Mavacamten for Treatment of Symptomatic Obstructive Hypertrophic Cardiomyopathy: a Double-blind, Randomized, Placebo-controlled Phase 3 Trial

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54 **RESEARCH IN CONTEXT**

55 **Evidence before this study**

56 The gaps in therapeutic options for hypertrophic cardiomyopathy (HCM) are well recognized.

57 Several agents, such as perhexiline, trimetazidine, ranolazine, eleclazine, spironolactone,

58 valsartan, and losartan, have demonstrated no or limited efficacy in prospective trials. In

59 patients with obstructive HCM (oHCM; also known as HOCM) guideline-recommended

60 pharmacological therapy is administered on an empirical basis, in the absence of randomized

61 controlled trials, and includes beta-blockers or non-dihydropyridine calcium channel blockers.

62 Disopyramide represents an additional agent in individuals refractory to first-line therapy. While

63 beneficial for some patients, use of these drugs is limited by side effects, and often fails to

64 provide optimal control of left ventricular outflow gradients and symptoms, leaving an unmet

65 burden of disease in many patients with oHCM.

66 Mavacamten, a first-in-class targeted inhibitor of cardiac myosin, has reduced hypercontractility,

67 eliminated systolic anterior motion (SAM) of the mitral valve, and relieved left ventricular outflow

68 tract (LVOT) obstruction in a mouse model of HCM. Moreover, mavacamten treatment

69 appeared to suppress the development of ventricular hypertrophy, cardiomyocyte disarray, and

70 myocardial fibrosis in mice. In the phase 2 PIONEER-HCM study, treatment of patients with

71 oHCM led to improvements in post-exercise LVOT gradients, exercise capacity, and symptoms,

72 and was generally well tolerated, with the majority of adverse effects being mild or moderate,

73 self-limiting, and unrelated to the study drug.

74 **Added value of this study**

75 This pivotal phase 3 EXPLORER-HCM trial is the largest placebo-controlled randomized clinical

76 trial conducted to date in HCM. The majority of patients in the active treatment and placebo

77 arms continued to receive currently available background HCM therapy except disopyramide

78   (i.e., monotherapy with beta-blockers or non-dihydropyridine calcium channel blockers). The

79   primary composite functional end point as well as sequential secondary end points were

80   designed and discussed with HCM experts, patients, and regulatory authorities to

81   comprehensively assess treatment benefits for oHCM. The end points comprise measures of

82   symptoms and functional capacity as well as LVOT obstruction and health status. After 30

83   weeks of treatment with mavacamten, there was a significant benefit across the composite

84   primary end point, its components, and all secondary end points, as well as relevant

85   improvements in patient-reported measures and reductions in biomarkers of cardiac wall stress

86   and injury. Treatment with mavacamten was generally well tolerated and the safety profile was

87   comparable to placebo. Seven patients on mavacamten (3 patients during the 30-week

88   treatment and 4 patients at the end of treatment) and 2 on placebo experienced a transient

89   decrease in LVEF to <50%. All completed the study.

90   **Implications of all the available evidence**

91   Results from this phase 3 trial demonstrate significant efficacy of the first targeted

92   pharmacologic therapy designed specifically to address the primary underlying pathophysiologic

93   basis of oHCM. Treatment with mavacamten led to clinically meaningful improvements in

94   hemodynamic status, functional capacity, and subjective well-being. An ongoing, long-term

95   extension of the study will provide further evidence for clinical benefit and safety of mavacamten

96   in the treatment of oHCM over 5 years.

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SUMMARY

Background: Cardiac muscle hypercontractility is a key pathophysiologic abnormality in hypertrophic cardiomyopathy (HCM), and a major determinant of dynamic left ventricular outflow tract (LVOT) obstruction. Available pharmacological options for HCM are limited and non-disease–specific. We assessed the efficacy and safety of mavacamten, a first-in-class cardiac myosin inhibitor, in symptomatic obstructive HCM (oHCM).

Methods: In this phase 3, randomized, double-blind trial, HCM patients with LVOT gradient ≥50 mm Hg and New York Heart Association (NYHA) class II-III symptoms received mavacamten (starting at 5 mg) or placebo for 30 weeks. The primary end point was 1) ≥1·5 ml/kg/min increase in peak oxygen consumption (pVO_2) and ≥1 NYHA class improvement *OR* 2) ≥3·0 ml/kg/min pVO_2 increase without NYHA class worsening. Secondary end points assessed changes in post-exercise LVOT gradient, pVO_2, NYHA class, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS), and HCM Symptom Questionnaire Shortness-of-Breath subscore (HCMSQ-SoB). This trial is registered with ClinicalTrials.gov, NCT03470545.

Findings: Forty-five of 123 (36·6%) patients on mavacamten versus 22 of 128 (17·2%) on placebo achieved the primary end point (difference, +19·4%; 95% confidence interval [CI], 8·7 to 30·1; p=0·0005). Patients on mavacamten achieved greater reduction versus placebo in post-exercise LVOT gradient (–36 mm Hg [95% CI, –43·2 to –28·1]; p<0·0001), greater increase in pVO_2 (+1·4 mL/kg/min [95% CI, 0·6 to 2·1]; p=0·0006), and improved symptom scores (KCCQ-CSS [+9·1; 95% CI, 5·5 to 12·7], HCMSQ-SoB [–1·8; 95% CI, –2·4 to –1·2]; p<0·0001). Thirty-four percent more mavacamten-treated patients improved ≥1 NYHA class (95% CI, 22·2 to 45·4; p<0·0001). Safety and tolerability were comparable to placebo.

