Health Status Benefits of Mavacamten in Patients With Symptomatic Obstructive Hypertrophic Cardiomyopathy: Results From the EXPLORER-HCM Randomized Clinical Trial

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Research in Context

Evidence before this study

Obstructive hypertrophic cardiomyopathy (oHCM) is a primary myocardial disorder characterized by left ventricular (LV) hypertrophy, hyperdynamic contraction, and impaired relaxation related to excessive cardiac actin-myosin interactions. A primary goal of treating patients with oHCM is to improve their health status: their symptoms, function, and quality of life. While there have been no major advances for treating the symptoms or pathophysiology of oHCM treatment in more than 30 years, mavacamten, a direct myosin inhibitor, has recently been shown to reduce post-exercise LV outflow tract gradients in the phase 2 PIONEER-HCM study, which was confirmed in a pivotal phase 3 placebo-controlled randomized trial, EXPLORER-HCM. EXPLORER-HCM, the largest placebo-controlled trial in oHCM to date, demonstrated that treatment with mavacamten for 30 weeks resulted in a substantially greater proportion of patients having a ≥1.5 mL/kg/min increase in peak oxygen consumption with an improved, physician-assessed New York Heart Association (NYHA) class, or a ≥3 mL/kg/min increase in peak oxygen consumption without a deterioration in NYHA class. A more complete understanding of the impact of mavacamten on patients' health status from the patients' perspective is needed.

Added value of this study

Using the Kansas City Cardiomyopathy Questionnaire (KCCQ), a validated, reliable, and sensitive measure of patients' health status, we found large, clinically important improvements in the KCCQ Overall Summary score, and each of its sub-domains, throughout 30 weeks of treatment. Moreover, these benefits regressed 8 weeks after stopping treatment. These benefits were clinically important, with an estimated absolute difference in the proportions of patients experiencing very large clinical improvements (change in KCCQ Overall Summary score ≥20 points) of 21% (95% CI=8.8%, 33.4%) and number

needed to treat for a very large benefit of 5 (95%CI=3, 11). Once treatment was stopped, there were no longer significant differences in health status between groups.

Implications of all the available evidence

Extending the original insights from the EXPLORER-HCM trial this study better characterizes the health status benefits of mavacamten and will assist clinicians in describing the potential benefits of treatment to their patients in improving symptoms, function, and quality of life. Moreover, the regression of these benefits after stopping treatment underscores the direct role of myosin inhibition on improving the health status of patients with oHCM.

Summary

Background: Improving symptoms is a primary treatment goal in patients with obstructive hypertrophic cardiomyopathy (oHCM). We tested the impact of mavacamten, a first-in-class cardiac myosin inhibitor, on patients' health status (symptoms, function, and quality of life).

Methods: EXPLORER-HCM was a phase 3, double-blind, randomized, placebo-controlled trial conducted from May 2018 until May 2020 at 68 clinical cardiovascular centers in 13 countries. Adult patients with symptomatic oHCM (N=251; gradient ≥50 mm Hg and New York Heart Association [NYHA] class II-III) were randomly assigned to mavacamten (n=123 [49%]) or placebo (n=128 [51%]) for 30 weeks, followed by an 8-week washout. The primary outcome for this secondary analysis was the Kansas City Cardiomyopathy Questionnaire (KCCQ), a well-validated disease-specific measure of patients' health status. It was administered at baseline and weeks 6, 12, 18, 30 (end of treatment), and 38 (end of study). Changes from baseline to week 30 in KCCQ Overall Summary (OS) score and all subscales were analyzed using mixed model repeated measures. Responder analyses at Week 30 and impact of withdrawing treatment on patients' health status are also described.

Findings: A total of 92 and 88 completed the KCCQ at both baseline and week 30, respectively. At 30 weeks, the change in KCCQ-OS score was greater with mavacamten than placebo (mean ± SD, 14·9±16 vs. 5·4±14; difference=9·1 (95%CI: 5·5-12·8; p<0·001), with similar benefits across all KCCQ subscales. The proportion of patients with a very large change (KCCQ-OS ≥20 points) was 36% [33/92] vs. 15% [13/88], with an estimated absolute difference of 21% (95%CI=88%, 33.4%) and number needed to treat of 5 (95% CI=3, 11). These gains returned to baseline after treatment was stopped.

Interpretation: Mavacamten markedly improved health status of patients with symptomatic oHCM compared with placebo with a low number needed to treat for marked improvement.

