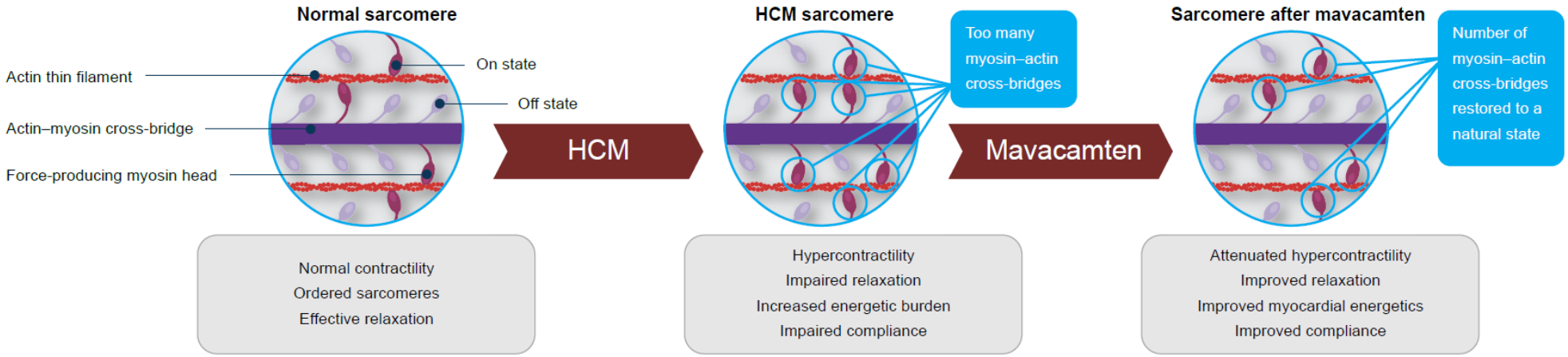
Corresponding author: Robert McDowell

Address: 1000 Sierra Point Parkway, Brisbane, CA, 94005

Tel: (650) 741-0904; e-mail: robert.mcdowell@bms.com

Appendix

Supplementary Figure S1 The mechanism of action of mavacamten



Supplementary Table S1 Mavacamten dosage regimen and titration criteria in the PIONEER-HCM, PIONEER-OLE, MAVERICK-HCM, EXPLORER-HCM, and MAVA-LTE studies

Study	Dosage	Titration criteria	Temporary discontinuation criteria
PIONEER-HCM (NCT02842242)	Cohort A: 10–20 mg/day; starting dosage, 10 mg/day or 15 mg/day (*n* = 11) Cohort B: 2–5 mg/day; starting dosage, 2 mg/day (*n* = 10)	Cohort A: change in LVEF Cohort B: change in LVOT gradient	NA
PIONEER-OLE (NCT03496168)	Starting dosage: 5 mg/day	Target plasma concentration: 250–500 ng/mL	LVEF < 45%, mavacamten plasma concentration > 1000 ng/mL, or increased QTcF
MAVERICK-HCM (NCT03442764)	Starting dosage: 5 mg/day	Group 1: target plasma concentration ~200 ng/mL (*n* = 19) Group 2: target plasma concentration ~500 ng/mL (*n* = 21)	NA
EXPLORER-HCM (NCT03470545)	Starting dosage: 5 mg/day	LVOT < 30 mm Hg and plasma concentration with a target plasma concentration 350–700 ng/mL	LVEF < 50%, mavacamten plasma concentration > 1000 ng/mL, or increased QTcF
MAVA-LTE (NCT03723655)	EXPLORER-LTE cohort: 5 mg/day MAVERICK-LTE cohort: same dosage as parent study or 5 mg/day if in the placebo group	EXPLORER-LTE: clinically guided with site-read echo—Valsalva LVOT gradient and LVEF MAVERICK-LTE: same as MAVERICK-HCM using plasma concentration; previously placebo-treated patients randomized into groups 1 and 2	LVEF < 50%, mavacamten plasma concentration > 1000 ng/mL, or increased QTcF

HCM hypertrophic cardiomyopathy, *LTE* long-term extension, *LVEF* left ventricular ejection fraction, *LVOT* left ventricular outflow tract, *NA* not applicable, *OLE* open-label extension *QTcF* QT interval with Fridericia correction

Supplementary Table S2 Change in key endpoints from baseline to end of treatment in the PIONEER-HCM, PIONEER-OLE, MAVERICK-HCM, EXPLORER-HCM, EXPLORER-HCM CMR, and MAVA-LTE studies