Interpretation: Treatment with mavacamten improved exercise capacity, LVOT obstruction, symptoms, and health status in oHCM patients. The results of this pivotal trial support a role for disease-specific treatment in HCM.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a myocardial disorder characterized by primary left

ventricular (LV) hypertrophy.[1,2] This complex disease can be broadly defined by pathologically

enhanced cardiac myosin-actin interactions, with core pathophysiologic features that include

hypercontractility, diastolic abnormalities, and dynamic left ventricular outflow tract (LVOT)

obstruction.[2-4] Patients with obstructive HCM (oHCM; also known as HOCM) are often

symptomatic and may experience atrial fibrillation, heart failure, and malignant ventricular

arrhythmias.[2,5] Current treatment for oHCM focuses on symptomatic relief using beta-blockers,

non-dihydropyridine calcium channel blockers, and disopyramide.[6-9] However, these nonspecific

agents are often inadequate or poorly tolerated,[10] fail to address the underlying molecular

mechanisms of HCM, and do not modify natural history. Invasive septal reduction therapy

(SRT), including surgical septal myectomy and alcohol septal ablation, can effectively help

patients with drug-refractory symptoms,[6,7] but carries risks inherent to invasive procedures and

requires expertise that is not universally available.[11-13] Thus, developing effective

pharmacological therapy for oHCM is an important unmet need.

Mavacamten is a first-in-class, small molecule, selective allosteric inhibitor of cardiac myosin-

ATPase specifically developed to target the underlying pathophysiology of HCM by reducing

actin-myosin cross-bridge formation, [14,15] thereby reducing contractility and improving

myocardial energetics.[16] In preclinical and early clinical studies, treatment with mavacamten

successfully relieved LVOT gradients and improved parameters of LV filling.[15,17-20] In the phase

2 open-label PIONEER-HCM study (NCT02842242), mavacamten was well tolerated and

significantly reduced post-exercise LVOT gradients in oHCM.[19] Treatment was also associated

with improvements in exercise capacity and New York Heart Association (NYHA) functional

class. Based on these results, the pivotal EXPLORER-HCM trial (NCT03470545) was

155 conducted to assess the efficacy and safety of mavacamten for targeted medical treatment of

156 oHCM.

157 **METHODS**

158 **Trial Design and Oversight**

159 EXPLORER-HCM was a phase 3, multicenter, randomized, double-blind, placebo-controlled,

160 parallel-group trial. The trial design was published previously,[21] and the protocol was approved

161 by site institutional review boards at 68 sites in 13 countries and conducted in accordance with

162 the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided informed

163 consent. The trial was overseen by a Steering Committee, independent data monitoring

164 committee, and a clinical event adjudication committee. Data were collected, managed, and

165 analyzed by the sponsor according to a predefined statistical analysis plan, and results were

166 independently validated by the Duke Clinical Research Institute. Analysis outputs were provided

167 to the investigators/authors who were involved in data interpretation. Both the authors and

168 sponsor employees participated in data analysis and vouch for the accuracy and completeness

169 of the data and fidelity of the trial to the final protocol. The first draft of the manuscript was

170 written by the first author and members of the Steering Committee. All authors critically

171 reviewed and approved the manuscript.

172 **Patients**

173 The inclusion and exclusion criteria were primarily developed to prioritize safety and include a

174 patient population adequately representative of a real-world symptomatic oHCM. Eligible

175 patients were at least 18 years old with a diagnosis of oHCM (unexplained LV hypertrophy with

176 maximal LV wall thickness of ≥15 mm [or ≥13 mm if familial HCM]); peak LVOT gradient at least

177 50 mm Hg at rest, after Valsalva maneuver, or post-exercise; LV ejection fraction (LVEF) at

least 55%; and NYHA class II or III symptoms. Patients must have been able to safely perform

upright cardiopulmonary exercise testing (CPET). Key exclusion criteria included a history of

syncope or sustained ventricular tachyarrhythmia with exercise ≤6 months prior to screening,

QT interval corrected using Fridericia's formula (QTcF) >500 ms, paroxysmal or intermittent

atrial fibrillation present on screening electrocardiogram, and persistent or permanent atrial

fibrillation not on anticoagulation for ≥4 weeks and/or not adequately rate-controlled within 6

months prior to screening. Patients who underwent SRT more than 6 months prior to screening

were enrolled if otherwise eligible.[21] Patients were allowed to continue standard HCM medical

therapy except disopyramide (for safety reasons), including monotherapy with beta-blockers or

calcium channel blockers, if dosing remained stable for at least 2 weeks prior to screening and

no changes were anticipated during the study.

Procedures

Patients were randomized 1:1 to receive once-daily treatment with mavacamten (starting dose 5

mg) or placebo for 30 weeks (end of treatment). Randomization was stratified by NYHA class (II

or III), current beta-blocker use (yes/no), ergometer type (treadmill or bicycle), and consent for

cardiovascular magnetic resonance imaging substudy (yes/no). Mavacamten dose adjustments

occurred per a blinded dose titration scheme at weeks 8 and 14. Individualized doses of 2·5, 5,

10, or 15 mg were ultimately administered to achieve target reduction in LVOT gradient less

than 30 mm Hg and a mavacamten plasma concentration between 350 and 700 ng per mL.[21]

Prespecified criteria for temporary discontinuation of study drug, including LVEF less than 50%,

are described in the Supplementary Appendix.

Patients were evaluated every 2 or 4 weeks during the 30-week treatment period. CPET and

post-exercise transthoracic echocardiography (TTE) were performed at screening and week 30.

Resting TTE, electrocardiograms, safety laboratory testing, and determination of mavacamten

202 plasma concentration were performed serially throughout the study. Results were determined by

203 central core laboratories blinded to treatment assignment.[21] Genetic testing for a 60-gene HCM

204 genetic testing panel (if consent provided) was also performed.

205 **End points**

206 The primary end point was a composite to assess clinical response at week 30 compared with

207 baseline, defined as achieving 1) at least 1·5 ml per kg per minute improvement in pVO_2 and at

208 least one NYHA class reduction **OR** 2) at least 3·0 ml per kg per minute improvement in pVO_2

209 and no worsening of NYHA class.

210 Secondary end points included change from baseline to week 30 in post-exercise LVOT

211 gradient, pVO_2, proportion of patients with at least one NYHA class improvement, and measures

212 of patient-reported outcomes (PROs), including Kansas City Cardiomyopathy Questionnaire-

213 Clinical Summary Score (KCCQ-CSS) and HCM Symptom Questionnaire Shortness-of-Breath

214 (HCMSQ-SoB) subscore.[21] These were tested and Type-I error controlled in hierarchical order

215 (sequence as indicated above) upon achieving significance in the primary end point (with two-

216 tailed $p<0.05$ required to proceed). Additional prespecified exploratory end points assessed

217 complete response (all LVOT gradients less than 30 mm Hg and NYHA class I), proportion of

218 patients with improvement in LVOT gradients, and serum concentrations of N-terminal pro B-

219 type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin I (hs-cTnI).