Introduction

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder characterized by left ventricular (LV) hypertrophy, hyperdynamic contraction, and impaired relaxation related to excessive cardiac actin-myosin interactions.[1] Patients may experience exercise intolerance, fatigue, shortness of breath, and chest pain.[2] The symptoms of obstructive HCM (oHCM) can have profound effects on peoples' lives.[3,4] The primary goal of treatment for oHCM focuses on alleviating symptoms, but symptomatic improvement has not been prospectively studied with any currently recommended therapies.[5,6] Guideline-recommended pharmacological therapy is thus administered on an empirical basis and includes β-blockers or nondihydropyridine calcium channel blockers, as well as disopyramide for individuals refractory to first-line therapy. These medications were originally developed for other cardiovascular diseases but can be beneficial for some patients with oHCM, although their tolerability can be limited by side effects and they often do not provide optimal control of LV outflow tract (LVOT) gradients and symptoms. For patients refractory to medical management, invasive septal reduction therapy that mechanically reduces septal obstruction may be an alternative to ameliorate symptoms, although its impact on quality of life has not been formally assessed.[7-9] Thus, there is an unmet need for safe, effective, and disease-specific noninvasive therapy for oHCM to improve quality of life and health status.

Significant therapeutic advances in medical therapy for HCM to directly address the pathophysiologic mechanisms of the disease have been lacking for more than 30 years.[2] Against this backdrop, mavacamten, a selective inhibitor of cardiac myosin, has been developed.[10,11] The pivotal EXPLORER-HCM, a phase 3 placebo-controlled randomized trial, was the first and largest clinical study of its kind to prospectively measure patient-reported outcomes in oHCM. It randomly assigned 251 participants with symptomatic oHCM from 68 clinics in 13 countries to active treatment with mavacamten or placebo for 30 weeks with a subsequent washout period.[12,13] The primary outcome, a functional composite of improved peak oxygen consumption and New York Heart Association (NYHA) class significantly favored mavacamten, as compared with placebo. Here, we report the impact of mavacamten treatment on

patients' health status (their symptoms, function, and quality of life) as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ).

Methods

Study Design and Patient Population

The design of the EXPLORER-HCM trial, a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial, has been previously described and registered at www.clinicaltrials.gov (NCT03470545).[12] Briefly, eligible patients were 18 years or older with a diagnosis of oHCM (unexplained LV hypertrophy with maximal LV wall thickness of ≥15 mm [or ≥13 mm if familial HCM]); peak LVOT gradient ≥50 mm Hg at rest, after Valsalva maneuver, or with exercise; LV ejection fraction (LVEF) ≥55%; and NYHA class II–III. Participants had to be able to safely perform upright cardiopulmonary exercise testing. Key exclusion criteria included a history of syncope or sustained ventricular tachyarrhythmia with exercise within 6 months of screening, corrected QT interval using Fridericia's formula >500 ms, and atrial fibrillation at the screening examination. Background β-blocker and nondihydropyridine calcium channel blocker therapy was permitted if dosing remained stable for at least 2 weeks before screening and no changes were anticipated during the study. Dual therapy or disopyramide was not allowed.

Patients were randomly assigned (1:1) to receive once-daily oral mavacamten (starting dose, 5 mg orally per day with dose increases at weeks 8 and 14 to 15 mg per day maximum) or placebo for 30 weeks (end of treatment) followed by an 8-week washout period. Randomization was stratified by NYHA class (II or III), current β-blocker use, ergometer type (treadmill or bicycle), and consent for the cardiovascular magnetic resonance imaging substudy.

The protocol was approved by a central or site-specific institutional review board, as required by the local site, and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical

Practice guidelines. All patients provided written informed consent before any protocol-specific procedures or study drug administration.

Patient-Reported Health Status Assessments

Patient-reported health status was measured using the disease-specific 23-item KCCQ (KCCQ-23),[14] which has a recall period of 2 weeks over which patients describe the frequency and severity of their symptoms, their physical and social limitations, and how they perceive their heart failure symptoms to affect their quality of life. The KCCQ Clinical Summary (KCCQ-CS) score, a prespecified secondary outcome of EXPLORER-HCM, combines the Physical Limitation and Total Symptom scores to mirror the NYHA class from the patient's perspective, while the KCCQ Overall Summary (KCCQ-OS) score combines the Total Symptom, Physical and Social Limitation, and Quality of Life scales to provide a more holistic summary of patients' health status. Linguistically and culturally validated translations were used at each site (www.cvoutcomes.org). Scores for each domain range from 0–100, for which 0 represents the worst symptoms, function, and quality of life and 100 represents the best; scores of 0–24 represent very poor to poor; 25–49, poor to fair; 50–74, fair to good; and 75–100 represents good to excellent health status. The psychometric properties of the KCCQ are sufficiently well-established that the US Food and Drug Administration has qualified the KCCQ as a clinical outcome assessment,[15,16] and a qualitative study of 26 patients was performed to ensure that the concepts of the KCCQ were understood and relevant to patients with oHCM to supplement the limited data of its validity in this population[17] (Appendix 1). The KCCQ is independently associated with mortality, hospitalizations, and costs,[18-20] and changes in the KCCQ-OS score of 5, 10, and 20 points are associated with clinically important small, moderate to large, and large to very large changes from both patients' and providers' perspectives.[21-23] These changes are also significantly and independently associated with mortality and hospitalization rates in patient with heart failure due to reduced and preserved EF, regardless of etiology, although this has not been explicitly demonstrated in oHCM.[24,25]

In EXPLORER-HCM, the KCCQ was administered electronically (using a study-specific app via a provisioned handheld device) before other study procedures at baseline (before or on the first dose day) and at weeks 6, 12, 18, and 30 (end of treatment). It was also administered at week 38 (end of study), 2 months after stopping study medication. Both patients and staff collecting the scores were blinded to study treatment.

