Mavacamten
(obstructive hypertrophic cardiomyopathy)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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IQWiG thanks the medical and scientific advisor for her contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Eric de Mello and Sven Lorenz.

IQWiG thanks the respondents and the organization HOCM Deutschland e.V. for participating in the written exchange and for their support. The respondents and HOCM Deutschland e.V. were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACC	American College of Cardiology
ACT	appropriate comparator therapy
AHA	American Heart Association
ESC	European Society of Cardiology
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HOCM	hypertrophic obstructive cardiomyopathy
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LVEF	left ventricular ejection fraction
NYHA	New York Heart Association
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug mavacamten. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 28 July 2023.

Research question

The aim of this report is to assess the added benefit of mavacamten compared to treatment of physician's choice as an appropriate comparator therapy (ACT) in patients with symptomatic (New York Heart Association [NYHA] classes II to III) hypertrophic obstructive cardiomyopathy (HOCM).

The research question presented in Table 2 has been derived from the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of mavacamten

Therapeutic indication	**ACT**[a]
Adult patients with symptomatic (NYHA classes II-III) HOCM	Therapy of physician's choice[b,c,d,e,f] taking into account non-vasodilating beta-blockers, verapamil, and diltiazem

a. Presented is the ACT specified by the G-BA.
b. In the guideline [1], non-vasodilating beta blockers or calcium channel blockers (verapamil or diltiazem) are recommended for the treatment of symptomatic HOCM 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 methods are not deemed to be a relevant therapeutic option in the present case.
e. Presumably, the treatment of any concomitant diseases in adults with symptomatic HOCM (NYHA classes II-III) will be carried out 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 directly comparative study. The investigators are expected to have a choice between several treatment options (multicomparator study).

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

The company followed the G-BA's specification on the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks are used for the derivation of added benefit.

Study pool and study design

Evidence provided by the company

The company has identified the EXPLORER-HCM study for the direct comparison of mavacamten versus treatment of physician's choice. For a large percentage of the study's total population, it is unclear whether comparator-arm participants received therapy of physician's choice as in the ACT. The analyses of this study presented by the company are therefore unsuitable for this benefit assessment. This is justified below.

Design of the EXPLORER-HCM study

EXPLORER-HCM is a double-blind, placebo-controlled, multicentre RCT. It enrolled adult patients with symptomatic (NYHA class II or III) HOCM. HOCM had to be diagnosed in accordance with the guidelines of the American College of Cardiology (ACC) / American Heart Association (AHA) and the European Society of Cardiology (ESC). Additionally, the left ventricular ejection fraction (LVEF) measured during screening had to be ≥ 55% at rest.

The study enrolled a total of 251 patients who were allocated in a 1:1 ratio to mavacamten treatment (N = 123) or placebo (N = 128). Randomization in the EXPLORER-HCM study was stratified according to NYHA class (II versus III), concomitant HOCM therapy with beta-blockers (yes versus no), type of cardiopulmonary exercise test (treadmill versus bicycle ergometer), and consent to a magnetic resonance substudy (yes versus no).

Patients in both study arms were to receive adequate concomitant drug therapy for HOCM (see section on the implementation of the ACT).

The study had a planned treatment duration of 30 weeks. After the treatment phase, patients underwent an 8-week follow-up until the end of the study without mavacamten treatment or placebo.

The primary outcome of the EXPLORER-HCM study is the combined outcome of clinical response. Furthermore, patient-relevant outcomes in the categories of morbidity, health-related quality of life, and side effects were surveyed.

Implementation of the ACT

The G-BA has determined the ACT for adult patients with symptomatic (NYHA classes II to III) HOCM to be treatment of physician's choice, taking into account nonvasodilating beta-blockers, verapamil, and diltiazem. For the treatment of HOCM, the guidelines recommend the use of nonvasodilating beta-blockers, titrated up to an effective or maximum tolerated dose. Calcium channel blockers were to be used for patients in whom beta-blockers are insufficient or not tolerated.

Comparator-arm participants of the EXPLORER-HCM study received placebo. Both treatment arms allowed concomitant therapy of physician's choice with nonvasodilating beta-blockers or calcium channel blockers. As per study protocol, all patients who received concomitant medication for HOCM were to be optimally adjusted according to guidelines at the investigator's discretion prior to their enrolment. 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.