220 Prespecified safety end points included frequency and severity of treatment-emergent adverse

221 events and serious adverse events.

222 **Statistical Analysis**

223   The study was designed to randomize a minimum of 220 patients. The sample size was

224   estimated to provide 96% power to detect a 25% difference between treatment arms in the

225   primary end point, at a two-sided $p < 0.05$.[21]

226   All randomized patients received at least one dose of study drug. Efficacy and safety analyses

227   were based on this population, and efficacy analyses followed intention-to-treat principle.

228   Missing data were not imputed unless prespecified in the statistical analysis plan. The missing

229   NYHA class at week 30 were imputed with week 26 value, if available, in the case of primary

230   end point and NYHA response. Patients with non-evaluable primary end point and NYHA

231   secondary end point were considered as nonresponders, whereas LVOT gradient and pVO_2

232   were analyzed with all available data without imputation performed, and PROs were analyzed

233   with all available data using mixed-effects model repeated measures, which implicitly handles

234   the missing data in the patients that have baseline and ≥1 post-baseline value in the analysis

235   (additional details provided in Supplementary Appendix). The primary efficacy end point and

236   improvement in NYHA class were analyzed using the Cochran–Mantel–Haenszel test for

237   stratified categorical data. Continuous variables in secondary efficacy end points were

238   compared between treatment groups by analysis of covariance (ANCOVA) or by mixed model

239   for repeated measurements. Efficacy was also assessed in prespecified subgroups based on

240   baseline demographic and disease characteristics. Safety data were analyzed using descriptive

241   statistics without statistical inference. SAS version 9.4 was used for statistical analyses. Details

242   are provided in the Supplementary Appendix and Statistical Analysis Plan.

243   This trial is registered with ClinicalTrials.gov, NCT03470545.

244   **Role of funding source**

245   The study was funded by MyoKardia. MyoKardia co-authors were involved in trial design,

246   statistical analysis, data interpretation, and were involved in reviewing the manuscript, in

247 collaboration with academic co-authors. All authors had access to the study data and had final

248 responsibility for the decision to submit for publication.

249 **RESULTS**

250 **Patient Characteristics**

251 From May 2018 to August 2019, 429 adults with oHCM were screened, of which 251 (59%)

252 were enrolled and randomized to mavacamten (123 patients) or placebo (128 patients) (figure

253 S1, Supplementary Appendix). Enrolled patients showed the expected features of oHCM

254 cohorts in terms of mean LV wall thickness, rates of positive HCM family history, and rate of ICD

255 implantation (table 1). Mean age was 58.5 years in both treatment arms, and the study included

256 a broad age range, with 21% of patients aged <50 years, 45% aged 50-64 years, and 34% aged

257 ≥65 years. Baseline characteristics were balanced between groups, except for a smaller

258 proportion of males and patients with a history of atrial fibrillation, and higher baseline NT-

259 proBNP level in the mavacamten arm (table 1). Most patients (73%) had NYHA class II

260 symptoms at baseline, and almost all (92%) were on background beta-blocker or calcium

261 channel blocker therapy – only 4 patients in the mavacamten group and 16 in the placebo group

262 were not on background HCM therapy. Almost all patients were compliant and maintained their

263 background HCM therapy unchanged throughout the study or required minor adjustments (16

264 patients in the mavacamten arm and 10 patients in the placebo arm adjusted dose of beta-

265 blocker therapy). Nineteen patients had prior SRT.

266 Overall, 244 (97·2%) patients completed treatment. Five patients discontinued treatment

267 prematurely (figure S1, Supplementary Appendix); three due to adverse events (two on

268 mavacamten [atrial fibrillation and syncope], one on placebo [sudden death]); two patients

269 withdrew (one on mavacamten, one on placebo). No patients were lost to follow-up.

270 **Efficacy**

271 *Primary End Point*

272 At end of treatment, 36·6% (45 of 123) of patients on mavacamten achieved the primary end

273 point, compared with 17·2% (22 of 128) on placebo (+19·4%, 95% confidence interval [CI] 8·7

274 to 30·1; p=0·0005) (table 2). Furthermore, 20·3% of patients on mavacamten had both at least

275 3·0 ml per kg per minute increase in pVO_2 and at least one class improvement in NYHA class,

276 versus 7·8% on placebo (difference, +12·5% [95% CI, 4·0 to 21·0]).

277

278 *Secondary End Points*

279 Mavacamten treatment was associated with significant improvement in all secondary end points

280 compared with placebo (table 2), with patients showing reduced LVOT gradient, increased

281 pVO_2, and improved symptoms as assessed by physicians (NYHA class) or by themselves

282 (PROs). Peak post-exercise LVOT gradient decreased from 86 mm Hg (95% CI, 79·5 to 91·8)

283 to 38 mm Hg (95% CI, 32·3 to 44·0) with mavacamten, while for placebo the change was from

284 84 mm Hg (95% CI, 78·4 to 91·0) to 73 mm Hg (95% CI, 67·2 to 79·6) (figure 1A),

285 demonstrating a greater reduction by 36 mm Hg with mavacamten (95% CI, −43·2 to −28·1;

286 p<0·0001) (table 2).

287 In parallel, patients on mavacamten showed a greater increase in pVO_2 by 1·4 ml per kilogram

288 per minute on average compared with placebo (95% CI, 0·58 to 2·12; p=0·0006). Also, 65·0%

289 (80 of 123) of mavacamten-treated patients had at least one NYHA class improvement versus

290 31·3% (40 of 128) on placebo (difference, 33·8% [95% CI, 22·2 to 45·4]; p<0·0001). The

291 proportion of patients who achieved NYHA class I status was 50% (61 of 123) with mavacamten

292 and 21% (27 of 128) with placebo (figure 2). Mavacamten treatment was also associated with

293 improved PROs. Both KCCQ-CCS (positive change better) and HCMSQ-SoB (negative change

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294   better) scores improved more with mavacamten than with placebo (+9·1 [95% CI, 5·5 to 12·7],

295   −1·8 [95% CI, −2·4 to −1·2], respectively; p<0·0001 for both comparisons).