Statistical Analyses

The study was analyzed for the KCCQ population, which included all randomly assigned patients who had a baseline KCCQ score and at least one postbaseline KCCQ score. The KCCQ-CS was prespecified as a secondary outcome in EXPLORER-HCM, because this is the scale that the US Food and Drug Administration's Center for Drug Evaluation and Research has qualified as a clinical outcome assessment.[15] We prioritized the KCCQ-OS for these analyses to provide a more complete picture of the impact of treatment on patients' disease-specific health status. All other KCCQ subscales are also reported. Descriptions of patients' baseline characteristics were stratified by treatment group. Changes from baseline in KCCQ scores were presented in the plots of mean values with standard errors over time, including descriptive changes in KCCQ scores by categories of physiologic changes. Comparison of those changes between treatment groups was analyzed using a restricted maximum likelihood-based repeated measures approach (mixed model repeated measures). This approach includes fixed effects for treatment group, visit, baseline KCCQ score, variables used in stratifying treatment allocation (NYHA class, current treatment with a β-blocker, and planned type of ergometer used during the study), and interaction between treatment group and visit. The primary outcome was the change from baseline to week 30. Finally, we examined the impact of withdrawing treatment on patients' health status, as captured by the KCCQ. This was done by comparing the week 38 (end of washout) KCCQ scores with those from the end of treatment (week 30) and at baseline.

To render the population-level differences in KCCQ scores more clinically interpretable, we also performed a comparison across clinically meaningful ranges of change in KCCQ scores from baseline to week 30. In accordance with recent recommendations,[23] scores were categorized into clinically worse (change in score from baseline to week 30 of ≤-5 points), no significant change (>−5 to <5 points), small but clinically important improvement (5 to <10 points), moderate to large clinical improvement (10 to <20 points), and large to very large clinical improvements (≥20 points). The differences in proportions of each category of change were converted into the number needed to treat (NNT) by dividing 1 by the absolute differences in proportions of patients between treatment arms.[26]

Handling of Missing Data

KCCQ data were missing for 71 of 251 patients (28% overall; 31 of 123 treated with mavacamten and 40 of 128 treated with placebo) for the primary comparison of 30-week change in KCCQ outcomes. Extensive investigation was performed to explore potential biases that could be introduced from the missing data. These are fully described in Appendix 2 and include a review of the reasons for missingness submitted in the protocol deviation listings (32 of 71 [45%] due to administrative error or operational issues), comparisons of patient characteristics and treatment responses with and without missing data revealing minimal differences, pattern-mixture models showing comparability of other outcomes in those with and without missing data, and sensitivity analyses examining the impact of implausibly extreme selection biases showing no impact on the statistical significance of health status differences between mavacamten and placebo. Travel restrictions due to the coronavirus disease 2019 (COVID-19) pandemic were the primary reason reported for missing the KCCQ assessment at week 38. Collectively, these analyses do not provide strong evidence of nonrandom missing KCCQ data and therefore the main analyses, including the comparison of the KCCQ changes between treatment groups, are performed on all available data without imputation. To provide an even more conservative estimate of the responder analyses, these were repeated considering all patients with missing data as nonresponders and restricting the analyses to those with the potential to respond by different clinical magnitudes (Appendix 3 Table 1).

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All statistical tests were 2-sided tests without adjustments for multiplicity. P-values <0·05 were considered significant.

Role of the Funding Source

Results

Study Population

Among the 123 patients randomly assigned to mavacamten and 128 randomly assigned to placebo, 92 (75%) and 88 (69%), respectively, completed both the baseline and 30-week KCCQ, although higher rates of questionnaire completion were available at intervening assessments (Appendix 3 Table 2). Baseline characteristics of the 2 groups are shown in Table 1 and demonstrate that the treatment arms were well balanced. Overall, participants had significant LV hypertrophy with marked dynamic outflow obstruction (mean LVOT gradient after exercise, 85·4 mm Hg) and moderately impaired health status (mean baseline KCCQ-OS score, 67·2 [SD 17·2] in the mavacamten arm and 65·7 [19·6] in the placebo

arm), as shown in more detail in Table 1. After randomization, almost all patients continued their background HCM therapy without any changes or with minor adjustments (16 patients in the mavacamten arm and 10 patients in the placebo arm had an adjustment to their beta-blocker dose).