Inconsistent information on concomitant therapy for HOCM

The company provides information on concomitant therapies for HOCM at various points in the dossier, with said information being contradictory, sometimes to a relevant extent. According to the study report, 77 comparator-arm patients (60%) received a beta-blocker and 14 (11%) a calcium channel blocker as HOCM treatment. Contrary to this information from the study report, the company's Module 4 A (Table 4-17) states that 95 comparator-arm patients (74%) received a beta blocker and 27 patients (21%) a calcium channel blocker as concomitant HOCM therapy. The inconsistencies between the data cannot be explained on the basis of the available information, and these data are indispensable for an adequate assessment of the available study data.

High proportion of patients not treated according to the ACT

According to the therapeutic indication, all patients were symptomatic and therefore required treatment at the start of the study. Treatment in the sense of the ACT includes non-vasodilating beta-blockers, verapamil, and diltiazem. Taking into account the information provided in the study report, 34% of comparator-arm patients did not receive HOCM treatment in accordance with the ACT. Thus, a relevant proportion of comparator-arm participants were not treated appropriately, while all patients in the intervention arm received mavacamten treatment in addition to their concomitant treatment for HOCM. The effects of mavacamten versus treatment of physician's choice as shown in the EXPLORER-HCM study are therefore potentially biased in favour of mavacamten.

The company's approach of conducting the benefit assessment on the basis of the total population of the EXPLORER-HCM study is therefore not appropriate. The subpopulation of patients treated according to the ACT is required for the assessment.

Overall, the total population of the EXPLORER-HCM study is unsuitable for the benefit assessment due to the high proportion of comparator-arm patients who did not receive treatment according to the ACT.

Uncertainties regarding the optimal adjustment of concomitant therapy for HOCM patients

Whether EXPLORER-HCM participants who received concomitant therapy for HOCM were optimally adjusted at baseline as well as in the course of the study remains unclear. The company provides no information on the dosage of the concomitant therapy, e.g. whether all patients were on the maximum tolerated dose of beta-blockers at baseline. Additionally, no information is available on whether patients who received a calcium channel blocker at baseline exhibited intolerance to or insufficient effectiveness of 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 unclear whether all patients received optimally adjusted concomitant therapy during the course of the study.

The uncertainties arising from the questionable optimal adjustment of the concomitant medication at baseline and the presumably limited possibility of adjusting the therapy during the course of the study must be taken into account when interpreting the results for the subpopulation.

Summary

Within the dossier, the information provided on the concomitant therapy of EXPLORER-HCM participants is inconsistent. To allow an adequate assessment of the study, these inconsistencies must be clarified. Assuming the data on concomitant HOCM therapy as provided in the study report to be correct, no data suitable for the benefit assessment are available due to the high proportion of comparator-arm patients who did not receive therapy of physician's choice as per ACT. The subpopulation of patients treated according to the ACT is required for the assessment.

Results

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of mavacamten in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of the probability and extent of added benefit of mavacamten.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [2,3].

Table 3: Mavacamten – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with symptomatic (NYHA classes II-III) HOCM	Therapy of physician's choice[b, c, d, e,f] taking into account nonvasodilating beta-blockers, verapamil, and diltiazem	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. In the guideline [1], non-vasodilating beta-blockers or calcium channel blockers (verapamil or diltiazem) are recommended for the treatment of symptomatic HOCM 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 methods are not deemed to be a relevant therapeutic option in the present case.
e. Presumably, the treatment of any concomitant diseases in adults with symptomatic HOCM (NYHA classes II-III) will be carried out 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 directly comparative study. The investigators are expected to have a choice between several treatment options (multicomparator study).

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

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of mavacamten compared with treatment of physician's choice as the ACT in patients with symptomatic (NYHA classes II to III) hypertrophic obstructive cardiomyopathy (HOCM).

The research question presented in Table 4 has been derived from the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of mavacamten

Therapeutic indication	**ACT**[a]
Adult patients with symptomatic (NYHA classes II-III) HOCM	Therapy of physician's choice[b, c, d, e,f] taking into account nonvasodilating beta-blockers, verapamil, and diltiazem
a. Presented is the ACT specified by the G-BA. b. In the guideline [1], non-vasodilating beta-blockers or calcium channel blockers (verapamil or diltiazem) are recommended for the treatment of symptomatic HOCM 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 methods are not deemed to be a relevant therapeutic option in the present case. e. Presumably, the treatment of any concomitant diseases in adults with symptomatic HOCM (NYHA classes II-III) will be carried out 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 directly comparative study. The investigators are expected to have a choice between several treatment options (multicomparator study). ACT: appropriate comparator therapy; G-BA: Joint Federal Committee; HOCM: hypertrophic obstructive cardiomyopathy; NYHA: New York Heart Association	