296   *Exploratory End Points*

297   Patients treated with mavacamten showed rapid and sustained improvement in resting and

298   Valsalva LVOT gradients compared with placebo (figure 1C-D). Complete response (defined as

299   reduction in all LVOT gradients to less than 30 mm Hg and NYHA class I) was achieved by

300   27·4% (32 of 117) of patients on mavacamten versus 0·8% (1 of 126) on placebo (+26·6%; 95%

301   CI, 18·3 to 34·8) (table 3). Mavacamten treatment relieved LVOT obstruction (post-exercise

302   gradient less than 30 mm Hg) in 50% more patients (64 of 113 [57%] vs 8 of 114 [7%]; 95% CI,

303   39·3 to 59·9), and reduced it below the standard threshold for invasive SRT (<50 mm Hg) in

304   54% more patients (75 of 101 [74%] vs 22 of 106 [21%]; 95% CI, 42·0 to 65·0) compared with

305   placebo (table 3). In contrast to the sharp decline in LVOT gradients, changes in baseline

306   systolic function associated with mavacamten were small: mean reduction in LVEF was –3·9%,

307   versus–0·01% with placebo (difference, –4·0%; 95% CI, –5·5 to –2·5) (figure 1B). Decreases in

308   cardiac biomarkers were similarly rapid and sustained, parallel to the hemodynamic changes

309   observed (figure 1E-F). At week 30 compared with baseline, the reduction in NT-proBNP after

310   mavacamten treatment was 80% greater than for placebo (proportion of geometric mean ratio

311   between the two arms, 0·202 [95% CI, 0·169 to 0·241]); reduction in hs-cTnI was 41% greater

312   (0·589 [95% CI, 0·500 to 0·693]).

313   *Subgroup Analyses*

314   Patients treated with mavacamten showed consistent benefit for the primary end point across

315   prespecified subgroups. We further examined the subgroups of patients receiving versus not

316   receiving background beta-blockade therapy. Importantly, the majority of patients not using

317   beta-blockers were prescribed non-dihydropyridine calcium channel blockers, with very few

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318   patients in each treatment arm taking neither (4 of 123 in the mavacamten group and 16 of 128

319   in the placebo were not on any background HCM therapy). In patients without concomitant beta-

320   blockade, the effect was greater (29 on mavacamten, 33 on placebo; difference 52·6% [95% CI,

321   32·9 to 72·2]) versus those on beta-blockers (94 on mavacamten, 95 on placebo; difference

322   8·7% [95% CI, —3·6 to 21·1]), and this observation remained in a multivariable model after

323   adjusting for baseline covariates (figure 3A). As expected, the mean peak heart rate with

324   exercise tended to be lower for the subgroup of patients using beta-blockers compared with

325   those not using beta-blockers (119 bpm vs 138 bpm, respectively at baseline). Similarly, mean

326   pVO_2, a component of the primary end point, was lower for the beta-blocker subgroup at

327   baseline, and the mean (SD) change at week 30 in pVO_2 was also observed to be lower (1·1

328   [3·1] ml/kg/min) for patients using beta-blockers compared with (2·2 [3·0] mL/kg/min) for those

329   who were not using beta-blockers. Heart rate independent parameters of CPET, including

330   VE/VCO_2 slope, showed improvements with mavacamten treatment compared to placebo

331   irrespective of beta-blocker use. The VE/VCO_2 slope change from baseline at week 30 was

332   —2·5 (95% CI, —3·7 to —1·4) in the beta-blocker subgroup, —2·5 (95% CI —4·8 to —0·2) in the

333   non-beta-blocker subgroup, and —2·6 (95% CI —3·6 to —1·5) in the overall cohort. Rates of

334   improvement by at least one NYHA class with mavacamten treatment were also similar among

335   patients receiving beta-blockers or not (65%). Furthermore, all secondary end points, including

336   change in LVOT gradient (figure 3B), showed consistent benefit for mavacamten across

337   prespecified subgroups, irrespective of beta-blocker use.

338   **Safety**

339   Treatment-emergent adverse events were largely mild (table 4 and table S1, Supplementary

340   Appendix). Eleven serious adverse events were reported by 8·1% of patients on mavacamten

341   versus 20 events reported by 8·6% on placebo (table 4). Serious cardiac adverse events

342   occurred in four patients in the mavacamten group (two atrial fibrillation, two stress

343 cardiomyopathy; one of these presented at time of a study visit and simultaneously triggered a

344 temporary discontinuation for LVEF less than 50% (table S2, Supplementary Appendix) and four

345 in the placebo group (three with atrial fibrillation, one with atrial fibrillation and congestive heart

346 failure). One patient in the placebo group experienced sudden death. Overall, nine patients

347 (seven on mavacamten and two on placebo) had a transient decrease in LVEF to less than

348 50%. Five patients (three on mavacamten, two on placebo) had protocol-driven temporary

349 treatment discontinuation for LVEF less than 50% during the 30-week treatment (median LVEF

350 48%, range 35 to 49%; table S2, Supplementary Appendix). LVEF normalized in all patients,

351 and they resumed treatment and completed the study. Four additional patients on mavacamten

352 had LVEF less than 50% (range 48 to 49%) at week 30 (end-of-treatment visit). LVEF was

353 confirmed to recover to baseline after the 8-week washout period in three patients. The fourth

354 patient experienced a procedural complication and severe LVEF drop following atrial fibrillation

355 ablation during the washout period, followed by partial recovery (to LVEF 50%). Six patients

356 (three on mavacamten, three on placebo) met predefined criteria for changes in QT interval

357 corrected using Fridericia's formula and underwent temporary discontinuation followed by

358 resumption and completion of treatment. There were no temporary discontinuations for

359 mavacamten plasma concentration greater than 1000 ng per ml.