Mean Differences in Health Status by Treatment Group

Figure 1A and 1B shows the mean (SE) changes in KCCQ-OS and -CS scores, respectively, from baseline over time, and Appendix 3 Figures 1A-D show these data for each of the KCCQ domain scores. These figures demonstrate rapid separation of the groups within the first 6 weeks of treatment that is sustained throughout 30 weeks of treatment (p<0·001 for all scales), followed by a rapid diminution of these differences with cessation of study drug. Table 2 shows the least-square mean differences between treatment arms for the change from baseline to 30 weeks in KCCQ scores. At 30 weeks, the mean change from baseline in KCCQ-OS scores (mean [SD]) was 14·9 (15·8) in participants treated with mavacamten and 5·4 (13·7); in those treated with placebo with a difference between groups of 9·1 (95% CI: 5·5-12·8) favoring mavacamten. The subdomains of the KCCQ show substantially similar benefits across all domains, with the numerically largest benefits observed in the Physical Limitation domain.

Categorical Differences in Health Status by Treatment Group

Categories of clinically important thresholds of change for the KCCQ-OS and KCCQ-CS scores from baseline to 30 weeks are shown in Figure 2 and the other scales are shown in Appendix 3 Figure 2. Across all domains of disease-specific health status, and collectively captured by the summary scores, there are marked differences favoring mavacamten in the proportions of patients whose health status worsens and those whose health status substantially improves. Subtracting the differences in the proportions and converting to NNT suggests that for every four to ten patients treated with mavacamten, as compared with placebo, one patient would have a large to very large improvement in their health status, with the greatest benefit being in the Physical Limitation domain. In addition, for every four to eight patients treated with mavacamten, depending on the KCCQ domain, one patient is less likely to

deteriorate over 30 weeks of treatment as compared with placebo treatment, with the most dramatic

numeric difference being in the Quality of Life domain.

Impact of Withdrawing Treatment on Participants' Health Status

As described in Figure 1, among patients with data available at the end of study, cessation of therapy was

associated with a marked deterioration in KCCQ scores by 38 weeks among the 59 participants treated

with mavacamten, but not in the 58 patients treated with placebo (mean [SD] change in the KCCQ-OS

scores from 30 to 38 weeks was −12·9 [16·1] vs. −1·3 [9·7]; p<0·0001). Comparing the 38-week scores

with baseline revealed little difference between either group (KCCQ-OS score, −0·1 [16·5] vs. 4·5 [12·7];

p=0·1; KCCQ-CS score, 1·0 [14·4] vs. 3·0 [13·2]; p=0·4), suggesting that with withdrawal of treatment,

the benefits in health status that patients experienced while treated with mavacamten returned to baseline

levels.

Association of Physiological Parameters with Participants' Health Status

In the EXPLORER-HCM trial 7 patient experienced a reduction in their ejection fractions to below 50%.

Of these, 6 had baseline and 30-week KCCQ scores available for analysis, which revealed similar mean

improvements in their KCCQ scores (mean ± Standard Deviation of Overall Summary = +18·5±19·2

points; Clinical Summary = +13·3±15·2; Physical Limitation = 11·1±9·4; Total Symptom = 15·.5±23·2;

Social Limitation = 12·8±28·2 and Quality of Life = 34·7±25·5). When examining the changes in VO_2

amongst all study participants by the categories of clinically significant change pre-defined in the

EXPLORER-HCM trial, we found a large difference in the mean KCCQ Overall Summary score in those

with the largest improvements in oxygen consumption (+8.7±15 points in those with a <1.5ml/kg/min

improvement, +8.9±14 points improvement in those with a 1.5 to <3ml/kg/min improvement and

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+18±17.2 point improvement in those with a >3.0ml/kg/min improvement in VO$_2$; Appendix 3 Supplemental Figure 3).

Discussion

A principal goal of treating symptomatic patients with oHCM is to alleviate their symptoms so as to improve their function and quality of life.[6] The recent 2020 American Heart Association/American College of Cardiology professional treatment guidelines for patients with HCM identified a clear unmet need for novel trial designs and patient-reported outcome tools to assess the impact of new therapies on meaningful endpoints, such as quality of life. Evidence supporting the health status benefits of alternative therapeutic approaches was limited and the benefits of direct myosin modulation were not available.[27] The EXPLORER-HCM trial showed significant benefits of mavacamten treatment in peak oxygen consumption and clinician-assigned NYHA status.[13] This report extends these initial descriptions of benefit by providing detailed insights into the benefits of treatment on patients' self-reported health status measured by the KCCQ, included as an alpha-controlled prespecified secondary endpoint. We found substantial changes in KCCQ scores, with the greatest benefits being on the Physical Limitation scale, followed by Symptoms, Quality of Life, and Social Limitations, resulting in very large benefits in the overall health status of patients with oHCM. By extending the prior analyses to show the distributions of patients' health status changes,[23] we found that for every five patients treated with mavacamten, one would be likely to have a very large improvement in their health status (an improvement of >20 points at 30 weeks) and one would be less likely to have a deterioration in their health status (a reduction of >5 points at 30 weeks), as reflected by the KCCQ-OS score. These benefits occurred within 6 weeks, were maintained throughout the duration of therapy, and returned to baseline levels when treatment was stopped, supporting the direct benefits of mavacamten on the health status of patients with symptomatic oHCM.

