Mavacamten
(obstructive hypertrophic cardiomyopathy)

Addendum to Project A23-76
(dossier assessment)[1]

ADDENDUM

Project: A23-132 Version: 1.0 Status: 11 Jan 2024 DOI: 10.60584/A23-132_en

[1] Translation of the addendum *Mavacamten (hypertrophe obstruktive Kardiomyopathie) – Addendum zum Projekt A23-76 (Dossierbewertung)*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Mavacamten (obstructive hypertrophic cardiomyopathy) – Addendum to Project A23-76

Commissioning agency

Federal Joint Committee

Commission awarded on

12 December 2023

Internal Project No.

A23-132

DOI-URL

https://doi.org/10.60584/A23-132_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum

- Michael Hort
- Merlin Bittlinger
- Moritz Felsch
- Simone Johner
- Volker Vervölgyi

Keywords

Mavacamten, Cardiomyopathy – Hypertrophic, Benefit Assessment, NCT03470545

Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ANCOVA	analysis of covariance
CI	confidence interval
CPET	cardiopulmonary exercise testing
EMA	European Medicines Agency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HCMSQ	Hypertrophic Cardiomyopathy Symptom Questionnaire
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	left ventricular ejection fraction
LVOT	left ventricular outflow tract
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model with repeated measures
NYHA	New York Heart Association
OSS	overall summary score
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PT	Preferred Term
pVO_2	peak oxygen consumption
RCT	randomized controlled trial
RPE	received perception of exertion
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

1 Background

On 12 December 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-76 (Mavacamten – Benefit assessment according to §35a Social Code Book V) [1].

In its comments, the pharmaceutical company (hereinafter referred to as “the company”) submitted supplementary information, which went beyond the information provided in the dossier, to prove the added benefit. The commission comprises the assessment of the sensitivity analyses of the subpopulation of the EXPLORER-HCM study presented by the company in the commenting procedure [2,3], taking into account the information provided in the dossier [4].

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The research question of the benefit assessment in A23-76 [1] was to assess the added benefit of mavacamten compared with treatment of physician's choice, taking into account non-vasodilating beta-blockers, verapamil, and diltiazem, in adult patients with symptomatic (New York Heart Association [NYHA] class II-III) obstructive hypertrophic cardiomyopathy (oHCM).

In its dossier, the company presented the results for the total population of the randomized controlled trial (RCT) EXPLORER-HCM [4]. For a large percentage of the study's total population, it was unclear whether patients in the comparator arm received treatment of physician's choice in accordance with the ACT. This was due to inconsistent information on the patients' concomitant therapy within the dossier. Based on the information on the concomitant therapy of oHCM provided in the clinical study report, 34% of comparator-arm patients had not received oHCM treatment in accordance with the ACT. The subpopulation of patients treated in accordance with the ACT is required for the assessment.

Within the commenting procedure and following the oral hearing, the company subsequently submitted further data [2,3,5]. On the one hand, these data provide comprehensible reasons for the different information on concomitant therapy in the various parts of the dossier. Secondly, the company presented a sensitivity analysis of the subpopulation of patients who were treated in accordance with the ACT (referred to by the company as "rITT population").

The subsequently submitted results of the subpopulation are assessed below and are used for the present benefit assessment. All information in the following sections refers to the subpopulation (N = 210), unless explicit reference is made to the total population (N = 251).

2.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 1: Study pool – RCT, direct comparison: mavacamten + treatment of physician's choice vs. placebo + treatment of physician's choice

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
MYK-461-005 (EXPLORER-HCM[d])	Yes	Yes	No	Yes [6]	Yes [7,8]	Yes [9-14]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool for the benefit assessment of mavacamten in comparison with the ACT coincides with the company's study pool and consists of the EXPLORER-HCM study.

2.2 Study characteristics

Detailed characteristics of the double-blind, placebo-controlled, multicentre RCT EXPLORER-HCM can be found in dossier assessment A23-76 [1].

Relevant subpopulation

Not all patients in the total population of the EXPLORER-HCM study (N = 251) were treated in accordance with the ACT (see also section on the implementation of the ACT). With the comments, the company presented the results of a subpopulation (N = 210) of those patients who received treatment in accordance with the ACT at the start of the study. The exclusion of patients who did not receive such therapy at the start of the study is adequate and affects 22% of patients in the comparator arm.

The EXPLORER-HCM study contains information on the concomitant therapy used specifically for the treatment of oHCM as well as information on any concomitant therapies. When forming the subpopulation, the company considered those patients who received any concomitant therapy with a drug corresponding to the ACT. This results in uncertainty as to whether those patients who did not receive the concomitant treatment specifically for the treatment of oHCM (28% in relation to the total study population) received adequate treatment in terms of the ACT.

The subpopulation is used for the benefit assessment, taking into account the described uncertainty in the certainty of conclusions (see Section 2.3.2).

Patient characteristics

Table 2 shows the patient characteristics in the subpopulation of the included study.

Table 2: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: mavacamten + treatment of physician's choice vs. placebo + treatment of physician's choice (multipage table)

Study Characteristic Category	Mavacamten + treatment of physician's choice N[a] = 110	Placebo + treatment of physician's choice N[a] = 100
EXPLORER-HCM		
Age [years], mean (SD)	58 (13)	58 (11)
Sex [F/M],%	45/55	38/62
Family origin, n (%)		
White	104 (95)	90 (90)
Other[b]	6 (5)[c]	10 (10)[c]
Duration of oHCM [years]		
Median [Q1; Q3]	4.5 [2.0; 10.7]	6.5 [3.5; 9.8]
Mean (SD)	7.3 (7.5)	7.4 (6.1)
BMI (kg/m^2), median [Q1; Q3]	29.4 [27.1; 31.6]	28.7 [25.6; 32.5]
oHCM concomitant therapy at baseline		
Beta-blockers, n (%)	85 (77)	83 (83)
Calcium antagonists [d], n (%)	25 (23)	17 (17)
LVEF at rest, n (%)		
< 75%	60 (55)	56 (56)
≥ 75%	50 (45)	44 (44)
LVOT gradient at rest, n (%)		
≤ 30 mmHg	30 (27)	29 (29)
> 30 mmHg	80 (73)	71 (71)
Maximum left ventricular wall thickness [mm], mean (SD)	19.8 (3.8)	19.8 (3.3)
NYHA class, n (%)		
II	82 (75)	70 (70)
III	28 (25)	30 (30)
Treatment discontinuation, n (%)	No data[e]	
Study discontinuation, n (%)	No data[f, g]	

Table 2: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: mavacamten + treatment of physician's choice vs. placebo + treatment of physician's choice (multipage table)

Study Characteristic Category	Mavacamten + treatment of physician's choice N[a] = 110	Placebo + treatment of physician's choice N[a] = 100

a. Number of randomized patients.
b. Other includes patients with the following family origins: Black/African American, American Indian/Alaska Native, Asian, and unknown.
c. Institute's calculation.
d. Restricted to calcium antagonists of the verapamil or diltiazem type.
e. In the total population, 4 patients in the intervention arm (3%) and 3 patients in the control arm (2%) discontinued treatment. The most common reason for treatment discontinuation in the intervention arm vs. the control arm was AEs (2 vs. 0).
f. In the total population, 4 patients in the intervention arm (3%) and 2 patients in the control arm (2%) discontinued the study. The most common reason for study discontinuation in the intervention arm vs. the control arm was AEs (2 vs. 0).
g. During the COVID-19 pandemic, a total of 67 patients in the total population (27%; intervention vs. control arm: 31 [25%] vs. 36 [28%]) completed the visit by telephone instead of on site at Week 38. The company categorized these patients as study discontinuations, although they completed the study.

