Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): health status analysis of a randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background Improving symptoms is a primary treatment goal in patients with obstructive hypertrophic cardiomyopathy. Currently available pharmacological options for hypertrophic cardiomyopathy are not disease-specific and are often inadequate or poorly tolerated. We aimed to assess the effect of mavacamten, a first-in-class cardiac myosin inhibitor, on patients' health status—ie, symptoms, physical and social function, and quality of life.

Methods We did a health status analysis of EXPLORER-HCM, a phase 3, double-blind, randomised, placebo-controlled trial. The study took place at 68 clinical cardiovascular centres in 13 countries. Adult patients (≥18 years) with symptomatic obstructive hypertrophic cardiomyopathy (gradient ≥50 mm Hg and New York Heart Association class II–III) were randomly assigned (1:1) to mavacamten or placebo for 30 weeks, followed by an 8-week washout period. Both patients and staff were masked to study treatment. 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 analysed using mixed model repeated measures. This study is registered with ClinicalTrials.gov, NCT03470545.

Findings Between May 30, 2018, and July 12, 2019, 429 adults were assessed for eligibility, of whom 251 (59%) were enrolled and randomly assigned. Of 123 patients randomly assigned to mavacamten, 92 (75%) completed the KCCQ at baseline and week 30 and of the 128 patients randomly assigned to placebo 88 (69%) completed the KCCQ at baseline and week 30. At 30 weeks, the change in KCCQ-OS score was greater with mavacamten than placebo (mean score 14·9 [SD 15·8] *vs* 5·4 [13·7]; difference +9·1 [95% CI 5·5–12·8]; p<0·0001), with similar benefits across all KCCQ subscales. The proportion of patients with a very large change (KCCQ-OS ≥20 points) was 36% (33 of 92) in the mavacamten group versus 15% (13 of 88) in the placebo group, with an estimated absolute difference of 21% (95% CI 8·8–33·4) and number needed to treat of five (95% CI 3–11). These gains returned to baseline after treatment was stopped.

Interpretation Mavacamten markedly improved the health status of patients with symptomatic obstructive hypertrophic cardiomyopathy compared with placebo, with a low number needed to treat for marked improvement. Given that the primary goals of treatment are to improve symptoms, physical and social function, and quality of life, mavacamten represents a new potential strategy for achieving these goals.

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Introduction

Hypertrophic cardiomyopathy is a primary myocardial disorder characterised by left ventricular hypertrophy, hyperdynamic contraction, and impaired relaxation related to excessive cardiac actin–myosin interactions.[1] Symptoms include exercise intolerance, fatigue, shortness of breath, and chest pain,[2] which can have profound effects on peoples' lives.[3,4] The primary goal of treatment for obstructive hypertrophic cardiomyopathy 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 non-dihydropyridine 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 obstructive hypertrophic cardiomyopathy, although their tolerability can be limited by side-effects and they often do not provide optimal control of left ventricular outflow tract (LVOT) gradients and

Research in context

Evidence before this study

Obstructive hypertrophic cardiomyopathy is a primary myocardial disorder characterised by left ventricular hypertrophy, hyperdynamic contraction, and impaired relaxation related to excessive cardiac actin–myosin interactions. A primary goal of treating patients with obstructive hypertrophic cardiomyopathy is to improve their health status: their symptoms, physical and social function, and quality of life. Although there have been no major advances in the treatment of symptoms or pathophysiology of obstructive hypertrophic cardiomyopathy in more than 30 years, mavacamten, a direct myosin inhibitor, has been shown in the past 3 years to reduce post-exercise left ventricular outflow tract gradients in the phase 2 PIONEER-HCM study, which was confirmed in the pivotal EXPLORER-HCM placebo-controlled, randomised, phase 3 trial. EXPLORER-HCM, the largest placebo-controlled trial in obstructive hypertrophic cardiomyopathy to date, showed that treatment with mavacamten for 30 weeks resulted in a substantially greater proportion of patients having a 1·5 mL/kg per min or greater increase in peak oxygen consumption with an improved, physician-assessed New York Heart Association (NYHA) class, or a 3 mL/kg per min or greater increase in peak oxygen consumption without a deterioration in NYHA class. A more complete understanding of the effects 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 subdomains, throughout 30 weeks of treatment. Moreover, once treatment was stopped, there were no longer significant differences in health status between groups. The benefits were clinically important, with an estimated absolute difference in the proportions of patients having a very large clinical benefit with mavacamten compared with placebo of 21% (95% CI 8·8–33·4). These results suggest that for every five patients given mavacamten, one would have a substantial improvement.