360 There were no treatment differences noted on laboratory values, ECGs, or vital signs at rest,

361 including no significant changes in heart rate and blood pressure from baseline to week 30 with

362 mavacamten. Continuous cardiac monitoring with 48-hour Holter was conducted at baseline,

363 week 12, and week 26. There were no significant differences during treatment between groups

364 in the number (%) of patients with any atrial fibrillation detected (eg, in each group there were 2

365 [2%] at week 12 and 4 [3.5%] at week 26). There were similar numbers of patients with

366 episodes of non-sustained ventricular tachycardia (NSVT) detected in each group and at each

367 timepoint (eg, n [%] at baseline: 35 [31%] in the mavacamten group and 35 [30%] in the placebo

368   group; week 12: 26 [26%] with mavacamten vs 33 [34%] with placebo, and week 26: 24 [21%]

369   with mavacamten vs 23 [20%] with placebo). The summary of episodes per subject at each time

370   point showed 1.5-2 times more episodes in patients on placebo compared to those on

371   mavacamten.

372

373   **DISCUSSION**

374   In this phase 3 trial in symptomatic oHCM, treatment with mavacamten, a first-in-class cardiac

375   myosin inhibitor, was well tolerated and superior to placebo across the primary and all

376   secondary end points. Mavacamten treatment was effective in reducing LVOT gradients and

377   improving symptoms, exercise performance, and health status in a representative population of

378   patients with oHCM. Significantly more patients treated with mavacamten achieved the primary

379   end point that leveraged both objective (pVO_2) and subjective (NYHA class) assessments of

380   functional capacity and symptoms. Specifically, the proportion improving at least one NYHA

381   class or achieving both primary end point components (at least 3·0 ml per kg per minute pVO_2

382   increase and at least one NYHA class improvement) was 34% and 13% greater, respectively,

383   than placebo. Findings were consistent across all secondary efficacy end points. Furthermore,

384   complete response, defined as reduction in all LVOT gradients below 30 mm Hg and reaching

385   NYHA class I, was achieved in 27% of patients treated with mavacamten and <1% of patients

386   on placebo, demonstrating that mavacamten may be capable of achieving marked relief of

387   symptoms and LVOT obstruction. Assessing severely symptomatic oHCM patients eligible for

388   SRT, the VALOR-HCM study (NCT04349072) will investigate the ability of mavacamten to

389   provide a non-invasive treatment option reducing the need for surgical or percutaneous

390   procedures.

391   PRO assessments, using KCCQ-CSS and the novel HCMSQ-SoB specifically designed to

392   evaluate symptomatic burden in HCM patients, showed a favorable impact of mavacamten on

393   subjective well-being. Notably, the improvement seen in KCCQ-CSS scores is several-fold

394   higher than that observed in recent heart failure drug trials and is nearly half of that achieved

395   with placement of a left ventricular assist device for end-stage heart failure.[22,23] Clinical benefit

396   was sustained, achieved in addition to treatment with beta-blockers or calcium antagonists and

397   accompanied by a reduction in serum NT-proBNP and hs-cTnI levels, two predictors of long-

398   term outcome in HCM.[24-26] Similar decreases in cardiac biomarkers were recently reported in

399   the MAVERICK-HCM study in nonobstructive patients, suggesting that gradient reduction may

400   only partially explain the benefit observed in EXPLORER-HCM.[20] These effects require further

401   investigation in a translational setting.[16,18]

402   Benefit from mavacamten extended across most prespecified subgroups. Not unexpectedly,

403   patients receiving concomitant beta-blockers showed an attenuated effect on the composite

404   primary end point, which includes pVO_2, compared with those not on beta-blockers. We do not

405   believe that the use of beta-blockers attenuates the primary mechanism by which mavacamten

406   works, as is evident by the extent of gradient reduction and other improvements observed.

407   Rather, the observed effect on the primary end point is related to the well-established heart rate

408   limitations on CPET performance.[27,28] Indeed, the mean peak heart rate with exercise tended to

409   be lower for the subgroup of patients using beta-blockers compared with those not using beta-

410   blockers. Improvements in mean pVO_2, were smaller for patients receiving versus not receiving

411   background beta-blockers. However, the change in VE/VCO_2 slope, a heart-rate independent

412   CPET parameter associated with cardiac output,[29] showed similar improvements with

413   mavacamten versus placebo regardless of beta-blocker use, and where the starting mean

414   VE/VCO_2 slope for each was at levels associated with elevated risk for mortality in patients with

415   chronic heart failure (e.g., 33 to 35). In terms of hemodynamic status, symptoms and general

416 well-being as well as reductions in biomarkers of cardiac wall stress and injury (outcomes and

417 assessments not captured by CPET performance), patients on background beta-blockers

418 benefitted the same as those not on beta-blockers. Further detailed analyses of this finding will

419 be pursued in a future study.

420 Mavacamten was generally well tolerated, whether used with beta-blockers or calcium channel

421 blockers, and/or in those with prior, unsuccessful SRT or as monotherapy in a small number of

422 patients. Only modest reductions in mean global LV systolic function were observed, with seven

423 patients on mavacamten (four patients at the end of treatment) developing LVEF less than 50%,

424 which normalized after temporary interruption of therapy in all patients and did not impact study

425 completion. Otherwise, the safety profile of mavacamten was comparable to that of placebo.

426 Studies are ongoing to assess the long-term efficacy and safety of mavacamten over 5 years

427 (MAVA-LTE; NCT03723655).

428 Study limitations include the exclusion of patients on disopyramide and patients with severe

429 (NYHA class IV) symptoms. Both populations will be examined in the VALOR-HCM study.

430 Furthermore, younger patients and non-Caucasians had low representation in this study.

431 In conclusion, in this first positive randomized phase 3 trial in patients with oHCM, mavacamten

432 treatment improved functional capacity, LVOT gradient, symptoms, and key aspects of health

433 status. The results of this pivotal trial support a role for disease-specific treatment in HCM.

434 **Contributors**

435 IO, AJS, JME, CBW, SJL, AW, DZ, CYH, and DJ designed the trial and study protocol and

436 contributed to data analysis. IO, DJ, and CYH drafted the manuscript. DZ and WL were

437 responsible for statistical analysis. IO, A Oreziak, RB-V, TPA, AM, PG-P, SS, NKL, MTW, A

438 Owens, MK, WW, MKJ, JG-B, KA, JM, SMH, SDS, SJL, AW, CYH, and DJ participated in data

439   collection. All authors contributed to data interpretation and the critical review and revision of the

440   manuscript, had access to the study data, and had final responsibility for the decision to submit

441   for publication.