BMI: body mass index; COVID-19: coronavirus disease 2019; F: female; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; M: male; n: number of patients in the category; N: number of randomized patients; NYHA: New York Heart Association; oHCM: obstructive hypertrophic cardiomyopathy; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation

The demographic and clinical characteristics of the subpopulation in both treatment arms are largely comparable. The patients' mean age was 58 years, most of them were male and of white family origin. The average duration of oHCM until then was just over 7 years. All patients received a beta-blocker or calcium channel blocker as concomitant oHCM therapy. In 45% of patients, the left ventricular ejection fraction (LVEF) at rest was ≥ 75%. The majority of patients showed a slight limitation of physical activity due to their heart disease (NYHA class II). The remaining patients (25% in the intervention arm and 30% in the comparator arm) had more severe limitation of physical activity due to their heart disease (NYHA class III). It is unclear how many of these patients also had a left ventricular outflow tract (LVOT) gradient > 50 mmHg, which would make them potential candidates for invasive therapy according to the guideline recommendations [15]. Overall, a small number of patients (approx. 3%) in the total population discontinued treatment or the study prematurely. The company did not submit any information on treatment or study discontinuation in the subpopulation.

Implementation of the appropriate comparator therapy

The G-BA determined the ACT for adult patients with symptomatic (NYHA class II to III) oHCM to be treatment of physician's choice, taking into account non-vasodilating beta-blockers, verapamil, and diltiazem. The guidelines [15,16] recommend the use of non-vasodilating beta-

blockers for the treatment of oHCM, titrated up to an effective or maximum tolerated dose. Calcium channel blockers were to be used for patients with intolerance to or insufficient response to beta-blockers.

Comparator-arm participants of the EXPLORER-HCM study received placebo. Both treatment arms allowed concomitant treatment of physician's choice with non-vasodilating beta-blockers or calcium channel blockers. According to the study protocol, all patients who received concomitant medication for oHCM were to be optimally titrated according to guidelines (not specified at this point) at the investigator's discretion prior to study inclusion. Disopyramide treatment was disallowed. The concomitant therapy was to have been well tolerated for at least 2 weeks before screening. It was to be kept stable during the study, unless safety or tolerability concerns arose.

Since not all patients in the EXPLORER-HCM study received concomitant treatment of oHCM or concomitant treatment with a drug in accordance with the ACT, the company presented a correspondingly tailored subpopulation with the comments. Table 3 shows the available data on concomitant therapy for this subpopulation (referring to the data on any concomitant therapy, without restriction to the therapeutic indication of oHCM).

Table 3: Information on concomitant therapies with beta-blockers or calcium channel blockers[a] – RCT, direct comparison: mavacamten + treatment of physician's choice vs. placebo + treatment of physician's choice

Study **Drug class**[b] **Drug**	**Patients with concomitant treatment with beta-blockers or calcium channel blockers n (%)**	
	Mavacamten + treatment of physician's choice **N = 110**	**Placebo + treatment of physician's choice** **N = 100**
EXPLORER-HCM		
Beta-blockers	87 (79.1)	83 (83)
Bisoprolol	25 (22.7)	20 (20)
Bisoprolol fumarate	5 (4.5)	10 (10)
Metoprolol	21 (19.1)	19 (19)
Metoprolol succinate	20 (18.2)	21 (21)
Metoprolol tartrate	6 (5.5)	6 (6)
Atenolol	6 (5.5)	5 (5)
Nadolol	3 (2.7)	2 (2)
Propranolol	4 (3.6)	1 (1)
Propranolol hydrochloride	2 (1.8)	0 (0)
Sotalol	1 (0.9)	2 (2)
Esmolol	1 (0.9)	0 (0)
Labetolol[c]	1 (0.9)	0 (0)
Calcium channel blockers	29 (26.4)	21 (21)
Verapamil	18 (16.4)	11 (11)
Verapamil hydrochloride	3 (2.7)	3 (3)
Diltiazem	3 (2.7)	2 (2)
Diltiazem hydrochloride	3 (2.7)	4 (4)
Amlodipine[c]	2 (1.8)	1 (1)
Amlodipine besilate[c]	1 (0.9)	0 (0)

a. Concomitant medication is defined as medication that was discontinued on or after the first dose of study medication or was not yet completed at the time of the data cut-off.
b. Classification according to ATC code.
c. The vasodilating beta-blocker labetolol and the calcium channel blocker amlodipine are not part of the ACT.

ACT: appropriate comparator therapy; ATC code: Anatomical Therapeutic Chemical code; min: minimum; n: number of patients with concomitant beta-blocker or calcium channel blocker therapy; N: number of patients analysed; RCT: randomized controlled trial

The subsequently submitted information on the subpopulation shows that 79% of patients in the mavacamten arm and 83% of patients in the control arm received a beta-blocker during the course of the study; with the exception of the concomitant treatment of one patient, these were exclusively non-vasodilating beta-blockers. Furthermore, 26% of patients in the

mavacamten arm and 21% of patients in the control arm received a calcium channel blocker (almost exclusively verapamil or diltiazem) during the course of the study.

The company did not provide any information on the change and discontinuation of concomitant therapy during the course of the study for the subpopulation. In the total population, there were only a few cases of drug discontinuation (< 1% only in the mavacamten arm) or switching (3% in the mavacamten arm versus < 1% in the control arm) during the course of the study. In the total population, approximately 10% of patients (9% in the mavacamten arm versus 10% in the control arm), had at least one dose adjustment of the concomitant therapy [1].

Risk of bias across outcomes (study level)

Table 4 shows the risk of bias across outcomes (risk of bias at study level).

Table 4: Risk of bias across outcomes (study level) – RCT, direct comparison: mavacamten + treatment of physician's choice vs. placebo + treatment of physician's choice

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
EXPLORER-HCM	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for the EXPLORER-HCM study.