Implications of all the available evidence

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

symptoms. For patients refractory to medical management, invasive septal reduction therapy that mechanically reduces septal obstruction might be an alternative to ameliorate symptoms, although its effect on quality of life has not been formally assessed.[7–9] There is an unmet need for a safe, effective, and disease-specific non-invasive therapy for obstructive hypertrophic cardiomyopathy to improve quality of life and health status.

Clinically significant therapeutic advances in medical therapy for hypertrophic cardiomyopathy, which directly address the pathophysiological mechanisms of the disease, have been absent 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 placebo-controlled, randomised, phase 3 trial, was the first and largest clinical study of its kind to prospectively measure patient-reported outcomes in obstructive hypertrophic cardiomyopathy. Participants with symptomatic obstructive hypertrophic cardiomyopathy were randomly assigned 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 (pVO_2) and New York Heart Association (NYHA) class significantly favoured mavacamten compared with placebo. In this study, we aimed to assess the effect of mavacamten treatment on patients' health status (ie, symptoms, physical and social function, and quality of life) as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ).

Methods

Study design and participants

The design of the EXPLORER-HCM trial, a phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group trial, has been described previously.[12] Briefly, the study took place in 68 clinics in 13 countries. Eligible patients were aged 18 years or older with a diagnosis of obstructive hypertrophic cardiomyopathy (unexplained left ventricular hypertrophy with maximal left ventricular wall thickness of ≥15 mm [or ≥13 mm if familial hypertrophic cardiomyopathy]; peak LVOT gradient ≥50 mm Hg at rest, after Valsalva manoeuvre, or with exercise; left ventricular ejection fraction ≥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 more than 500 ms, and atrial fibrillation at the screening examination. Background β blocker and non-dihydropyridine 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. The protocol was

approved by a central or site-specific institutional review board, as required by the local site, and the study was done 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.

Randomisation and masking

Patients were randomly assigned (1:1) via an interactive response system 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. The trial was double-blind, and the principal investigator, site staff including the pharmacist, and the patient were masked to which study drug was being administered. In addition, the sponsor, the central and core laboratories, and clinical site monitors were masked to assigned treatment. Mavacamten and matching placebo were identical in appearance to preserve the masking. Mavacamten or matching placebo was labelled with a unique identifying number that was assigned to a patient through the interactive response system. Both patients and staff collecting scores were masked to study treatment. Randomisation was stratified by NYHA class (II or III), current β blocker use, ergometer type (treadmill or bicycle), and consent for the cardiovascular MRI substudy.

Outcomes

Patient-reported health status was measured using the disease-specific 23-item KCCQ,[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. Scores for each domain range from 0 to 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 represent poor to fair; 50–74 represent fair to good; and 75–100 represent 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 has been done to ensure that the concepts of the KCCQ were understood and relevant to patients with obstructive hypertrophic cardiomyopathy to supplement the limited data of its validity in this population[17] (appendix p 2). The KCCQ is independently associated with mortality, hospital admissions, 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 hospital admission rates in patients with heart failure due to reduced and preserved left ventricular ejection fraction, regardless of cause, although this finding has not been explicitly shown in obstructive hypertrophic cardiomyopathy.[24,25]

See Online for appendix

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.

Statistical analysis

Data were analysed in the population with KCCQ available for analysis, which included all randomly assigned patients who had a baseline KCCQ score and at least one post-baseline 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 prioritised the KCCQ-OS for these analyses to provide a more complete picture of the effect 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 SEs over time, including descriptive changes in KCCQ scores by categories of changes in pVO_2 and among those with a decrease in ejection fraction to less than 50%. Comparison of those changes between treatment groups was analysed 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 effect of withdrawing treatment on patients' health status, as captured by the KCCQ. This examination was done by comparing the week 38 (end of washout) KCCQ scores with those from the end of treatment (week 30) and at baseline.