Understanding patients' perspectives of the impact of a disease on their health status (their symptoms, function and quality of life) is becoming an important outcome of clinical investigation. In heart failure, the KCCQ, is increasingly being accepted as a relevant outcome for regulatory approval of new treatments[15,16] and has recently been endorsed as a measure for quantifying the quality of healthcare.[28] Thus, while the primary results from EXPLORER-HCM demonstrated improvements in VO_2, and the KCCQ has been shown to be independently associated with VO_2 in the HF-ACTION trial,[29] providing a richer description of the impact of mavacamten therapy on the health status of patients, from their perspectives, provides important information to better communicate the potential benefits of treatment. Importantly, these data are not necessarily captured by traditional physiological parameters, underscoring the importance of directly assessing and reporting patients' health status outcomes.

The magnitude of benefit observed with mavacamten on the KCCQ is closer to that of percutaneous valvular interventions,[30,31] in which the pathophysiologic mechanism of heart failure is also directly addressed, than it is to other novel therapies for heart failure,[32-34] and the improvements stand in contrast to other recent medical therapies, such as tafamidis, that prevent progression of the disease.[35] Further strengthening the association between mavacamten treatment and improvements in patients' health status is the unprecedented complete reversal of KCCQ improvements observed 8 weeks after treatment withdrawal. This suggests that continuity of therapy will be important to maximize treatment benefits. Because of these directly appreciable benefits of mavacamten for patients with symptomatic oHCM, we think it will be interesting to study the adherence to mavacamten therapy, as the adherence to other guideline-directed medical therapies for heart failure is notoriously poor.[36-38]

More work is needed to better define longer-term outcomes and patient characteristics associated with greater or lesser health status benefits from mavacamten. To better define outcomes beyond 30 weeks of therapy, the EXPLORER-HCM is being extended with open-label follow-up for 5 years to better establish safety and efficacy of treatment over time (MAVA-LTE; NCT03723655). To better define the heterogeneity of treatment benefit, future studies should examine which sociodemographic, clinical, or

physiologic parameters are most strongly associated with the health status benefits of treatment. In particular, more work defining changes of physiologic parameters with variations in health status in oHCM is needed. For example, the intended reduction in ejection fraction with a direct myosin inhibitor resulted in some patients having a transient ejection fraction below 50%, but the KCCQ benefits in these patients were still substantial. Such work is especially important given that the recent guidelines emphasize the importance of shared medical decision making[6] and it would be important to be able to explain to patients how treatment with mavacamten would be expected to improve their health status.

The findings of this study should be interpreted in the context of the following potential limitations. First, a number of randomly assigned patients were missing either baseline or follow-up KCCQ data which could have potentially biased our results. However, extensive analyses suggest that no observable biases were introduced by these missing data. Second, EXPLORER-HCM included patients with hemodynamically significant and symptomatic oHCM. Whether comparable benefits would be observed in other patient populations, such as worse functional NYHA disease, less severe obstruction, or patients with nonobstructive HCM, will require additional study.

In conclusion, mavacamten, a novel myosin inhibitor, is associated with substantial improvements in physical function, symptom relief, and quality of life in patients with symptomatic oHCM. In particular, the proportion of patients with very large (≥20 points) improvements in their KCCQ-OS score is much greater than that of patients randomly assigned to placebo, suggesting that for every five patients treated, one will feel substantially better. These data can support better explanations to patients about the benefits of treatment and align well with the most recent treatment guidelines for oHCM that underscore the importance of shared decision making.[6]

Contributors

JAS wrote the first draft of the manuscript and was responsible for methodology and contributed to data analysis. JTF was responsible for conceptualization and project administration. IO, SS, PE, CYH, and DJ participated in data collection. WL was responsible for the statistical analysis. All authors contributed to data interpretation and the critical review and revision of the manuscript and had final responsibility for the decision to submit for publication. Both the authors and employees of the sponsor participated in data analysis and vouch for the accuracy and completeness of the data.

Declaration of Interests

JAS has received payments as a consultant from MyoKardia, Inc., a wholly owned subsidiary of Bristol Myers Squibb. He owns the copyright to the KCCQ and has provided consultative services to Bayer, Amgen, Merck, Novartis, Janssen, and United Healthcare. He serves on the Board of Directors for Blue Cross Blue Shield of Kansas City. JTF, WL, and AJS are employees of MyoKardia and report stock and stock options from MyoKardia. PE has received payments as a consultant and personal fees from MyoKardia and reports a patent GB1815111.8 issued to his institution. CYH has received payments as a consultant from MyoKardia, Ambry Genetics, Novartis, and Tenaya. IO has received grants from MyoKardia, Sanofi-Genzyme, Shire, and Bayer; personal fees from Sanofi-Genzyme, Shire, and Bayer; and payments as a consultant from MyoKardia. SS has received personal fees from MyoKardia. CD has received payments as a consultant from MyoKardia and has provided consultative services to Genentech, Puma Biotechnology, Gilead Sciences, Coagulant Therapeutics, Alexion Pharmaceuticals, Portola Pharmaceuticals, and Halozyme Therapeutics. MR is an employee of IQVIA and has received payments