The company followed the G-BA's specification on the ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on mavacamten (status: 24 May 2023)
- bibliographical literature search on mavacamten (last search on 23 May 2023)
- search in trial registries / trial results databases for studies on mavacamten (last search on 24 May 2023)
- search on the G-BA website for mavacamten (last search on 24 May 2023)

To check the completeness of the study pool:

- search in trial registries for studies on mavacamten (last search on 10 August 2023); for search strategies, see I Appendix A of the full dossier assessment

The company identifies the EXPLORER-HCM study for the direct comparison of mavacamten versus treatment of physician's choice [4-6]. For a large percentage of the study's total population, it is unclear whether comparator-arm participants received therapy of physician's choice as in the ACT. The analyses of this study presented by the company are therefore unsuitable for this benefit assessment. This is justified in the following sections.

No additional relevant study was identified from the check of the completeness of the study pool.

Study included by the company

Study design, patient population, and interventions

EXPLORER-HCM is a double-blind, placebo-controlled, multicentre RCT. It enrolled adult patients with symptomatic (NYHA class II or III) HOCM. The diagnosis of HOCM had to be in line with the guidelines of the ACC/AHA and the ESC [1,7]. In addition, the LVEF at the time of screening had to be ≥ 55% at rest. The study excluded patients with known infiltrative or storage diseases causing cardiac hypertrophy similar to HOCM. In addition, no invasive septal reduction (surgical myectomy or alcohol septal ablation) were to have been performed within the 6 months prior to screening, and no implantable cardioverter defibrillator was to have been inserted or replaced within 2 months prior to screening.

The study included a total of 251 patients who were allocated in a 1:1 ratio to mavacamten (N = 123) or placebo (N = 128). Randomization in the EXPLORER-HCM study was stratified according to NYHA class (II versus III), concomitant HOCM therapy with beta blockers (yes

versus no), type of cardiopulmonary exercise test (treadmill versus bicycle ergometer), and consent to a magnetic resonance substudy (yes versus no).

With regard to the dosing regimen, mavacamten treatment in the EXPLORER-HCM study exhibited several deviations from the Summary of Product Characteristics (SPC) [8]. The SPC differentiates the dosage regimen based on phenotype (slow or intermediate, normal, fast, and ultra-fast cytochrome P450 2C19 metabolizer). While the EXPLORER-HCM study did not provide for a separate dosing regimen based on phenotype, failure to do so has no consequences for the assessment because only 5 patients (2%) with a slow phenotype were included in the study. In addition, the dosing regimen used in the study differed from the SPC in that it took into account the plasma concentration of mavacamten in addition to the parameters left ventricular outflow tract (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 participants 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. However, it is deemed unlikely that the uncertainties are so great that they would completely call into question the relevance of the study for the present research question. The European Medicines Agency (EMA) also concludes that comparable efficacy can be expected between the different dosing regimens [9].

In both study arms, patients were to receive adequate concomitant drug therapy for HOCM in accordance with relevant guidelines, at the investigator's discretion, and as tolerated. Details on the concomitant medication as well as a discussion of the implementation of the ACT in the course of the study can be found below in the section on the implementation of the ACT.

The study had a planned treatment duration of 30 weeks. After the treatment phase, patients underwent an 8-week follow-up until the end of the study without mavacamten treatment or placebo. After the study, patients were invited to participate in a 5-year extension study (MAVA-LTE), in which all participants received mavacamten.

The primary outcome of the EXPLORER-HCM study is the combined outcome of clinical response (for a definition, see Table 7 of the full dossier assessment). Furthermore, patient-relevant outcomes in the categories of morbidity, health-related quality of life, and side effects were surveyed.

For a characterization of the study, see also Table 7 and Table 8 in I Appendix B of the full dossier assessment.

Implementation of the ACT

The G-BA has determined the ACT for adult patients with symptomatic (NYHA classes II to III) HOCM to be treatment of physician's choice, taking into account nonvasodilating beta blockers, verapamil, and diltiazem. The guidelines [1,7] recommend the use of nonvasodilating beta-blockers for the treatment of HOCM, 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 therapy of physician's choice with nonvasodilating beta-blockers or calcium channel blockers. According to the study protocol, all patients who received concomitant medication for HOCM were to be optimally adjusted 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.