Declaration of interests

443   IO has received grants from MyoKardia, Sanofi-Genzyme, Shire, and Bayer; personal fees from

444   Sanofi-Genzyme, Shire, and Bayer; payments as a consultant from MyoKardia. AM has

445   received grants from Pfizer and Akcea. SS, NKL, A Owens, and SMH report personal fees from

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448   Gilead, GlaxoSmithKline, Ionis, Lone Star Heart, Mesoblast, National Institutes of

449   Health/National Heart, Lung, and Blood Institute, Novartis, Sanofi Pasteur, Theracos; and

450   personal fees from MyoKardia, Alnylam, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb,

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453   Janssen, Tenaya, and Cardiac Dimensions. AJS, DZ, WL, MB, JME, and CBW are employees

454   of MyoKardia and report stocks or stock options from MyoKardia. SJL has received payments

455   as a consultant from MyoKardia. AW has received grants from MyoKardia; personal fees from

456   Cytokinetics; and payments as a consultant from MyoKardia. CYH has received payments as a

457   consultant from MyoKardia and Ambry Genetics Corp. DJ has received personal fees from

458   MyoKardia. All other authors declare no competing interests.

Data sharing

460   Data request may be submitted to MyoKardia via medinfo@myokardia.com and must include a

461   description of the research protocol.

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FIGURE LEGENDS

Figure 1: **LVOT gradients, LVEF, and cardiac biomarkers over time**

Mean (95% CI) post-exercise LVOT gradient over time (panel A), LVEF (panel B), resting LVOT

gradient (panel C), and Valsalva LVOT gradient (panel D). Geometric mean (95% CI) over time

is shown for NT-proBNP (panel E) and hs-cTnI (panel F). The dashed lines represent the

threshold for guideline-based invasive intervention (LVOT gradient >50 mm Hg) in panels A and

D, the threshold for guideline-based diagnosis of obstruction (LVOT gradient <30 mm Hg) in

panel C, and the protocol threshold for temporary discontinuation (LVEF<50%) in panel B. hs-

cTnI=high-sensitivity cardiac troponin I. LVEF=left ventricular ejection fraction. LVOT=left

ventricular outflow tract. NT-proBNP=N-terminal pro B-type natriuretic peptide.

Figure 2. **Change in NYHA Functional Class over Time.**

Percentage of patients who had NYHA class I, II, or III at baseline, after 14 and 30 weeks of

treatment, reported for mavacamten and placebo groups. NYHA=New York Heart Association.

Figure 3: **Forest plot of treatment effect on primary end point and post-exercise LVOT**

gradient by subgroups

Panel A shows the mean difference in patients meeting the primary end point. The dashed

vertical line (overall effect) represents the between-treatment group difference in the overall

study cohort (19·4), and the solid vertical line (no effect) indicates no difference between

treatment groups. Panel B shows the mean difference in LVOT gradient reduction between

mavacamten and placebo. The dashed vertical line (overall effect) represents the between-

treatment group difference in the overall study cohort (−36 mm Hg). The solid vertical line

indicates findings if there was no difference between treatment groups. Patients with non-

evaluable primary end point were considered as nonresponders. BMI=body mass index.

HCM=hypertrophic cardiomyopathy. LVEF=left ventricular ejection fraction. LVOT=left

574   ventricular outflow tract. NT-proBNP=N-terminal pro B-type natriuretic peptide. NYHA=New

575   York Heart Association. VUS=variant of uncertain significance.

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601   *Table 1:* **Baseline demographics and patient characteristics***

Characteristic	Mavacamten (N = 123)	Placebo (N = 128)
Age — yr	58·5±12.2	58·5±11·8
Female sex — no. (%)	57 (46·3)	45 (35·2)
White race — no. (%)	115 (93·5)	114 (89·1)
Region — no. (%)		
United States	53 (43·1)	55 (43·0)
Non-United States	70 (56·9)	73 (57·0)
HCM genetic testing performed — no. (%)	90 (73·2)	100 (78·1)
Pathogenic/likely pathogenic HCM gene variant — no./ no. tested (%)	28/90 (31·1)	22/100 (22·0)
Family history of HCM — no. (%)	33 (26·8)	36 (28·1)
History of atrial fibrillation — no. (%)	12 (9·8)	23 (18·0)
History of septal reduction therapy — no. (%)	11 (8·9)	8 (6·3)
History of hypertension — no. (%)	57 (46·3)	53 (41·4)
History of hyperlipidaemia — no. (%)	27 (22·0)	39 (30·5)
History of coronary artery disease — no. (%)	12 (9·8)	6 (4·7)
History of obesity — no. (%)	15 (12·2)	14 (10·9)
History of type 2 diabetes mellitus — no. (%)	6 (4·9)	7 (5·5)
History of asthma — no. (%)	17 (13·8)	11 (8·6)
History of chronic obstructive pulmonary disease — no. (%)	2 (1·6)	3 (2·3)
Background HCM therapy — no. (%)		
Beta-blocker	94 (76·4)	95 (74·2)
Calcium channel blocker	25 (20·3)	17 (13·3)
ICD — no. (%)	27 (22·0)	29 (22·7)

Body-mass index — kg/m^2	29·7±4·9	29·2±5·6
Heart rate — beats/min	63±10·1	62±10·6
Blood pressure — mm Hg		
Systolic	128±16·2	128±14·6
Diastolic	75±10·8	76±9·9
NYHA functional class — no. (%)		
II	88 (71·5)	95 (74·2)
III	35 (28·5)	33 (25·8)
pVO$_2$ — ml/kg/min	18·9±4·9	19·9±4·9
NT-proBNP, geometric mean (CV%) — ng/L†	777 (136)	616 (108)
hs-cTnI, geometric mean (CV%) — ng/L‡	12·5 (208)	12·5 (373)
Echocardiographic parameters		
LVEF — %	74±6	74±6
Maximum LV wall thickness — mm	20±4	20±3
LVOT gradient, rest — mm Hg	52±29	51±32
LVOT gradient, Valsalva — mm Hg	72±32	74±32
LVOT gradient, post-exercise — mm Hg§	86±34	84±36
LA volume index — ml/m^2‖	40±12	41±14
LA diameter — mm¶	42±5.3	42±6.0

602   *Plus–minus values are means ±SD, unless otherwise shown.