	Mavacamten (n=98*)	Placebo (n=96*)
Age, years	57·8 (12·7)	58·2 (11·6)
Sex		
Women	42 (43%)	34 (35%)
Men	56 (57%)	62 (65%)
Race		
White	92 (94%)	87 (91%)
Other†	6 (6%)	9 (9%)
Enrolled in the USA	45 (46%)	39 (41%)
Body-mass index, kg/m²	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%)	13 (14%)
Hypertension	51 (52%)	43 (45%)
Family history of hypertrophic cardiomyopathy	26 (27%)	25 (26%)
Coronary artery disease	8 (8%)	5 (5%)
Hyperlipidaemia	24 (24%)	27 (28%)
Type 2 diabetes	5 (5%)	5 (5%)
Asthma	13 (13%)	8 (8%)
Chronic obstructive pulmonary disease	2 (2%)	2 (2%)
β blocker use	79 (81%)	69 (72%)
Calcium channel blocker use	16 (16%)	15 (16%)
New York Heart Association functional class II	70 (71%)	71 (74%)
New York Heart Association functional class III	28 (29%)	25 (26%)
Implantable cardioverter-defibrillator or pacemaker	22 (22%)	21 (22%)
Septal reduction therapy	8 (8%)	7 (7%)
Resting LVOT gradient, mm Hg	52·6 (29·3)	51·1 (30·7)
Median	52·1 (27·2–71·9)	49·3 (25·9–71·7)
Valsalva LVOT gradient, mm Hg	74·2 (31·0)	73·7 (31·9)
Median	67·1 (55·1–94·9)	70·1 (50·8–97·6)
Post-exercise LVOT gradient, mm Hg	85·7 (34·7)	85·1 (35·7)
Median	85·0 (58·1–105·3)	79·6 (58·4–114·1)
Resting left ventricular ejection fraction	74·0% (5·7)	74·4% (5·6)
Maximum left ventricular wall thickness, mm	19·7 (3·6)	20·0 (3·3)
pVO_2, mL/kg per min	19·30 (5·1)	19·91 (5·1)
NT-proBNP, geometric mean, ng/L (%CV)	742·7 (135·3)	619·9 (104·6)
High-sensitivity cardiac troponin I, 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 (2%)	3 (3%)
≥25 to <50	13 (13%)	16 (17%)
≥50 to <75	50 (51%)	41 (43%)
≥75	33 (34%)	36 (38%)
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), n (%), or median (IQR), unless otherwise indicated. The variation number (%CV) is the coefficient of variation, which is defined as the ratio of the SD to the mean. KCCQ=Kansas City Cardiomyopathy Questionnaire. LVOT=left ventricular outflow tract. NT-proBNP=N-terminal pro B-type natriuretic peptide. pVO_2=peak oxygen consumption. *There were 25 participants with missing KCCQ data in the mavacamten group and 32 participants with missing KCCQ data in the placebo group. †Other included Black or African American, American Indian or Alaska Native, Asian, and unknown.

Table 1: **Baseline patient characteristics by treatment group**

To render the population-level differences in KCCQ scores more clinically interpretable, we also did a comparison across clinically meaningful ranges of change in KCCQ scores from baseline to week 30. In accordance with recommendations from 2020,[23] scores were categorised into clinically worse (change in score from baseline to week 30 of –5 points or less), no significant change (more than –5 to less than 5 points), small but clinically important improvement (5 to less than 10 points), moderate to large clinical improvement (10 to less than 20 points), and large to very large clinical improvements (20 points or more). The differences in proportions of each category of change were converted into the number needed to treat by dividing 1 by the absolute differences in proportions of patients between treatment groups.[26]

Extensive investigation was done to explore potential biases that could be introduced from the missing data. These are fully described in the appendix (pp 3–8) and include: a review of the reasons for missingness submitted in the protocol deviation listings (32 [45%] of 71 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 effect of implausibly extreme selection biases showing no effect on the statistical significance of health status differences between mavacamten and placebo. Travel restrictions due to the 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 non-random missing KCCQ data and therefore the main analyses, including the comparison of the KCCQ changes between treatment groups, are made 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 non-responders and restricting the analyses to those with the potential to respond by different clinical magnitudes (appendix p 12).