Inconsistent information on concomitant therapy for HOCM

The company provides information on concomitant therapies for HOCM at various points in the dossier, with said information being contradictory, sometimes to a relevant extent. Table 5 shows the information available in the study report on the concomitant therapy of HOCM and changes in the concomitant therapy during the course of the study according to the information provided by the company in Module 4 A.

Table 5: Information on concomitant therapies for HCM – RCT, direct comparison: mavacamten + therapy of physician's choice versus placebo + therapy of physician's choice (multipage table)

Study **Drug class**[a] **Drug**	**Patients with subsequent therapy n (%)**	
	Mavacamten + treatment of physician's choice **N = 123**	**Placebo + treatment of physician's choice** **N = 128**
EXPLORER-HCM		
At the baseline[b, c]		
Beta-blockers	81 (65.9)	77 (60.2)
Bisoprolol	24 (19.5)	18 (14.1)
Metoprolol	18 (14.6)	17 (13.3)
Metoprolol succinate	18 (14.6)	17 (13.3)
Bisoprolol fumarate	3 (2.4)	10 (7.8)
Metoprolol tartrate	4 (3.3)	7 (5.5)
Atenolol	4 (3.3)	3 (2.3)
Nadolol	3 (2.4)	2 (1.6)
Propranolol	4 (3.3)	1 (0.8)
Carvedilol	1 (0.8)	3 (2.3)
Propranolol hydrochloride	2 (1.6)	0 (0)
Amlodipine; bisoprolol fumarate[d]	1 (0.8)	0 (0)
Betaxolol hydrochloride	0 (0)	1 (0.8)
Nebivolol hydrochloride	0 (0)	1 (0.8)
Calcium channel blockers	23 (18.7)	14 (10.9)
Verapamil	16 (13)	6 (4.7)
Diltiazem hydrochloride	3 (2.4)	3 (2.3)
Verapamil hydrochloride	2 (1.6)	3 (2.3)
Diltiazem	2 (1.6)	0 (0)
Amlodipine	0 (0)	1 (0.8)
Nifedipine	0 (0)	1 (0.8)
Adjustments in the course of the study[e]		
Point exposure[f]	1 (0.8)	3 (2.3)[g]
Permanent discontinuation	2 (1.6)	0 (0)
Change of medication	4 (3.3)[g]	1 (0.8)
At least 1 dose adjustment	11 (8.9)[g]	13 (10.2)[g]
Overlapping of different medications	4 (3.3)[g]	2 (1.6)

Table 5: Information on concomitant therapies for HCM – RCT, direct comparison: mavacamten + therapy of physician's choice versus placebo + therapy of physician's choice (multipage table)

Study	Patients with subsequent therapy n (%)	
Drug class[a] Drug	Mavacamten + treatment of physician's choice N = 123	Placebo + treatment of physician's choice N = 128

a. Classification according to ATC code.
b. Data from study report, limited to the drug classes relevant for the ACT.
c. Concomitant medication with a discontinuation date on or after the day of the first dose of mavacamten or still ongoing at the time of data cutoff.
d. Data taken from the study report without adjustment.
e. Information relating to beta-blockers and calcium channel antagonists.
f. Maximum treatment duration of 2 days.
g. Institute's calculation.

ACT: appropriate comparator therapy; ATC code: Anatomical Therapeutic Chemical code; HCM: hypertrophic cardiomyopathy; min: minimum; n: number of patients with concomitant HCM therapy; N: number of patients analysed; RCT: randomised controlled trial

According to the study report, 77 comparator-arm patients (60%) received a beta-blocker and 14 (11%) a calcium channel blocker as HOCM treatment. In deviation from this information presented in Table 5 of the study report, the company' Module 4 A (Table 4-17) states that 95 comparator-arm patients (74%) received a beta blocker and 27 patients (21%) a calcium channel blocker as concomitant HOCM therapy. In Module 4 A Table 4-21, the company additionally lists the concomitant therapies for HOCM according to the ACT which were received at baseline, without indicating the total percentages per drug class. However, even these data on the individual drugs differed from the data in the study report (e.g. metoprolol in the comparator arm reported as n = 20 [16%] in Module 4 A versus n = 17 [13%] in the study report). In addition to providing information on concomitant medication for HOCM, the study report contains data on any concomitant medication without restrictions. However, these data likewise conflict with the information provided by the company in Module 4 A (which lists, e.g. n = 22 [17%] for metoprolol in the comparator arm). The inconsistencies between the data cannot be explained on the basis of the available information, and these data are indispensable for an adequate assessment of the available study data. Irrespective of the inconsistencies, the relevance of the data for the present benefit assessment is described below based on the information in the study report.