603   †Data on NT-proBNP were missing in three patients in the mavacamten group and two patients

604   in the placebo group. The variation numbers (CV%) are coefficient of variation, which is defined

605   as the ratio of the standard deviation to the mean.

606   ‡Data on hs-cTnI were missing in three patients in the mavacamten group and nine patients in

607   the placebo group.

608   §Data on post-exercise LVOT gradient were missing in one patient in the mavacamten group

609   and one patient in the placebo group.

610   ‖Data on LA volume index were missing in one patient in the mavacamten group.

611   ¶Data on LA diameter were missing in five patients each in the mavacamten and placebo

612   groups.

613   HCM=hypertrophic cardiomyopathy. hs-cTnI=high sensitivity-cardiac troponin I.

614   ICD=implantable cardioverter-defibrillator. LA=left atrial, LVEF=left ventricular ejection fraction.

615   LVOT=left ventricular outflow tract. NYHA=New York Heart Association. NT-proBNP=N-terminal

616   pro B-type natriuretic peptide. pVO_2=peak oxygen consumption.

Table 2: **Primary and secondary end points***

	Mavacamten (N = 123)	Placebo (N = 128)	Difference† (95% CI) p value
Primary End Point§			
EITHER ≥1·5 ml/kg/min increase in pVO$_2$ with ≥1 NYHA class improvement **OR** ≥3·0 ml/kg/min increase in pVO$_2$ with no worsening of NYHA class — no. (%)	45 (36·6)	22 (17·2)	19·4 (8·7 to 30·1) 0·0005
≥1·5 ml/kg/min increase in pVO$_2$ with ≥1 NYHA class improvement — no. (%)	41 (33·3)	18 (14·1)	19·3 (9·0 to 29·6)
≥3·0 ml/kg/min increase in pVO$_2$ with no worsening of NYHA class — no. (%)	29 (23·6)	14 (10·9)	12·6 (3·4 to 21·9)
BOTH ≥3·0 ml/kg/min increase in pVO$_2$ **AND** ≥1 NYHA class improvement — no. (%)	25 (20·3)	10 (7·8)	12·5 (4·0 to 21·0)
Secondary End Points‡			
Post-exercise LVOT gradient			
Change from baseline to week 30 — mm Hg	−47±40 (n = 117)	−10±30 (n = 122)	−36 (−43·2 to −28·1) <0·0001
pVO$_2$			
Change from baseline to week 30 — ml/kg/min	1·40±3·1 (n = 120)	−0.05±3·0 (n = 125)	1·35 (0·58 to 2·12) 0·0006
≥1 NYHA class improvement§			
Improvement from baseline to week 30 — no. (%)	80 (65·0) (n = 123)	40 (31·3) (n = 128)	34 (22·2 to 45·4) <0·0001
KCCQ-CSS‖			
Change from baseline to week 30 in KCCQ-CSS	13·6±14·4 (n = 92)	4·2±13·7 (n = 88)	9·1 (5·5 to 12·7) <0·0001
HCMSQ-SoB‖			

Change from baseline to week 30 in HCMSQ-SoB	−2·8±2·7 (n = 85)	−0·9±2·4 (n = 86)	−1·8 (−2·4 to −1·2) <0·0001

*Plus–minus values are means ±SD.

†Model estimated least-square mean differences were reported for continuous variables.

‡N = number analyzable for secondary end point based on availability of both baseline and week 30 values.

§Patients with non-evaluable primary end point and NYHA secondary end point were considered as nonresponders. The response rates were calculated with N value as the denominator.

||Due to the smaller numbers evaluable for PRO end points, additional post-hoc analyses comparing the reasons for missing data were performed. Baseline demographic and disease characteristics, and key efficacy and safety parameters for patients with or without missing data in KCCQ-CSS or HCMSQ-SoB revealed no consistent pattern of differences between those groups. Furthermore, worst case scenario analyses showed that, even after imputing the missing data with unfavorable results toward the mavacamten group, the estimated treatment effects on KCCQ-CSS or HCMSQ-SoB remained statistically significant ($p<0·05$). These analyses supported the notion that missingness-at-random assumption was not violated. Data in the Table reflect the pre-specified analyses.

HCMSQ-SoB=Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath Score. KCCQ-CSS=Kansas City Cardiomyopathy Questionnaire-Clinical Symptom Score. LVOT=left ventricular outflow tract. NYHA=New York Heart Association. pVO_2=peak oxygen consumption.

Table 3: **Key exploratory efficacy end points**

	Mavacamten	**Placebo**	**Difference (95% CI)**
Complete response — no./total no. (%)*	32/117 (27·4)	1/126 (0·8)	26·6 (18·3, 34·8)
Post-exercise LVOT peak gradient <50 mm Hg — no./total no. (%)†	75/101 (74·3)	22/106 (20·8)	53·5 (42·0· 65·0)
Post-exercise LVOT peak gradient <30 mm Hg — no./total no. (%)‡	64/113 (56·6)	8/114 (7·0)	49·6 (39·3, 59·9)

*Defined as New York Heart Association class I and all LVOT peak gradients less than 30 mm Hg (post-exercise, resting, and Valsalva).

†Threshold for guideline-based invasive intervention. Only patients with baseline post-exercise LVOT peak gradient at least 50 mm Hg were assessed.

‡Threshold for guideline-based diagnosis of obstruction. Only patients with baseline post-exercise LVOT peak gradient at least 30 mm Hg were assessed.

LVOT=left ventricular outflow tract.