Transferability to the German health care context

The company stated that the patient population of the EXPLORER-HCM study corresponds to the therapeutic indication approved in Germany [17]. All study participants were recruited and treated in the United Kingdom, Europe, Israel or the United States. According to the company, the treatment of oHCM was carried out in particular with drugs that correspond to the German standard of care. According to the company, the dosing regimen based on the parameters of LVOT gradients (efficacy) and LVEF (tolerability) and the additional measurement of mavacamten plasma concentration, which was used in the EXPLORER-HCM study, was further developed as part of the European approval procedure for mavacamten. According to the company, the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA) concluded from the investigation within the framework of

the European approval procedure that comparable efficacy could be achieved with both dosing regimens [18].

Furthermore, the company stated that an adapted dosing regimen for CYP2C19 slow metabolizers was also defined during the approval procedure in consultation with the EMA. In the EXPLORER-HCM study, 2 patients in the mavacamten arm (1.6%) and 3 patients in the ACT arm (2.3%) were classified as CYP2C19 slow metabolizers. According to the company, this proportion is in line with the expected proportion of CYP2C19 slow metabolizers of about 2% in the German health care context [19,20].

Overall, the company therefore presumed good transferability of the study results to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.3 Results on added benefit

2.3.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - perceived exertion (Borg received perception of exertion [RPE] scale)
  - symptoms
    - Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ)
    - Patient Global Impression of Change (PGIC)
    - Patient Global Impression of Severity (PGIS)
  - health status, recorded using the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
  - Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score (OSS)
- Side effects
  - serious adverse events (SAEs)
  - discontinuation due to adverse events (AEs)
  - systolic dysfunction (Preferred Term [PT], SAEs)

The choice of patient-relevant outcomes deviates from that taken by the company, which used other outcomes in the dossier (Module 4 A).

Table 5 shows the outcomes for which data were available in the included study.

Table 5: Matrix of outcomes – RCT, direct comparison: mavacamten + treatment of physician's choice versus placebo + treatment of physician's choice

Study	Outcomes									
	All-cause mortality[a]	Perceived exertion (Borg RPE scale)[b]	Symptoms (HCMSQ)	Symptoms (PGIC, PGIS)	Health status (EQ-5D VAS)	Health-related quality of life (KCCQ OSS)	SAEs	Discontinuation due to AEs	Systolic dysfunction (PT, SAEs)	Other specific AEs
EXPLORER-HCM	No[c]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[c]	No[d]

a. Recording of deaths in the framework of the recording of side effects.
b. Recorded during the CPET.
c. The company presented no data for the subpopulation of patients who were treated in accordance with the ACT.
d. No further specific AEs were identified based on the AEs occurring in the relevant study.

AE: adverse event; CPET: cardiopulmonary exercise testing; HCMSQ: Hypertrophic Cardiomyopathy Symptom Questionnaire; KCCQ: Kansas City Cardiomyopathy Questionnaire; OSS: overall summary score; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PT: Preferred Term;
RCT: randomized controlled trial; RPE: received perception of exertion; SAE: serious adverse event; VAS: visual analogue scale

Note on the included outcomes

Morbidity and health-related quality of life

Perceived exertion (Borg RPE scale)

In the EXPLORER-HCM study, cardiopulmonary exercise testing (CPET) with successively increasing intensity on a treadmill or cycle ergometer with connected electrocardiogram (ECG) was performed during screening and at Week 30 (maximum 11 stages of 2 minutes each). Patients (after 5 minutes in the supine position and 2 minutes standing) were asked to indicate their perceived exertion on a Borg RPE scale from 6 to 20 (6: "no effort at all", 20: "maximal effort") before and at each minute during the examination. The stress test could be terminated prematurely by the patient or the attending physician in the event of abnormal clinical symptoms or an abnormal ECG. The perceived exertion, recorded using the Borg RPE scale, was not prespecified as an outcome in the study protocol or statistical analysis plan. As an analysis, the company presented the change in perceived exertion (area under the Borg

curve) at Week 30 compared with the start of the study using an analysis of covariance (ANCOVA).

Physical endurance is a patient-relevant outcome. Albeit not prespecified, the Borg RPE scale and the analysis presented by the company are considered suitable for recording perceived exertion and are used for the benefit assessment. The company also presented the patients' maximum exercise time. As this is already included in the BORG RPE scale, the outcome is only presented as supplementary information in the present benefit assessment.

Symptoms (HCMSQ total score)

The HCMSQ is a validated questionnaire developed for patients with hypertrophic cardiomyopathy [21,22] to record the disease-specific symptoms of shortness of breath, fatigue, palpitations, chest pain, dizziness and syncopes. The questionnaire (version 1.0) comprises a total of 11 items, of which, in accordance with the scoring for the final version (version 2.0), 9 items are summarized in the domains of shortness of breath, fatigue and cardiovascular symptoms. The total score summarizes the 3 domains as a weighted sum (scale range: 0 to 12.5). For the relevant subpopulation, the company presented only continuous analyses using the mixed-effects model with repeated measures (MMRM).

Symptoms (PGIC, PGIS)

The PGIC and PGIS each consist of a single question that the patients could use to assess the severity of the symptoms or their change. Using the PGIS, patients were asked to indicate the severity of their symptoms on a five-point scale ("no symptoms", "mild", "moderate", "severe", "very severe") for the previous week. Using the PGIC, patients were asked to indicate the change in symptom severity on a seven-point scale ("very much improved", "much improved", "slightly improved", "no change", "slightly worse", "much worse", "very much worse") in relation to the symptom severity before the first dose of the study drug. For both instruments, the company presented analyses of any improvement at Week 30 compared with baseline for the relevant subpopulation.

Health-related quality of life (KCCQ OSS)

The KCCQ is an established and validated instrument in the therapeutic indication of heart failure. The validation study [23] shows that the KCCQ is a valid instrument also in the therapeutic indication of HCM.

For the relevant subpopulation, the company presented only continuous analyses using the MMRM.

Note on other outcomes included by the company

Primary composite outcome

In its present operationalization, the primary composite outcome on clinical response presented by the company is not used for the benefit assessment. The composite outcome comprises the components of improvement of ≥ 1.5 mL/kg/min in peak oxygen consumption (pVO_2) as determined by CPET and improvement by ≥ 1 class in NYHA classification, or improvement of ≥ 3 mL/kg/min in the CPET with no worsening in NYHA class. Being a laboratory parameter, the component of the pVO_2value is not per se patient relevant. The company presented no evidence for the use of the pVO_2as a valid surrogate for a patient-relevant outcome. The NYHA class as the second component of the composite outcome is primarily used to classify the severity of the disease. This categorization does not reflect any late complications and symptoms of the disease with sufficient sensitivity. In addition, morbidity and health-related quality of life events can be measured directly and are recorded via other relevant outcomes. Therefore, the primary composite outcome on clinical response is not used for the benefit assessment.

2.3.2 Risk of bias

Table 6 describes the risk of bias for the results of the relevant outcomes.