High proportion of patients not treated according to the ACT

According to the therapeutic indication, all patients were symptomatic and therefore required treatment at the start of the study. Treatment in the sense of the ACT includes non-vasodilating beta blockers, verapamil, and diltiazem. Taking into account the information in Table 5, which also lists vasodilating beta blockers (nebivolol, carvedilol, betaxolol) and the

calcium channel blockers amlodipine and nifedipine, 34% of comparator-arm patients did not receive treatment for HOCM in accordance with the ACT. Thus, a relevant proportion of comparator-arm participants were not treated appropriately, while all patients in the intervention arm received mavacamten treatment in addition to their concomitant treatment for HOCM. The effects of mavacamten versus treatment of physician's choice as shown in the EXPLORER-HCM study are therefore potentially biased in favour of mavacamten.

The company's approach of conducting the benefit assessment on the basis of the total population of the EXPLORER-HCM study is therefore not appropriate. The subpopulation of patients treated according to the ACT is required for the assessment. For this purpose, at least patients who did not receive HOCM treatment with nonvasodilating beta-blockers or calcium channel blockers (verapamil and diltiazem) should be excluded from both the intervention arm and the comparator arm. Whether or not the participant received concomitant treatment for HOCM is recorded in the electronic data collection form.

Overall, the total population of the EXPLORER-HCM study is unsuitable for the benefit assessment due to the high proportion of comparator-arm patients who did not receive treatment according to the ACT.

Uncertainties regarding the optimal adjustment of concomitant therapy for HOCM patients

Whether EXPLORER-HCM participants who received concomitant therapy for HOCM were optimally adjusted at baseline as well as in the course of the study remains unclear. The company provides no information on the dosage of the concomitant therapy, e.g. whether all patients were on the maximum tolerated dose of beta-blockers at baseline. Additionally, no information is available on whether patients who received a calcium channel blocker at baseline exhibited intolerance to or insufficient effectiveness of 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 unclear whether all patients received optimally adjusted concomitant therapy during the course of the study. Particularly against the background of the blinded, placebo-controlled study in combination with the complex dosing algorithm of mavacamten, it must rather be assumed that it was impossible to fully carry out any necessary dose adjustments of the concomitant therapy. This is supported by the adjustments in the course of study shown in Table 5. During the course of the study, there were only 2 cases (< 1%) of discontinuation and 5 cases (2%) of a change in medication. Only 24 (10%) of the patients underwent at least 1 dose adjustment of the concomitant therapy. It is also noteworthy that there are only minor differences between the groups in terms of dose adjustment. Since an additional therapy was used in the intervention arm, more dose adjustments would be expected to be necessary in the comparator arm.

The uncertainties arising from the questionable optimal adjustment of the concomitant medication at baseline and the presumably limited possibility of adjusting the therapy during the course of the study must be taken into account when interpreting the results for the subpopulation.

Summary

Within the dossier, the information provided on the concomitant therapy of EXPLORER-HCM participants is inconsistent. To allow an adequate assessment of the study, these inconsistencies must be clarified. Assuming the data on concomitant HOCM therapy as provided in the study report to be correct, no data suitable for the benefit assessment are available due to the high proportion of comparator-arm patients who did not receive therapy of physician's choice as per ACT. The subpopulation of patients treated according to the ACT is required for the assessment.

I 4 Results on added benefit

For the assessment of the added benefit of mavacamten in adult patients with symptomatic HOCM, no suitable data are available for comparison with the ACT. This results in no hint of an added benefit of mavacamten in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 6 summarizes the result of the assessment of added benefit of mavacamten in comparison with the ACT.

Table 6: Mavacamten – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with symptomatic (NYHA classes II-III) HOCM	Therapy upon physician's choice [b, c, d, e,f] taking into account non-vasodilating beta-blockers, verapamil, and diltiazem	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. In the guideline [1], nonvasodilating beta-blockers or calcium channel blockers (verapamil or diltiazem) are recommended for the treatment of symptomatic HOCM 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 methods are not deemed to be a relevant therapeutic option in the present case.
e. Presumably, the treatment of any concomitant diseases in adults with symptomatic HOCM (NYHA classes II-III) will be carried out 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 directly comparative study. The investigators are expected to have a choice between several treatment options (multicomparator study).

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

The assessment described above deviates from that of the company, which derived an indication of considerable to major added benefit.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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