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Table 1: Baseline Patient Characteristics by Treatment Group

	Mavacamten (n=98)	Placebo (n=96)
Age, y	57·8 (12·7)	58·2 (11·6)
Male sex	56 (57·1%)	62 (64·6%)
White race	92 (93·9%)	87 (90·6%)
Enrolled in US	45 (45·9%)	39 (40·6%)
Body mass index, kg/m^2	29·9 (4·9)	29·6 (5·9)
Heart rate, beats per min	62·1 (10·5)	62·8 (10·6)
Systolic blood pressure, mm Hg	129·0 (16·1)	128·3 (14·7)
Diastolic blood pressure, mm Hg	75·2 (10·8)	75·6 (9·7)
Atrial fibrillation	10 (10·2%)	13 (13·5%)
Hypertension	51 (52·0%)	43 (44·8%)
Family history of HCM	26 (26·5%)	25 (26·0%)
Coronary artery disease	8 (8·2%)	5 (5·2%)
Hyperlipidemia	24 (24·5%)	27 (28·1%)
Type 2 diabetes mellitus	5 (5·1%)	5 (5·2%)
Asthma	13 (13·3%)	8 (8·3%)
COPD	2 (2·0%)	2 (2·1%)
β-blocker use	79 (80·6%)	69 (71·9%)
Calcium channel blocker use	16 (16·3%)	15 (15·6%)
NYHA class		
Class II	70 (71·4%)	71 (74·0%)
Class III	28 (28·6%)	25 (26·0%)
Presence of ICD or pacemaker	22 (22·4)	21 (21·9%)
Septal reduction therapy	8 (8·2%)	7 (7·3%)
Resting LVOT gradient, mm Hg	52·6 (29·3)	51·1 (30·7)
Median	52·1	49·3

	Mavacamten (n=98)	Placebo (n=96)
Q1, Q3	27·2, 71·9	25·9, 71·7
Valsalva LVOT gradient, mm Hg	74·2 (31·0)	73·7 (31·9)
Median	67·1	70·1
Q1, Q3	55·1, 94·9	50·8, 97·6
Postexercise LVOT gradient, mm Hg	85·7 (34·7)	85·1 (35·7)
Median	85·0	79·6
Q1, Q3	58·1, 105·3	58·4, 114·1
Resting LVEF, %	74·0 (5·7)	74·4 (5·6)
Max LV wall thickness, mm	19·7 (3·6)	20·0 (3·3)
pVO_2, mL/kg/min	19·30 (5·1)	19·91 (5·1)
NT-proBNP, geometric mean, ng/L (%CV)	742·7 (135·3)	619·9 (104·6)
hs-cTnI, geometric mean, ng/L (%CV)	12·2 (160·5)	12·6 (399·9)
KCCQ Overall Summary score	67·2 (17·2)	65·7 (19·6)
<25	2·0%	3·1%
≥25 to <50	13·3%	16·7%
≥50 to <75	51·0%	42·7%
≥75	33·7%	37·5%
KCCQ Clinical Summary score	70·9 (16·3)	70·3 (19·0)
KCCQ Total Symptom score	71·3 (16·6)	69·2 (21·7)
KCCQ Physical Limitation score	70·4 (18·4)	71·5 (19·1)
KCCQ Social Limitation score	71·8 (21·5)	67·3 (24·9)
KCCQ Quality of Life score	55·3 (23·2)	54·8 (22·6)

Data are mean (SD) or n (%) unless otherwise indicated. COPD = chronic obstructive pulmonary disease; CV = coefficient of variation; HCM = hypertrophic cardiomyopathy; hs-cTnI = high-sensitivity cardiac troponin I; ICD = implantable cardioverter-defibrillator; KCCQ = Kansas City Cardiomyopathy Questionnaire; LV = left ventricular; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; pVO_2 = peak oxygen consumption; Q = quartile; US = United States.

Table 2: Least Square Mean Differences in KCCQ Scores From Baseline to 30 Weeks

KCCQ scale	Mavacamten n=92	Placebo n=88	LS mean difference (95% CI)	p value
Overall Summary score	14·9 (15·8)	5·4 (13·7)	9·1 (5·5-12·8)	<0·0001
Clinical Summary score	13·6 (14·4)	4·2 (13·9)	9·1 (5·5-12·7)	<0·0001
Total Symptom score	12·4 (15·0)	4·8 (15·9)	7·7 (3·7-11·5)	0·0002
Physical Limitation score	14·7 (17·0)	3·6 (15·4)	10·6 (6·2-14·8)	<0·0001
Social Limitation score	13·5 (22·9)	5·1 (19·2)	9·3 (4·5-14·1)	0·0002
Quality of Life score	18·8 (21·6)	8·3 (18·8)	9·6 (4·7-14·5)	0·0001