Table 6: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: mavacamten + treatment of physician's choice vs. placebo + treatment of physician's choice

Study	Study level	Outcomes										
		All-cause mortality[a]	Perceived exertion (Borg RPE scale)[b]	Symptoms (HCMSQ)	Symptoms (PGIC)	Symptoms (PGIS)	Health status (EQ-5D VAS)	Health-related quality of life (KCCQ OSS)	SAEs	Discontinuation due to AEs	Systolic dysfunction (PT, SAEs)	Other specific AEs
EXPLORER-HCM	L	–[c]	H[d, e]	H[d]	L	H[d]	H[d]	H[d]	L	L	–[c]	–

a. Recording of deaths in the framework of the recording of side effects.
b. Recorded during the CPET.
c. The company presented no data for the subpopulation of patients who were treated in accordance with the ACT.
d. High proportion of patients excluded from the analysis.
e. Selective reporting is possible because the analyses presented deviate from the analyses planned a priori.

AE: adverse event; CPET: cardiopulmonary exercise testing; H: high; HCMSQ: Hypertrophic Cardiomyopathy Symptom Questionnaire; KCCQ: Kansas City Cardiomyopathy Questionnaire; L: low; OSS: overall summary score; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PT: Preferred Term; RCT: randomized controlled trial; RPE: received perception of exertion; SAE: serious adverse event; VAS: visual analogue scale

For the outcomes of all-cause mortality and systolic dysfunction (PT, SAEs), the company presented no data for the subpopulation of patients who were treated in accordance with the ACT. The risk of bias for the results of the outcomes on symptoms (PGIC) and side effects (SAEs, discontinuation due to AEs) is rated as low. Due to the high proportion of patients not included in the analysis, the risk of bias is rated as high for the results of the following outcomes: perceived exertion (recorded using the Borg RPE scale), symptoms (recorded using the HCMSQ and PGIS), health status (recorded using the EQ-5D VAS), and health-related quality of life (recorded using the KCCQ OSS). For perceived exertion (Borg RPE scale), the risk of bias of the results is additionally increased due to possible selective reporting.

Summary assessment of the certainty of conclusions

In the present benefit assessment, no more than indications, e.g. of an added benefit, can initially be derived on the basis of the individual EXPLORER-HCM study. However, there are various aspects that reduce the certainty of conclusions of the EXPLORER-HCM study. These are described below.

On the one hand, there are uncertainties regarding the approval-compliant dosage of mavacamten. As already described in benefit assessment A23-76 Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2023 #43}, the dosing regimen used in the study differed from the Summary of Product Characteristics (SPC) [17] in that it took into account the plasma concentration of mavacamten in addition to the parameters LVOT gradient and LVEF. Furthermore, dose increases were possible at an earlier point in time (from Week 8 in the EXPLORER-HCM study versus from Week 12 according to the SPC). Overall, it is impossible to estimate how many of the patients were treated with a dosage regimen that deviated from the SPC. The early dose increase at Week 8 applies to 40% of patients. The possible impact on the observed effects cannot be estimated. It is not assumed that these differences preclude an assessment of the study as a whole. The remaining uncertainties are taken into account in the certainty of conclusions.

On the other hand, there are still uncertainties regarding the optimal adjustment of the concomitant therapy. It is unclear whether the subpopulation of patients who were treated in accordance with the ACT were optimally titrated at the start of the study and during the course of the study. The company also did not provide any further information within the commenting procedure as to whether, for example, all patients were titrated to the maximum tolerated dose of beta-blockers at the start of the study, or whether patients who received a calcium channel blocker at study start had intolerance to or insufficient response to beta-blockers. Since the study protocol did not allow adjusting the study medication during the study except in case of safety or tolerability concerns, it is also still unclear whether all patients received optimally adjusted concomitant therapy during the course of the study (see also benefit assessment A23-76 [1]).

Finally, not all patients received concomitant therapy with non-vasodilating beta-blockers or calcium channel blockers based on the therapeutic indication of oHCM. The subpopulation also includes patients who were treated with drugs in accordance with the ACT due to comorbidities. There is insufficient information available to assess whether the dosage of concomitant therapy used was also optimal for oHCM.

As a result of the uncertainties described, the certainty of conclusions is downgraded, so that no more than hints can be determined for all outcomes in the present data situation.

2.3.3 Results

Table 7 and Table 8summarize the results of the comparison of mavacamten + treatment of physician's choice versus placebo + treatment of physician's choice in patients with symptomatic (NYHA class II-III) oHCM. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

The results on common AEs, SAEs and discontinuations due to AEs are presented in Appendix A.

Table 7: Results (mortality, morbidity, side effects, dichotomous)– RCT, direct comparison: mavacamten + treatment of physician's choice versus placebo + treatment of physician's choice

Study Outcome category Outcome	Mavacamten + treatment of physician's choice		Placebo + treatment of physician's choice		Mavacamten + treatment of physician's choice vs. placebo + treatment of physician's choice
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
EXPLORER-HCM					
Mortality					
All-cause mortality[a]				ND	
Morbidity					
Symptoms					
PGIC[b]	102	87 (85.3)	88	47 (53.4)	1.62 [1.31; 2.00]; < 0.001[c]
PGIS[d]	98	53 (54.1)	86	32 (37.2)	1.54 [1.12; 2.12]; 0.008[c]
Side effects[e]					
AEs (supplementary information)	110	99 (90)	100	83 (83)	–
SAEs	110	14 (12.7)	100	8 (8)	1.65 [0.70; 3.86]; 0.252[c]
Discontinuation due to AEs	110	2 (1.8)	100	1 (1)	1.94 [0.17; 22.18]; 0.594[c]
Systolic dysfunction (PT, SAEs)[f]				ND	

a. The company presented no data for the subpopulation of patients who were treated in accordance with the ACT. In the total population, one event (0.8%) occurred in the control arm. Deaths were recorded in the framework of the recording of side effects.
b. Proportion of patients with any improvement ("very much improved", "much improved" or "slightly improved") at Week 30.
c. Mantel-Haenszel method with the stratification factors NYHA class (II vs. III), concomitant oHCM therapy with beta-blockers (yes vs. no) and type of cardiopulmonary exercise testing (treadmill vs. cycle ergometer); 95% CI and p-value based on normal distribution approximation.
d. Proportion of patients with any improvement in symptom severity on a five-point scale ("no symptoms", "mild", "moderate", "severe" and "very severe") at Week 30 compared with baseline.
e. Side effects were recorded throughout the entire course of the study until Week 38 (end of study).
f. The company presented no data for the subpopulation of patients who were treated in accordance with the ACT. In the total population, one event (0.8%) occurred in the intervention arm.