All analyses were initially done by WL (MyoKardia) using SAS, version 9.4. The data and code were then provided to the Duke Clinical Research Institute (Durham, NC, USA), where the results were independently validated. The first author (JAS) helped design the analyses and all authors had access to the data results and the opportunity to request additional queries. All statistical tests were two-sided without adjustments for multiplicity. p values less than 0·05 were considered significant. The trial was overseen by a steering committee, independent data monitoring committee, and a clinical event adjudication committee. This study is registered with ClinicalTrials.gov, NCT03470545.

Role of the funding source
Co-authors employed by the funder were involved in study design, statistical analysis, data interpretation, and review of the manuscript, in collaboration with academic coauthors.

Results
Between May 30, 2018, and July 12, 2019, 429 adults were assessed for eligibility, of whom 251 (59%) were enrolled and randomly assigned. Among the 123 patients randomly assigned to mavacamten, 92 (75%) completed both the baseline and 30-week KCCQ, and among the 128 patients randomly assigned to placebo, 88 (69%) completed both the baseline and 30-week KCCQ, although higher rates of questionnaire completion were available at intervening assessments (appendix p 12). Baseline characteristics of the two groups show that the treatment groups were well balanced (table 1). Overall, participants had clinically significant left ventricular hypertrophy with marked dynamic outflow obstruction (mean LVOT gradient after exercise) and moderately impaired health status, as shown in more detail in table 1. After random assignment, almost all patients continued their background hypertrophic cardiomyopathy therapy without any changes or with minor adjustments (16 patients in the mavacamten group and ten patients in the placebo group had an adjustment to their β blocker dose). KCCQ data were missing for 71 of 251 patients (31 [25%] of 123 given mavacamten and 40 [31%] of 128 given placebo) for the primary comparison of 30-week change in KCCQ outcomes.

Regarding mean differences in health status by treatment group, figure 1A, B show the mean changes in KCCQ-OS and KCCQ-CS scores from baseline over time (see appendix p 9 for each of the KCCQ domain scores). These figures show rapid separation of the groups within the first 6 weeks of treatment, which was sustained throughout 30 weeks of treatment ($p<0·001$ for all scales; $p<0·0001$ for KCCQ-OS at 30 weeks), followed by a rapid diminution of these differences with cessation of study drug. Table 2 shows the least-square mean differences between treatment groups for the change from baseline to 30 weeks in KCCQ scores. At 30 weeks, the mean change from baseline in KCCQ-OS scores was greater in participants given mavacamten (mean 14·9 [SD 15·8]) than those given placebo (mean 5·4 [13·7]), with a difference between groups of +9·1 (95% CI 5·5–12·8; $p<0·0001$) favouring mavacamten. The subdomains of the KCCQ show very similar benefits across all domains, with the numerically largest benefits observed in the physical limitation domain.

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 the appendix (p 10). Across all domains of disease-specific health status, and collectively captured