Table 4: **Summary of treatment-emergent adverse events and serious adverse events**

Adverse Events Preferred Term	Mavacamten N = 123	Placebo N = 128
Patients with ≥1 treatment-emergent adverse event — no. (%)	108 (87·8)	101 (78·9)
Total number of serious adverse events	11	20
Patients with ≥1 serious adverse event — no. (%)	10 (8·1)	11 (8·6)
Atrial fibrillation	2 (1·6)	4 (3·1)
Syncope	2 (1·6)	1 (0·8)
Stress cardiomyopathy	2 (1·6)	0
Sudden death	0	1 (0·8)
Transient ischemic attack	0	1 (0·8)
Cardiac failure congestive	0	1 (0·8)
Diverticulitis	1 (0·8)	0
Viral gastroenteritis	0	1 (0·8)
Urinary tract infection	0	2 (1·6)
Infection	1 (0·8)	0
Rheumatoid arthritis	0	1 (0·8)
Contusion	1 (0·8)	0
Forearm fracture	1 (0·8)	0
Dehydration	0	1 (0·8)
Vocal cord polyp	0	1 (0·8)
Cholesteatoma	0	1 (0·8)
Prostate cancer	0	1 (0·8)

FIGURES

Figure 1: **Changes in LVOT gradient, LVEF, and cardiac biomarkers over time**

Figure 2: **Change in NYHA functional class over time.**

group

NYHA functional class
■ Class I ■ Class II ■ Class III ■ Missing

Figure 3: Forest plot of treatment effect on primary end point and post-exercise LVOT gradient by subgroups

A.

Subgroup	Mean difference, % (95% CI)	Mavacamten N (% response)	Placebo N (% response)	Difference, % (95% CI)
Age – yrs				
≤49		27 (37.0)	25 (24.0)	13.0 (−11.7 to 37.8)
50-64		51 (41.2)	63 (20.6)	20.5 (3.7 to 37.3)
≥65		45 (31.1)	40 (7.5)	23.6 (7.8 to 39.4)
Sex				
Female		57 (33.3)	45 (11.1)	22.2 (6.9 to 37.5)
Male		66 (39.4)	83 (20.5)	18.9 (4.3 to 33.6)
BMI – kg/m^2				
<30		77 (45.5)	77 (20.8)	24.7 (10.3 to 39.0)
≥30		46 (21.7)	51 (11.8)	10.0 (−4.9 to 24.8)
LVEF at baseline – %				
<75		69 (36.2)	70 (15.7)	20.5 (6.3 to 34.7)
≥75		54 (37.0)	58 (19.0)	18.1 (1.7 to 34.4)
NYHA class at baseline				
Class II		88 (33.0)	95 (16.8)	16.1 (3.7 to 28.5)
Class III		35 (45.7)	33 (18.2)	27.5 (6.4 to 48.6)
Beta-blocker usage at baseline				
Yes		94 (29.8)	95 (21.1)	8.7 (−3.6 to 21.1)
No		29 (58.6)	33 (6.1)	52.6 (32.9 to 72.2)
Type of exercise testing				
Bicycle		55 (27.3)	58 (19.0)	8.3 (−7.2 to 23.8)
Treadmill		68 (44.1)	70 (15.7)	28.4 (13.8 to 43.0)
NT-proBNP at baseline – ng/L				
≤Median		55 (32.7)	68 (19.1)	13.6 (−1.9 to 29.1)
>Median		65 (36.9)	58 (15.5)	21.4 (6.4 to 36.4)
HCM genetic testing result				
Pathogenic or likely pathogenic		28 (57.1)	22 (27.3)	29.9 (3.7 to 56.0)
VUS		32 (40.6)	43 (18.6)	22.0 (1.4 to 42.6)
Negative		30 (20.0)	35 (11.4)	8.6 (−9.2 to 26.3)

−20 0 20 40 60 80

← Favors placebo   Favors mavacamten →

B.

Subgroup	Mean difference, mm Hg (95% CI)	Mavacamten N (mean)	Placebo N (mean)	Difference, mm Hg (95% CI)
Age – yrs				
≤49		26 (−37.0)	23 (−12.2)	−24.8 (−41.4 to −8.1)
50-64		48 (−57.1)	61 (−12.2)	−44.9 (−59.2 to −30.6)
≥65		43 (−42.5)	38 (−6.5)	−36.0 (−51.5 to −20.5)
Sex				
Female		54 (−47.9)	43 (−5.5)	−42.4 (−57.7 to −27.1)
Male		63 (−46.7)	79 (−13.1)	−33.6 (−44.8 to −22.4)
BMI – kg/m²				
<30		72 (−47.5)	74 (−9.9)	−37.6 (−48.7 to −26.5)
≥30		45 (−46.9)	48 (−11.3)	−35.6 (−51.1 to −20.1)
LVEF at baseline – %				
<75		66 (−52.8)	64 (−7.6)	−45.2 (−58.0 to −32.5)
≥75		51 (−40.1)	58 (−13.6)	−26.5 (−39.0 to −14.0)
NYHA class at baseline				
Class II		82 (−48.7)	90 (−10.3)	−38.4 (−49.1 to −27.7)
Class III		35 (−43.9)	32 (−10.9)	−33.0 (−50.1 to −15.9)
Beta-blocker usage at baseline				
Yes		89 (−47.1)	92 (−9.1)	−37.9 (−48.0 to −27.9)
No		28 (−47.9)	30 (−14.4)	−33.5 (−53.6 to −13.3)
Type of exercise testing				
Bicycle		51 (−48.2)	57 (−11.4)	−36.9 (−49.8 to −23.9)
Treadmill		66 (−46.5)	65 (−9.6)	−36.9 (−49.5 to −24.2)
NT-proBNP at baseline – ng/L				
≤Median		53 (−48.8)	64 (−10.0)	−38.8 (−51.9 to −25.6)
>Median		61 (−45.7)	56 (−11.6)	−34.1 (−47.1 to −21.1)
HCM genetic testing result				
Pathogenic or likely pathogenic		25 (−49.8)	21 (−10.5)	−39.4 (−60.6 to −18.1)
VUS		32 (−49.5)	40 (−12.7)	−36.8 (−51.8 to −21.9)
Negative		28 (−38.9)	34 (−7.9)	−31.0 (−48.8 to −13.2)

−80 −60 −40 −20 0 20

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