AE: adverse event; CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; NYHA: New York Heart Association; oHCM: obstructive hypertrophic cardiomyopathy; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Table 8: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: mavacamten + treatment of physician's choice vs. placebo + treatment of physician's choice (multipage table)

Study **Outcome category** **Outcome**	**Mavacamten + treatment of physician's choice**			**Placebo + treatment of physician's choice**			**Mavacamten + treatment of physician's choice vs. placebo + treatment of physician's choice**
	N[a]	**Values at baseline mean (SD)**	**Change at Week 30 Mean [95% CI]**	**N[a]**	**Values at baseline mean (SD)**	**Change at Week 30 Mean [95% CI]**	**MD [95% CI]; p-value**
EXPLORER-HCM							
Morbidity							
Perceived exertion (Borg RPE scale)[b]	97	356.2 (38.0)	−8.3 [−14.7; −1.9][c]	88	352.4 (39.4)	2.6 [−4.1; 9.2][c]	−10.85 [−18.70; −3.01]; 0.007[c] SMD [95% CI]: −0.40 [−0.69; −0.11]
Maximum exercise time (shown as supplementary information)[d]	*107*	*10.1 (4.1)*	*0.9 [0.4; 1.4][c]*	*98*	*10.4 (4.2)*	*0.3 [−0.2; 0.9][c]*	*0.60 [−0.04; 1.23]; 0.064[c]*
Symptoms							
HCMSQ total score[e]	94	3.1 (1.5)	−1.3 [−1.6; −1.0][f]	82	2.9 (1.8)	−0.5 [−0.8; −0.1][f]	−0.87 [−1.25; −0.48]; < 0.001[f] SMD [95% CI]: −0.67 [−0.97; −0.37]
Shortness of breath	94	4.7 (2.5)	−2.3 [−2.8; −1.8][f]	82	4.3 (3.1)	−0.5 [−1.1; 0.0][f]	−1.75 [−2.43; −1.07][f]
Fatigue	94	1.3 (0.7)	−0.4 [−0.6; −0.3][f]	82	1.3 (0.8)	−0.2 [−0.4; −0.1][f]	−0.23 [−0.41; −0.05][f]
Cardiovascular symptoms	94	1.7 (1.5)	−0.8 [−1.1; −0.6][f]	82	1.7 (1.6)	−0.3 [−0.5; 0.0][f]	−0.57 [−0.88; −0.26][f]
Health status (EQ-5D VAS)[g]	89	70.5 (19.1)	9.0 [5.1; 12.9][f]	77	68.2 (19.8)	1.3 [−2.8; 5.5][f]	7.62 [2.55; 12.69]; 0.003[f] SMD [95% CI]: 0.46 [0.15; 0.77]

Table 8: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: mavacamten + treatment of physician's choice vs. placebo + treatment of physician's choice (multipage table)

Study Outcome category Outcome	Mavacamten + treatment of physician's choice			Placebo + treatment of physician's choice			Mavacamten + treatment of physician's choice vs. placebo + treatment of physician's choice
	N[a]	Values at baseline mean (SD)	Change at Week 30 Mean [95% CI]	N[a]	Values at baseline mean (SD)	Change at Week 30 Mean [95% CI]	MD [95% CI]; p-value
Health-related quality of life							
KCCQ OSS[h]	87	67.6 (17.3)	15.0 [11.7; 18.3][f]	76	65.2 (19.7)	6.4 [3.0; 9.9][f]	8.58 [4.49; 12.66]; < 0.001[f] SMD [95% CI]: 0.64 [0.33; 0.96]
Physical limitation	87	71.2 (18.3)	13.0 [9.2; 16.7][f]	76	70.3 (19.6)	1.9 [−2.1; 5.8][f]	11.11 [6.34; 15.89][f]
Psychological quality of life	87	55.8 (23.7)	17.8 [13.4; 22.1][f]	76	54.4 (22.3)	9.0 [4.5: 13.5][f]	8.75 [3.31; 14.18][f]
Social limitation	87	72.1 (21.2)	14.5 [10.3; 18.6][f]	76	67.4 (24.5)	6.0 [1.6; 10.4][f]	8.47 [3.19; 13.74][f]
Symptoms (KCCQ TSS)	87	71.4 (16.8)	12.8 [9.3; 16.2][f]	76	68.7 (21.8)	6.2 [2.6; 9.8][f]	6.56 [2.25; 10.87][f]

a. Number of patients taken into account in the analysis for calculating the effect estimation; baseline values may rest on different patient numbers.
b. Patients rate their subjective perceived exertion during CPET every minute on the Borg RPE scale from 6 (no effort at all) to 20 (maximal effort) at baseline and at Week 30. The area under the Borg scores results in a value range between 132 and 440. Lower (decreasing) values indicate lower perceived exertion.
c. Analysis of covariance adjusted for the value at baseline and the stratification factors NYHA class (II vs. III), concomitant oHCM therapy with beta-blockers (yes vs. no) and type of cardiopulmonary exercise testing (treadmill vs. cycle ergometer); the MD represents the difference between the treatment arms in the changes from baseline to Week 30.
d. Duration between start and regular end of CPET or premature discontinuation due to complete exhaustion or onset of clinical symptoms
e. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus control) indicate an advantage for the intervention (scale range of 0 to 12.5).
f. MMRM adjusted for the value at baseline and for the stratification factors NYHA class (II vs. III), concomitant oHCM therapy with beta-blockers (yes vs. no) and type of cardiopulmonary exercise testing (treadmill vs. cycle ergometer); MD represents the difference between the treatment arms in the changes from baseline to Week 30.
g. Higher (increasing) values indicate improved health status; positive effects (intervention minus control) indicate an advantage for the intervention (scale range 0 to 100).
h. Higher (increasing) values indicate better health-related quality of life; positive effects (intervention minus control) indicate an advantage for the intervention (scale range 0 to 100).

Table 8: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: mavacamten + treatment of physician's choice vs. placebo + treatment of physician's choice (multipage table)

Study Outcome category Outcome	Mavacamten + treatment of physician's choice			Placebo + treatment of physician's choice			Mavacamten + treatment of physician's choice vs. placebo + treatment of physician's choice
	N[a]	Values at baseline mean (SD)	Change at Week 30 Mean [95% CI]	N[a]	Values at baseline mean (SD)	Change at Week 30 Mean [95% CI]	MD [95% CI]; p-value
CI: confidence interval; CPET: cardiopulmonary exercise testing; HCMSQ: Hypertrophic Cardiomyopathy Symptom Questionnaire; KCCQ: Kansas City Cardiomyopathy Questionnaire; MD: mean difference; MMRM: mixed effects model with repeated measures; N: number of analysed patients; NYHA: New York Heart Association; oHCM: obstructive hypertrophic cardiomyopathy; OSS: overall summary score; RCT: randomized controlled trial; RPE: received perception of exertion; SD: standard deviation; SMD: standardized mean difference; TSS: total symptom score; VAS: visual analogue scale							

Due to the uncertainties described above (see Section 2.3.2), at most hints, e.g. of added benefit, can be derived on the basis of the available information.