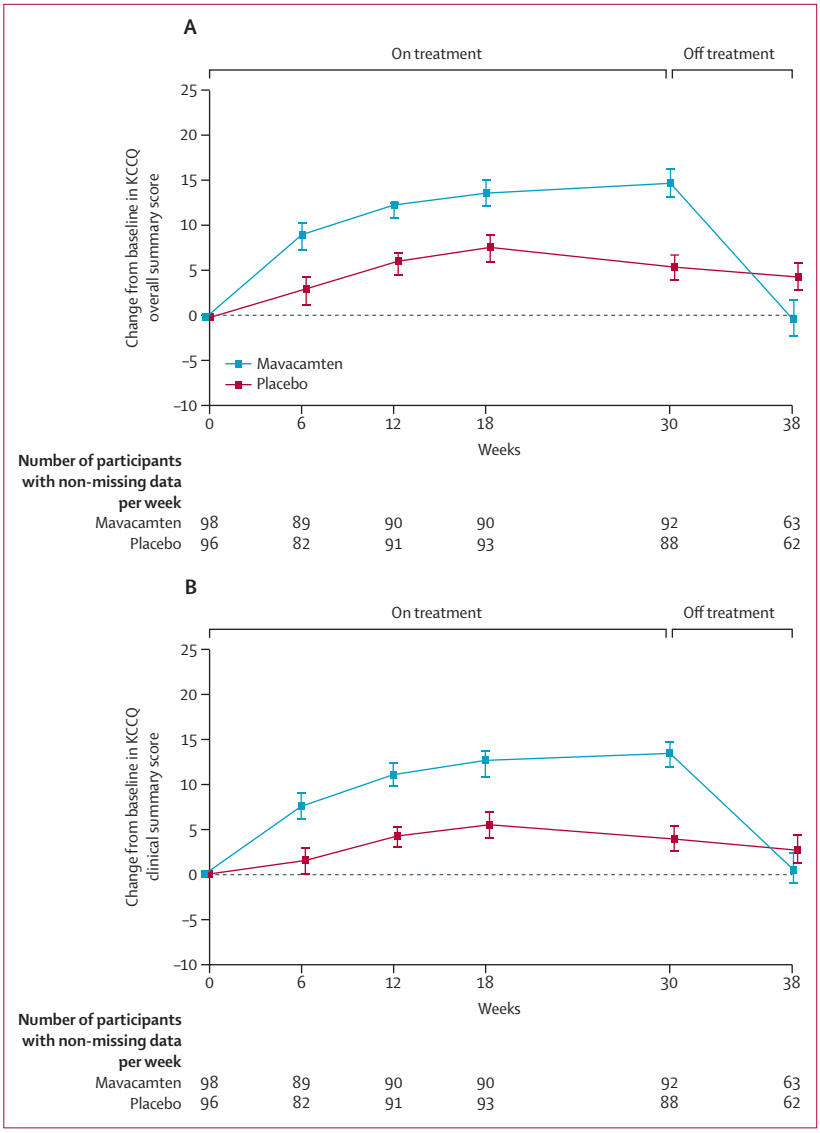

Figure 1: **Mean change in KCCQ scores from baseline over time by treatment group**
Mean change from baseline over time in (A) KCCQ overall summary score and (B) KCCQ clinical summary score. Error bars are SEs. KCCQ=Kansas City Cardiomyopathy Questionnaire.

	Mavacamten (n=92)	Placebo (n=88)	Least-square mean differences (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. There were 31 participants in the mavacamten group and 40 participants in the placebo group with missing data for the change of KCCQ score from baseline to week 30. The least-square mean differences and the p values were based on mixed model repeated measures, which are based on the KCCQ population (n=98 in mavacamten group and n=96 in placebo group). KCCQ=Kansas City Cardiomyopathy Questionnaire.

Table 2: **Least-square mean differences in KCCQ scores from baseline to 30 weeks**