Data are mean (SD) unless otherwise indicated. KCCQ = Kansas City Cardiomyopathy Questionnaire; LS = least squares.
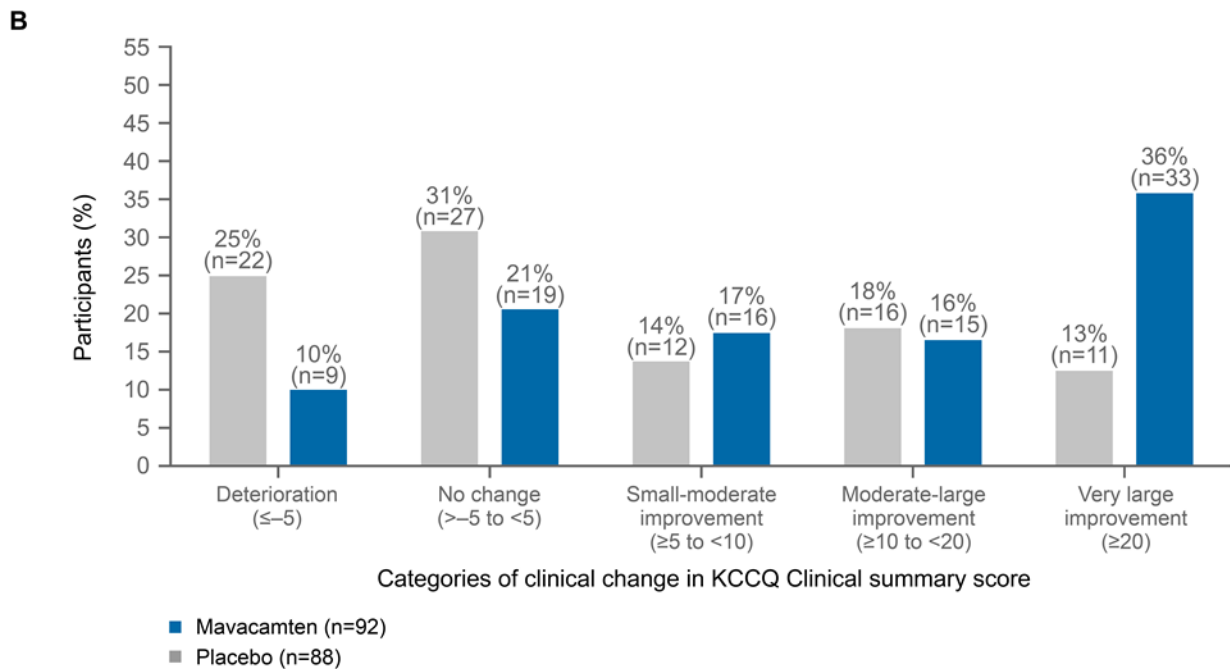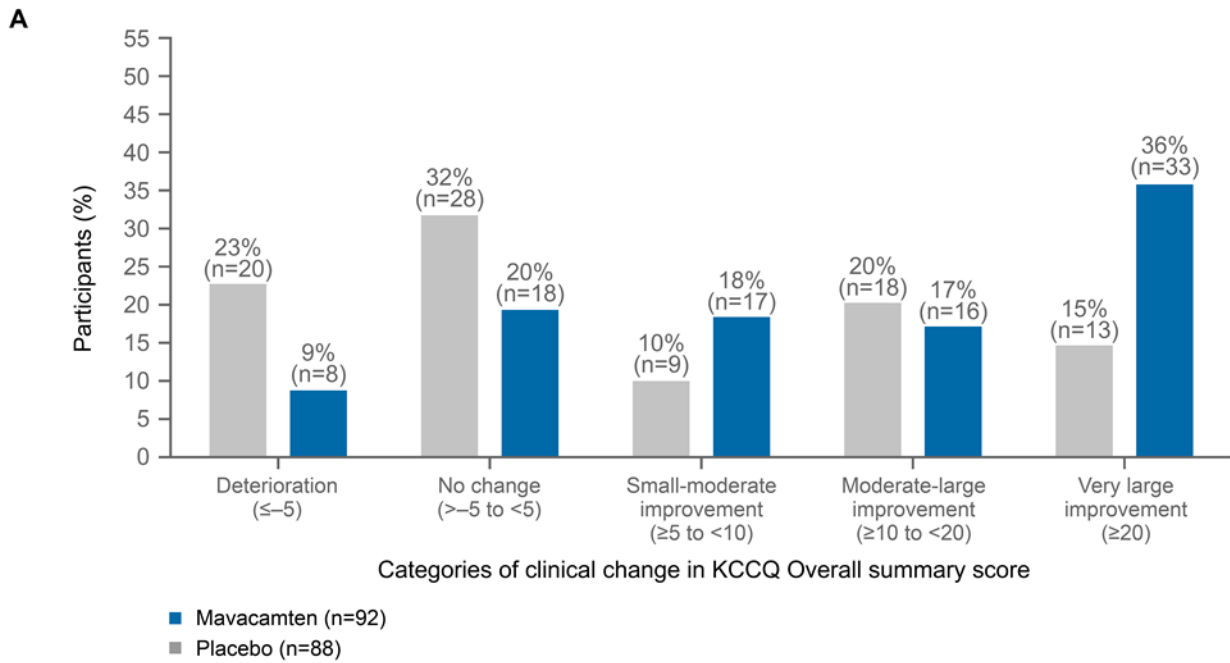
Figure 1: Mean Change in KCCQ Scores From Baseline Over Time by Treatment Group
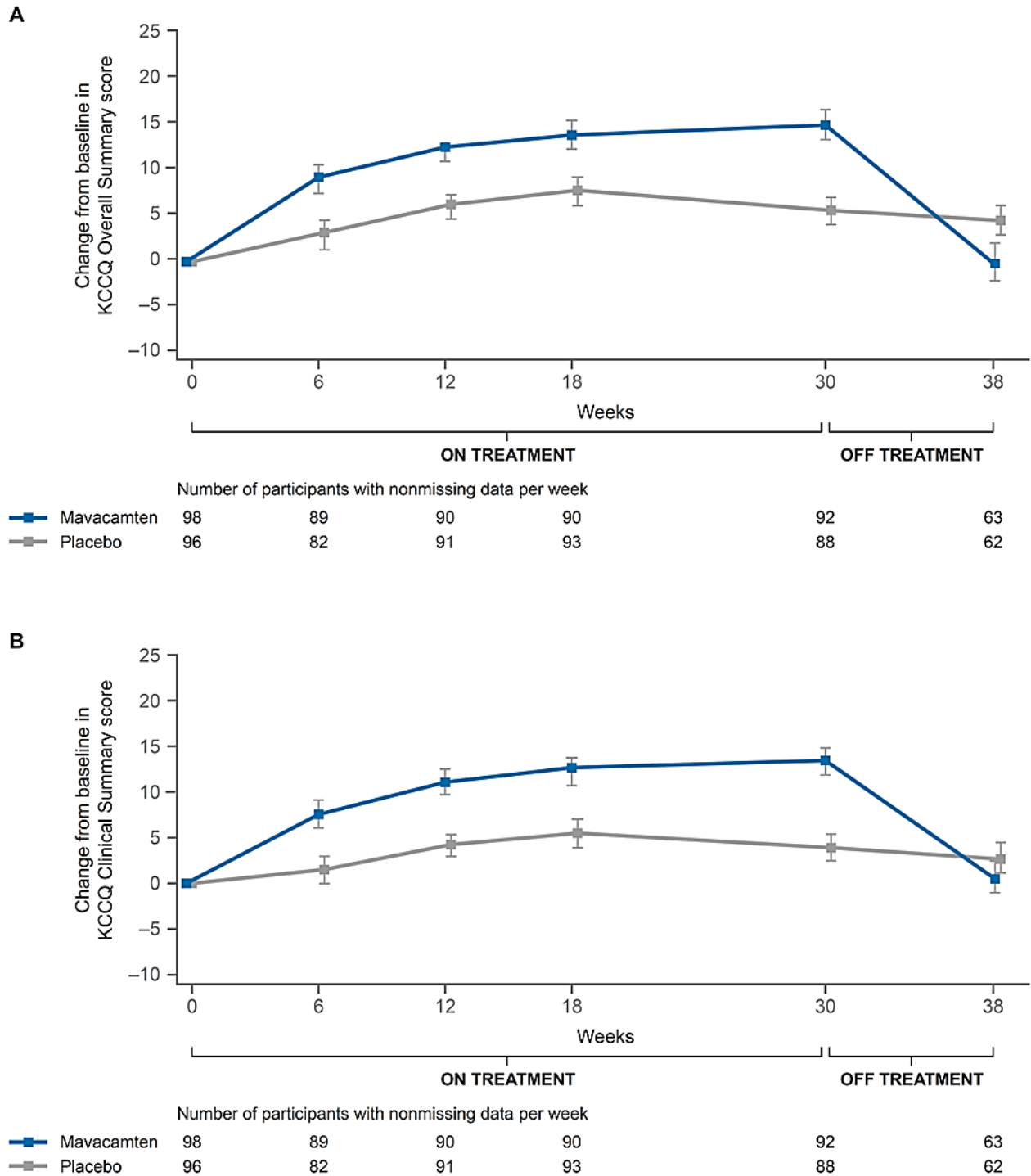
Mean change from baseline over time in (A) KCCQ Overall Summary score and (B) KCCQ Clinical Summary score. Error bars are SE. KCCQ = Kansas City Cardiomyopathy Questionnaire.

Figure 2: Percentage of Participants Who Changed by Clinically Important Amounts at 30 Weeks

Percentage of participants with clinically important changes in KCCQ Overall Summary score (A) and KCCQ Clinical Summary score (B). KCCQ = Kansas City Cardiomyopathy Questionnaire.