Mortality

All-cause mortality

For the outcome of all-cause mortality, the company presented no data for the subpopulation of patients who were treated in accordance with the ACT. In the total population, only one death occurred in the comparator arm. There is no hint of added benefit of mavacamten + treatment of physician's choice in comparison with treatment of physician's choice. An added benefit is therefore not proven.

Morbidity

Perceived exertion (Borg RPE scale)

There was a statistically significant difference in favour of mavacamten + treatment of physician's choice in comparison with placebo + treatment of physician's choice for perceived exertion (determined using the Borg RPE scale). The standardized mean difference (SMD) was analysed to examine the relevance of the result. The 95% confidence interval (CI) of the SMD was not completely outside the irrelevance range of −0.2 to 0.2. The observed effect can therefore not be inferred to be relevant. There is no hint of added benefit of mavacamten + treatment of physician's choice in comparison with treatment of physician's choice. An added benefit is therefore not proven.

Symptoms (HCMSQ total score)

There was a statistically significant difference in favour of mavacamten + treatment of physician's choice in comparison with placebo + treatment of physician's choice for the outcome of symptoms, measured using HCMSQ. The 95% CI of the SMD was completely outside the irrelevance range of −0.2 to 0.2. This was interpreted to be a relevant effect. There is a hint of added benefit of mavacamten + treatment of physician's choice in comparison with treatment of physician's choice.

Symptoms (PGIC and PGIS)

There were statistically significant differences in favour of mavacamten + treatment of physician's choice in comparison with placebo + treatment of physician's choice for the outcome of symptoms, measured using PGIS and PGIS. In each case, there is a hint of added benefit of mavacamten + treatment of physician's choice in comparison with treatment of physician's choice.

Health status (EQ-5D VAS)

There was a statistically significant difference in favour of mavacamten + treatment of physician's choice in comparison with placebo + treatment of physician's choice for the outcome of health status, measured using EQ-5D VAS. The SMD is analysed to examine the relevance of the result. The 95% CI of the SMD was not completely outside the irrelevance range of −0.2 to 0.2. The observed effect can therefore not be inferred to be relevant. There is no hint of added benefit of mavacamten + treatment of physician's choice in comparison with treatment of physician's choice. An added benefit is therefore not proven.

Health-related quality of life

KCCQ OSS

There was a statistically significant difference in favour of mavacamten + treatment of physician's choice in comparison with placebo + treatment of physician's choice for the outcome of health-related quality of life (recorded using KCCQ OSS). The 95% CI of the SMD was completely outside the irrelevance range of −0.2 to 0.2. This was interpreted to be a relevant effect. There is a hint of added benefit of mavacamten + treatment of physician's choice in comparison with treatment of physician's choice.

Side effects

SAEs

No statistically significant difference between treatment groups was found for the outcome of SAEs. There is no hint of greater or lesser harm from mavacamten + treatment of physician's choice in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

No statistically significant difference was found between treatment groups for the outcome of discontinuation due to AEs. There is no hint of greater or lesser harm from mavacamten + treatment of physician's choice in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

Specific AEs

Systolic dysfunction (PT, SAEs)

For the outcome of systolic dysfunction (PT, SAEs), the company presented no data for the subpopulation of patients who were treated in accordance with the ACT. In the total population, only one event occurred in the intervention arm. There is no hint of greater or lesser harm from mavacamten + treatment of physician's choice in comparison with treatment of physician's choice; greater or lesser harm is therefore not proven.

2.3.4 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present benefit assessment:

- age (≤ 49 years versus 50 to 64 years versus ≥ 65 years)
- sex (male versus female)
- NYHA class at baseline (NYHA class II vs. III)

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there have to be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

Using the methods described above, the available subgroup results did not show any effect modifications.

2.4 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [24].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.3.3 (see Table 9).

Determination of the outcome category for the morbidity outcomes

For the outcomes on symptoms and health status below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Symptoms (HCMSQ total score)

No information is available on the assignment of the severity grade for the outcome of symptoms (recorded using HCMSQ total score) that allows a classification as serious/severe. Therefore, this outcome was assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Symptoms (PGIS and PGIC)

The PGIS indicates symptom severity on a five-point scale from “no symptoms” to “very severe symptoms” for the previous week. At baseline, approx. 91% of patients in the total population stated that they had no to moderate symptoms (no corresponding information is available for the subpopulation). Therefore, the outcome of symptoms (determined with the PGIS and PGIC) was assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Health status (EQ-5D VAS)

No information is available on the assignment of the severity grade for the outcome of health status (recorded using EQ-5D VAS) that allows a classification as serious/severe. Therefore, this outcome was assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 9: Extent of added benefit at outcome level: mavacamten + treatment of physician's choice vs. placebo + treatment of physician's choice (multipage table)

Outcome category **Outcome**	**Mavacamten + treatment of physician's choice vs. placebo + treatment of physician's choice** **Event rate (%) or change at Week 30 (mean)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	No data[c]	Lesser/added benefit not proven
Morbidity		
Perceived exertion (Borg RPE scale)	−8.3 vs. 2.6 MD: −10.85 [−18.70; −3.01]; p = 0.007 SMD: −0.40 [−0.69; −0.11][d]	Lesser/added benefit not proven
HCMSQ total score	−1.3 vs. −0.5 MD: −0.87 [−1.25; −0.48]; p < 0.001 SMD: −0.67 [−0.97; −0.37][d] SMD: 0.67 [0.37; 0.97][e] Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.20 < CI_L < 0.40$ Added benefit, extent: "minor"
PGIC (any improvement at Week 30)	85.3% vs. 53.4% RR: 1.62 [1.31; 2.00] RR: 0.62 [0.50; 0.76][e]; p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ Added benefit; extent: "considerable"
PGIS (any improvement at Week 30)	54.1% vs. 37.2% RR: 1.54 [1.12; 2.12] RR: 0.65 [0.47; 0.89][e]; p = 0.008 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Added benefit, extent: "minor"
Health status (EQ-5D VAS)	9.0 vs. 1.3 MD: 7.62 [2.55; 12.69]; p = 0.003 SMD: 0.46 [0.15; 0.77][d]	Lesser/added benefit not proven
Health-related quality of life		
KCCQ OSS	15.0 vs. 6.4 MD: 8.58 [4.49; 12.66]; p < 0.001 SMD: 0.64 [0.33; 0.96][d] Probability: "hint"	Outcome category: health-related quality of life $0.30 < CI_L < 0.50$ Added benefit; extent: "considerable"

Table 9: Extent of added benefit at outcome level: mavacamten + treatment of physician's choice vs. placebo + treatment of physician's choice (multipage table)