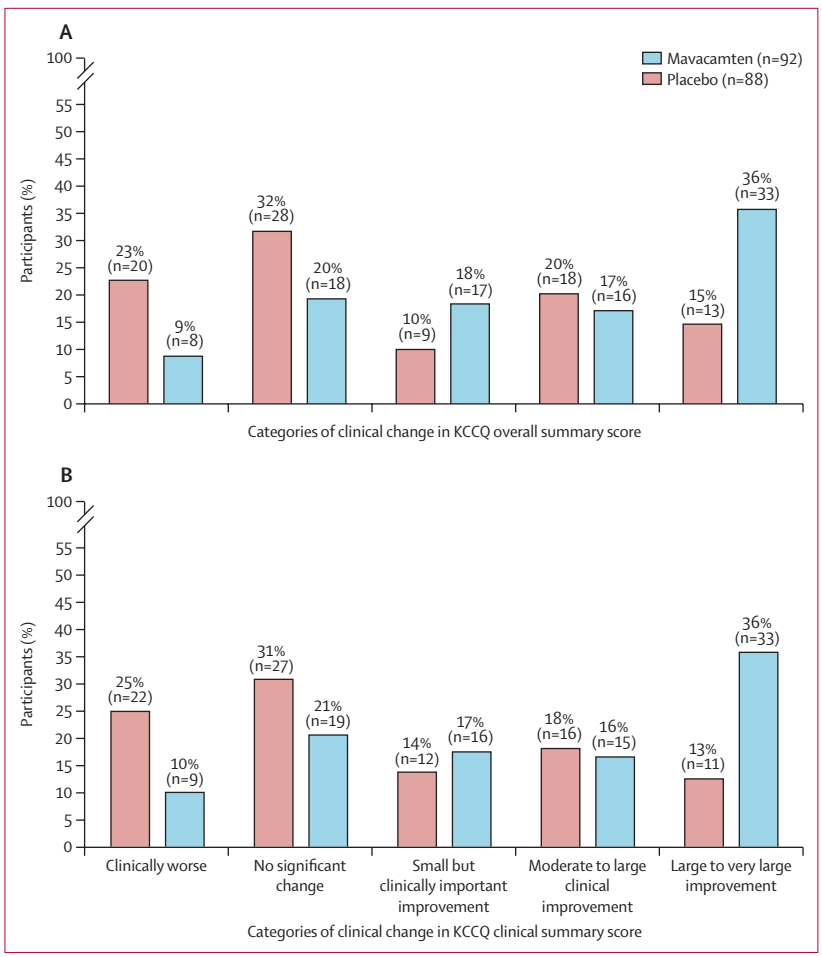

Figure 2: **Participants with clinically important changes at 30 weeks**
Percentage of participants with clinically important changes in KCCQ overall summary score (A) and KCCQ clinical summary score (B). Scores were categorised into clinically worse (change in score from baseline to week 30 of −5 points or less), no significant change (more than −5 to less than 5 points), small but clinically important improvement (5 to less than 10 points), moderate to large clinical improvement (10 to less than 20 points), and large to very large clinical improvements (20 points or more). KCCQ=Kansas City Cardiomyopathy Questionnaire.

by the summary scores, there were marked differences favouring 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 number needed to treat suggests that for every four to ten patients given mavacamten, as compared with placebo, one patient would have a large to very large improvement in their health status (eg, the proportion of patients given mavacamten who had a very large improvement in KCCQ-OS [≥20 points] was 36% compared with 15% in the placebo group, resulting in an absolute difference of 21% and a number needed to treat of around 5 [95% CI 3–11]), with the greatest benefit being in the physical limitation domain. In addition, for every four to eight patients given 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 marked numerical difference being in the quality of life domain.

As shown in figure 1, among patients with data available at weeks 30 and 38, cessation of therapy was associated with a marked deterioration in KCCQ scores (mean change in KCCQ-OS of –12·9 [SD 16·1, n=59] for patients given mavacamten *vs* –1·3 [9·7, n=58] in the patients given placebo). Comparing the 38-week scores with baseline revealed little difference between either group (KCCQ-OS score –0·1 [SD 16·5] *vs* 4·5 [12·7]; p=0·084; KCCQ-CS score 1·0 [14·4] *vs* 3·0 [13·2]; p=0·41), suggesting that with withdrawal of treatment, the benefits in health status that patients had while on mavacamten returned to baseline levels.

In the EXPLORER-HCM trial, seven patients had a reduction in their ejection fractions to less than 50% during mavacamten treatment. Of these, six patients had baseline and 30-week KCCQ scores available for analysis, which revealed similar mean improvements in their KCCQ scores to the other patients given mavacamten (mean points for overall summary 18·5 [SD 19·2]; 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 pVO_2 among all study participants by the categories of clinically significant change predefined in the EXPLORER-HCM trial, we found the largest improvement in KCCQ-OS score in those with the largest improvements in pVO_2 (8·7 [SD 15·0] point improvement in those with a <1·5 mL/kg per min improvement; 8·9 [14·0] point improvement in those with a 1·5 to <3 mL/kg per min improvement; and 18·0 [17·2] point improvement in those with a ≥3·0 mL/kg per min improvement; appendix p 11).

Discussion

A principal goal of treating symptomatic patients with obstructive hypertrophic cardiomyopathy is to alleviate their symptoms to improve their function and quality of life.[6] The 2020 American Heart Association/American College of Cardiology professional treatment guidelines for patients with hypertrophic cardiomyopathy identified a clear unmet need for novel trial designs and patient-reported outcome tools to assess the effect 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 substantial benefits of mavacamten treatment in pVO_2 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 α-controlled prespecified secondary endpoint. We found substantial changes in KCCQ scores in patients given mavacamten, 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 obstructive hypertrophic cardiomyopathy. By extending the previous analyses to show the distributions of patients' health status changes,[23] we found that for every five patients given 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 obstructive hypertrophic cardiomyopathy.