	PIONEER-HCM	PIONEER-OLE[a]	MAVERICK-HCM	EXPLORER-HCM		EXPLORER-HCM CMR	MAVA-LTE (at week 48)[b]
	Mavacamten Cohort A: *n* = 11 Cohort B: *n* = 10	**Mavacamten N = 13**	**Mavacamten Group 1: *n* = 19[c] Group 2: *n* = 21[c] Placebo: *n* = 19**	**Mavacamten *n* = 123**	**Placebo *n* = 128**	**Mavacamten *n* = 17**	**Mavacamten EXPLORER cohort *n* = 49 MAVERICK cohort *n* = 36**
Mean change from baseline to end of treatment							
LVEF, %	Cohort A: −14.6 ± 11.8 Cohort B: −5.5 ± 6.0	−1.6 ± 4.2 (*p* = 0.413)	Group 1: −2.3 ± 5.3 Group 2: –5.6 ± 9.6 Placebo: –2.3 ± 4.9	−3.9 ± 7.7	–0.01 ± 6.8	–6.6 ± 6.3	EXPLORER cohort: −8.6 ± 9.6 MAVERICK cohort: –5.4 ± 6.0
Resting LVOT gradient, mm Hg	Cohort A: –47.8 (95% CI −72.2, −23.4) Cohort B: −48.5 (95% CI −82.8, −14.1)	−58.1 ± 46.7	NA	−38.6 ± 29.5	–5.5 ± 27.9 (95% CI −10.5, −0.5)	NA	EXPLORER cohort: −27.4 ± 32.1
Valsalva maneuver LVOT gradient, mm Hg	Cohort A: −84.7 (95% CI −113.8, −55.7) Cohort B: −47.1 (95% CI −82.1, −12.1)	−72.5 ± 39.7	NA	−49.1 ± 34.4	–12.1 ± 31.0 (95% CI −17.6, −6.6)	NA	EXPLORER cohort: −38.8 ± 36.7
Postexercise LVOT gradient, mm Hg	Cohort A: −89.5 (95% CI −138.3, −40.7) Cohort B: −25.0 (95% CI −47.1, −3.0)	−86.9 ± 53.0	NA	−47.2 ± 40.3	–10.4 ± 29.6 (95% CI –15.7, –5.1)	NA	NA
Maximum LV wall thickness, mm	NA	−1.4 ± 2.3 (*p* = 0.042)	NA	NA	NA	−2.4 ± 2.5 (*p* < 0.05)	NA
E/e' average ratio	NA	NA	Group 1: −1.5 ± 2.4 Group 2: –3.5 ± 6.8 Placebo: –1.6 ± 6.4	−5.1 ± 5.4	−1.8 ± 4.3	NA	EXPLORER cohort: −3.1 ± 4.2 MAVERICK cohort: Group 1: –1.6 ± 3.0[c] Group 2: –3.1 ± 3.0[c] High-risk group: −2.4 ± 3.1[d] Non-high-risk group: −2.5 ± 3.0[d]

VE/VCO_2 slope	Cohort A: −2.2 (95% CI −6.1, 1.7) Cohort B: −2.5 (95% CI −4.3, −0.7)	NA	NA	−2.4 ± 4.6	0.4 ± 4.1	NA	NA
LA volume index, mL/m^2	NA	−12.5 ± 12.9	Group 1: 0.3 ± 7.2 Group 2: 2.4 ± 9.1 Placebo: −0.8 ± 8.7	−7.5 ± 7.8 (95% CI −9.0, −6.1)	–0.1 ± 8.7 (95% CI, –1.6 to 1.5)	NA	EXPLORER cohort: −9.1 ± 9.8 MAVERICK cohort: –4.3 ± 7.2
NT-proBNP, pg/mL	−425 (−748 to −68)[e]	−465 (−3952 to −99)[e]	Group 1: –47.1[f] Group 2: –57.9[f] Placebo: –0.7[f]	0.2 (266.91)[g,h]	1.0 (55.80)[g]	0.2 (81.4)[g]	EXPLORER cohort: 0.3 (128.8)[g] MAVERICK cohort: 0.4 (118.4)[f]
cTnI, ng/mL	NA	NA	Group 1: –23.4[f] Group 2: –41.0[f] Placebo: 3.8[f]	0.6 (49.17)[g,i]	1.0 (143.34)[g]	0.5 (53.3)[g]	NA
Global ECVF, %	NA	NA	NA	NA	NA	0.02 ± 0.07	NA

Data are mean ± SD unless otherwise stated

CI confidence interval, *CMR* cardiac magnetic resonance, *cTnI* cardiac troponin I, *CV* coefficient of variability, *E/e'* ratio between early mitral inflow velocity and early diastolic mitral annular velocity, *ECVF* extracellular volume fraction, *HCM* hypertrophic cardiomyopathy, *IQR* interquartile range, *LA* left atrial, *LTE* long-term extension, *LV* left ventricular, *LVEF* left ventricular ejection fraction, *LVOT* left ventricular outflow tract, *NA* not applicable, *NT-proBNP* N-terminal pro B-type natriuretic peptide, *OLE* open-label extension, *SD* standard deviation, *VE/VCO_2* minute ventilation to carbon dioxide production

[a]The cut-off date for the interim analysis of PIONEER-OLE was June 4, 2020; the data presented are change from baseline to week 72. [b]The cut-off date for the interim analysis of MAVA-LTE was October 30, 2020. [c]Group 1: mavacamten doses titrated to target a serum drug concentration of ~200 ng/mL. Group 2: mavacamten doses titrated to target a serum drug concentration of ~500 ng/mL. [d]High-risk group was defined as the presence of cTNI > 0.03 and/or E/e' average > 14 at baseline in parent study. [e]Median (IQR). [f]Percentage change in geometric mean (%). [g]Geometric mean ratio to baseline (geometric mean [%CV]). [h]This corresponds to an 80% reduction compared with placebo. [i]This corresponds to a 40% reduction compared with placebo