Outcome category **Outcome**	**Mavacamten + treatment of physician's choice vs. placebo + treatment of physician's choice** **Event rate (%) or change at Week 30 (mean)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	12.7% vs. 8% RR: 1.65 [0.70; 3.86]; p = 0.252	Greater/lesser harm not proven
Discontinuation due to AEs	1.8% vs. 1% RR: 1.94 [0.17; 22.18]; p = 0.594	Greater/lesser harm not proven
Systolic dysfunction (SAE)	No data[c]	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size and the scale of the outcome are made with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_L).
c. The company presented no data for the subpopulation of patients who were treated in accordance with the ACT. In the total population, only one event occurred in each case.
d. If the CI for the SMD is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
e. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CI_L: lower limit of confidence interval; HCMSQ: Hypertrophic Cardiomyopathy Symptom Questionnaire; KCCQ: Kansas City Cardiomyopathy Questionnaire; MD: mean difference; OSS: overall summary score; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity: RPE: received perception of exertion; RR: relative risk; SAE: serious adverse event; SMD: standardized mean difference; VAS: visual analogue scale

2.4.2 Overall conclusion on added benefit

Table 10 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 10: Positive and negative effects from the assessment of mavacamten + treatment of physician's choice in comparison with treatment of physician's choice

Positive effects	**Negative effects**
Morbidity Non-serious/non-severe symptoms/late complications ▪ HCMSQ total score: hint of added benefit – extent: "minor" ▪ PGIC (any improvement): hint of added benefit – extent "considerable" ▪ PGIS (any improvement): hint of added benefit – extent "minor"	–
Health-related quality of life ▪ KCCQ OSS: hint of added benefit – extent: "considerable"	–
HCMSQ: Hypertrophic Cardiomyopathy Symptom Questionnaire; KCCQ: Kansas City Cardiomyopathy Questionnaire; OSS: overall summary score; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity	

Overall, there are only positive effects of mavacamten + treatment of physician's choice in comparison with treatment of physician's choice. For each of the outcomes of symptoms (recorded using PGIC) and health-related quality of life (recorded using KCCQ OSS), there is a hint of a considerable added benefit. For each of the other outcomes on symptoms (recorded using the HCMSQ total score and PGIS), there is a hint of a minor added benefit.

In summary, there is a hint of a considerable added benefit of mavacamten + treatment of physician's choice in comparison with the ACT treatment of physician's choice, taking into account non-vasodilating beta-blockers, verapamil, and diltiazem, for patients with symptomatic (NYHA class II to III) oHCM.

2.5 Summary

The data subsequently submitted by the company in the commenting procedure changed the conclusion on the added benefit of mavacamten from dossier assessment A23-76.

The following Table 11 shows the result of the benefit assessment of mavacamten under consideration of dossier assessment A23-76 and the present addendum.

Table 11: Mavacamten – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with symptomatic (NYHA class II-III) obstructive hypertrophic cardiomyopathy (oHCM)	Treatment of physician's choice [b, c, d, e, f] taking into account non-vasodilating beta-blockers, verapamil, and diltiazem	Hint of considerable added benefit[g]

a. Presented is the ACT specified by the G-BA.
b. In the guideline [16], non-vasodilating beta-blockers or calcium channel blockers (verapamil or diltiazem) are recommended for the treatment of symptomatic oHCM if beta-blockers are insufficient or not tolerated.
c. The drug disopyramide is neither approved nor marketed in Germany.
d. Given the wording of the planned therapeutic indication, non-drug interventions are not deemed to be a relevant therapeutic option in the present case.
e. It is assumed that the treatment of any concomitant diseases in adults with symptomatic oHCM (NYHA class II-III) is carried out on a patient-specific basis, in accordance with the current state of medical knowledge, taking into account the special features of the present disease in the current German health care context.
f. A single-comparator study is typically insufficient for implementing treatment of physician's choice in a study of direct comparison. The investigators are expected to have a choice between several treatment options (multicomparator study).
g. In the population investigated, mavacamten was administered exclusively in combination with concomitant therapy with non-vasodilating beta-blockers or calcium channel blockers. No data are available for mavacamten as monotherapy.

ACT: appropriate comparator therapy; G-BA: Joint Federal Committee; NYHA: New York Heart Association; oHCM: obstructive hypertrophic cardiomyopathy

The G-BA decides on the added benefit.

3 References

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Mavacamten (hypertrophe obstruktive Kardiomyopathie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2023 [Accessed: 05.11.2023]. URL: https://www.iqwig.de/download/a23-76_mavacamten_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Bristol-Myers Squibb Pharma. Stellungnahme zum IQWiG-Bericht Nr. 1663: Mavacamten (hypertrophe obstruktive Kardiomyopathie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/979/#beschluesse in the document "Zusammenfassende Dokumentation"].

3. Bristol-Myers Squibb Pharma. Anhang der Stellungnahme zum IQWiG-Bericht Nr. 1663: Mavacamten (hypertrophe obstruktive Kardiomyopathie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [unpublished]. 2023.

4. Bristol-Myers Squibb Pharma. Mavacamten (Camzyos); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2023 [Accessed: 14.12.2023]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/979/#dossier.

5. Bristol-Myers Squibb Pharma. A Randomized, Double blind, Placebo-controlled Clinical Study to Evaluate Mavacamten (MYK_461) in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy; study MYK-461-005; Zusatzanalysen im Nachgang zur mündlichen Anhörung [unpublished]. 2023.

6. MyoKardia. A Randomized, Double blind, Placebo-controlled Clinical Study to Evaluate Mavacamten (MYK_461) in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy; study MYK-461-005; Clinical Study Report [unpublished]. 2020.

7. MyoKardia. A Randomized, Double blind, Placebo controlled Clinical Study to Evaluate Mavacamten (MYK-461) in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy [online]. [Accessed: 17.08.2023]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-002530-23.

8. MyoKardia. Clinical Study to Evaluate Mavacamten (MYK-461) in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy (EXPLORER-HCM) [online]. 2021 [Accessed: 17.08.2023]. URL: https://classic.clinicaltrials.gov/show/NCT03470545.

9. Hegde SM, Lester SJ, Solomon SD et al. Effect of Mavacamten on Echocardiographic Features in Symptomatic Patients With Obstructive Hypertrophic Cardiomyopathy. J Am Coll Cardiol 2021; 78(25): 2518-2532. https://doi.org/10.1016/j.jacc.2021.09.1381.

10. Ho CY, Olivotto I, Jacoby D et al. Study Design and Rationale of EXPLORER-HCM; Evaluation of Mavacamten in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy. Circ Heart Fail 2020; 13(6): e006853. https://doi.org/10.1161/CIRCHEARTFAILURE.120.006853.

11. Olivotto I, Oreziak A, Barriales-Villa R et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM); a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2020; 396(10253): 759-769. https://doi.org/10.1016/S0140-6736(20)31792-X.