Understanding patients' perspectives of the effect of a disease on their health status (their symptoms, physical and social function, and quality of life) is 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 in 2020 was endorsed as a measure for quantifying the quality of health care.[28] The primary results from EXPLORER-HCM showed improvements in pVO_2, which were associated with changes in KCCQ scores in this trial, as well as previously in the HF-ACTION trial.[29] Yet, the information between these two assessments is different, in that the maximal ventilatory threshold for a patient might not necessarily affect their routine symptoms, physical and social function, and quality of life. By providing a richer description of the effect of mavacamten therapy on the health status of patients, from their perspectives, important information is now available 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 pathophysiological mechanism of heart failure is also directly addressed, than it is to other novel therapies for heart failure.[32–34] The improvements with mavacamten in the KCCQ stand in contrast to tafamidis, the only other medical therapy approved in the past few years with such a large benefit in KCCQ scores.[35] In patients with amyloid heart disease, tafamidis sustained the health status of patients, whereas those given placebo deteriorated substantially. By contrast, mavacamten substantially improved patients' health status as compared with placebo. 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 finding suggests that continuity of therapy will be important to maximise treatment benefits. Because of these directly appreciable benefits of mavacamten for patients with symptomatic obstructive hypertrophic cardiomyopathy, it will be interesting to study adherence to mavacamten therapy, as 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 trial 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 physiological parameters are most strongly associated with the health status benefits of treatment. In particular, more work defining changes in physiological parameters with changes in health status in obstructive hypertrophic cardiomyopathy is needed. For example, the intended reduction in left ventricular ejection fraction with a direct myosin inhibitor resulted in some patients having a transient ejection fraction less than 50%, but the KCCQ benefits in these patients were still substantial. Such work is especially relevant given that the 2020 guidelines emphasise the importance of shared medical decision making,[6] and the necessity of being 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, 28% of randomly assigned patients were missing either baseline or follow-up KCCQ data, which could have potentially biased our results. However, extensive analyses suggested that no observable biases were introduced by these missing data. Second, EXPLORER-HCM included patients with haemodynamically significant and symptomatic obstructive hypertrophic cardiomyopathy. Whether similar benefits would be observed in other patient populations, such as those with worse functional NYHA disease, less severe obstruction, or patients with non-obstructive hypertrophic cardiomyopathy, 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 obstructive hypertrophic cardiomyopathy. In particular, the proportion of patients with very large (≥20 points) improvements in their KCCQ-OS score was 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

2020 treatment guidelines for obstructive hypertrophic cardiomyopathy, which underscore the importance of shared decision making.[6]

Contributors

JAS wrote the first draft of the manuscript, was responsible for methodology, and contributed to data analysis. JTF was responsible for conceptualisation and project administration. IO, SS, PE, CYH, and DJ participated in data collection. WL was responsible for the statistical analysis. Both the authors and employees of the sponsor participated in data analysis and vouch for the accuracy and completeness of the data. All authors had full access to all the data reports from the study and take responsibility for data veracity, contributed to the writing or editing of the report, contributed to data interpretation and critical review and revision of the manuscript, and had final responsibility for the decision to submit for publication.

Declaration of interests

JAS has received payments as a consultant from MyoKardia, a Bristol Myers Squibb company. He owns the copyright to the Kansas City Cardiomyopathy Questionnaire 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. JTF, WL, and AJS are employees of MyoKardia and report stock and stock options from the company. PE has received payments as a consultant and personal fees from MyoKardia, Sanofi Genzyme, AstraZeneca, Pfizer, and DinaQor 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, Halozyme Therapeutics, and REGENXBIO. MR is an employee of IQVIA and has received payments as a consultant from MyoKardia. DJ has received personal fees from MyoKardia and has received a grant through the SHaRe Cardiomyopathy Registry, which is funded by MyoKardia.

Data sharing

For **data sharing policy** see https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html

To **submit a request** see https://vivli.org/ourmember/bristol-myers-squibb

Bristol Myers Squibb's policy on data sharing is available online. Bristol Myers Squibb will honour legitimate requests for our clinical trial data from qualified researchers. To submit a research proposal for use of patient-level clinical data, please visit our online request system.

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