12. Spertus JA, Fine JT, Elliott P et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM); health status analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2021; 397(10293): 2467-2475. https://doi.org/10.1016/S0140-6736(21)00763-7.

13. Wheeler MT, Olivotto I, Elliott PM et al. Effects of Mavacamten on Measures of Cardiopulmonary Exercise Testing Beyond Peak Oxygen Consumption; A Secondary Analysis of the EXPLORER-HCM Randomized Trial. JAMA Cardiol 2023; 8(3): 240-247. https://doi.org/10.1001/jamacardio.2022.5099.

14. Xie J, Wang Y, Xu Y et al. Assessing health-related quality-of-life in patients with symptomatic obstructive hypertrophic cardiomyopathy; EQ-5D-based utilities in the EXPLORER-HCM trial. J Med Econ 2022; 25(1): 51-58. https://doi.org/10.1080/13696998.2021.2011301.

15. Arbelo E, Protonotarios A, Gimeno JR et al. 2023 ESC Guidelines for the management of cardiomyopathies. Eur Heart J 2023; 44(37): 3503-3626. https://doi.org/10.1093/eurheartj/ehad194.

16. Ommen SR, Mital S, Burke MA et al. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy; A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2020; 76(25): e159-e240. https://doi.org/10.1016/j.jacc.2020.08.045.

17. Bristol-Myers Squibb Pharma. CAMZYOS Hartkapseln [online]. 2023 [Accessed: 29.06.2023]. URL: https://www.fachinfo.de/.

18. European Medicines Agency. Assessment Report CAMZYOS; International non-proprietary name: mavacamten; Procedure No. EMEA/H/C/005457/0000 [online]. 2023 [Accessed: 25.07.2023]. URL: https://www.ema.europa.eu/en/documents/assessment-report/camzyos-epar-public-assessment-report_en.pdf.

19. Pisanu C, Welander NZ, Rukh G et al. Association between migraine prevalence, treatment with proton-pump inhibitors and CYP2C19 phenotypes in UK Biobank. Biomed Pharmacother 2021; 143: 112234. https://doi.org/10.1016/j.biopha.2021.112234.

20. Hashemizadeh Z, Malek-Hosseini SA, Badiee P. Prevalence of CYP2C19 Genetic Polymorphism among Normal People and Patients with Hepatic Diseases. Int J Organ Transplant Med 2018; 9(1): 27-33.

21. Reaney M, Addepalli P, Allen V et al. Longitudinal Psychometric Analysis of the Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ) Using Outcomes from the Phase III EXPLORER-HCM Trial. Pharmacoecon Open 2022; 6(4): 575-586. https://doi.org/10.1007/s41669-022-00340-8.

22. Reaney M, Allen V, Sehnert AJ et al. Development of the Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ); A New Patient-Reported Outcome (PRO) Instrument [unpublished]. 2021.

23. Nassif M, Fine JT, Dolan C et al. Validation of the Kansas City Cardiomyopathy Questionnaire in Symptomatic Obstructive Hypertrophic Cardiomyopathy. JACC Heart Fail 2022; 10(8): 531-539. https://doi.org/10.1016/j.jchf.2022.03.002.

24. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 06.10.2023]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

Appendix A Results on side effects

The tables below present events for Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes (SOCs) and PTs for the overall rates of AEs and SAEs, each on the basis of the following criteria:

- Overall rate of AEs (irrespective of severity): events that occurred in at least 10% of patients in one study arm
- Overall rates of SAEs: events that occurred in at least 5% of patients in one study arm
- Additionally, for all events irrespective of severity: events that occurred in at least 10 patients and at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs, a complete presentation of all results (SOCs/PTs) that resulted in discontinuation is provided.

Table 12: Common AEs[a] – RCT, direct comparison: mavacamten + treatment of physician's choice vs. placebo + treatment of physician's choice

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Mavacamten + treatment of physician's choice** **N = 110**	**Placebo + treatment of physician's choice** **N = 100**
EXPLORER-HCM		
Overall AE rate	99 (90)	83 (83)
Cardiac disorders	29 (26.4)	28 (28)
Atrial fibrillation	10 (9.1)	8 (8)
Gastrointestinal disorders	23 (20.9)	20 (20)
General disorders and administration site conditions	24 (21.8)	20 (20)
Infections and infestations	41 (37.3)	41 (41)
Nasopharyngitis	12 (10.9)	15 (15)
Injury, poisoning and procedural complications	13 (11.8)	9 (9)
Musculoskeletal and connective tissue disorders	37 (33.6)	23 (23)
Back pain	10 (9.1)	7 (7)
Nervous system disorders	39 (35.5)	28 (28)
Dizziness	22 (20)	14 (14)
Headache	15 (13.6)	7 (7)
Psychiatric disorders	10 (9.1)	5 (5)
Respiratory, thoracic and mediastinal disorders	31 (28.2)	20 (20)
Dyspnoea	16 (14.5)	9 (9)
Skin and subcutaneous tissue disorders	10 (9.1)	13 (13)
Vascular disorders	12 (10.9)	6 (6)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 21.0; SOC and PT notation taken without adaptation from the data subsequently submitted by the company in the commenting procedure.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 13: Common SAEs[a] – RCT, direct comparison: mavacamten + treatment of physician's choice vs. placebo + treatment of physician's choice

Study	Patients with event n (%)	
	Mavacamten + treatment of physician's choice N = 110	Placebo + treatment of physician's choice N = 100
EXPLORER-HCM		
Overall rate of SAEs[b]	14 (12.7)	8 (8)

a. Events that occurred in ≥ 5% of patients of at least 1 study arm.
b. For SAEs, no MedDRA SOCs and PTs met the criterion for presentation.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 14: Discontinuations due to AEs – RCT, direct comparison: mavacamten + treatment of physician's choice vs. placebo + treatment of physician's choice

Study	Patients with event n (%)	
SOC[a] **PT[a]**	Mavacamten + treatment of physician's choice N = 110	Placebo + treatment of physician's choice N = 100
EXPLORER-HCM		
Overall rate of discontinuations due to AEs[b]	2 (1.8)	1 (1)
Cardiac disorders	1 (0.9)	0 (0)
Atrial fibrillation	1 (0.9)	0 (0)
General disorders and administration site conditions	0 (0)	1 (1)
Sudden death	0 (0)	1 (1)
Nervous system disorders	1 (0.9)	0 (0)
Syncope	1 (0.9)	0 (0)

a. MedDRA version 21.0; SOC and PT notation taken without adaptation from Module 4.
b. The company presented no data for discontinuations due to AEs according to SOC/PT for the subpopulation of patients treated in accordance with the ACT. However, there were no differences in the overall rate of discontinuations due to AEs between the total population and the subpopulation, which is why the information on the total population was taken from Module 4.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class