Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende mavacamten til behandling af symptomatisk obstruktiv hypertrofisk kardiomyopati

Vers. 2.0

Bilagsoversigt

1. Ansøgers notater til Rådet vedr. mavacamten
2. Forhandlingsnotat fra Amgros vedr. mavacamten
3. Ansøgers endelige ansøgning vedr. mavacamten

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Dato: 7. august 2026

Notat til vurderingsrapporten for mavacamten (Camzyos)

Tak for muligheden for at kommenteret på Medicinrådets vurderingsrapport for mavacamten. Mavacamten er første målrettede medicinsk behandling til denne gruppe patienter og er godkendt, anbefalet og ibrugtaget i på de fleste lande i Europa, på nær enkelte lande hvor lægemidlet er under vurdering.

Hovedbudskab. Hovedanalysen i Medicinrådets evaluering er primært drevet af en række antagelser vedrørende SRT, som samlet set fremstiller septal reduktionsterapi (SRT) som en næsten universel, meget effektiv, næsten risikofri og langvarigt sygdomsmodificerende løsning. Antagelserne er ikke alle videnskabeligt underbyggede og på flere punkter i modstrid med tilgængelig evidens. Antagelserne reducerer kunstigt værdien af mavacamten, fordi patienter i komparatorarmen antages hurtigt at blive "reddet" af SRT, hvis de forværres til NYHA III.

Det understreges i rapporten at resultatet er "behæftet med væsentlig usikkerhed", men dette kommer ikke resultatet til gode i hovedanalysen, men derimod udelukkende i følsomhedsanalysen.

1. Problemet med SRT-antagelserne

Ansøgers antagelse om ca. 2 % årlig overgang til SRT er evidensbaseret men er ændret til 95 % på baggrund af en antagelse om klinisk praksis på området(1). En årlig rate på 95 % indebærer i praksis en livstidsrate tæt på 100 % og at alle danske patienter i NYHA III dermed både ønsker SRT og er kandidater til indgrebet. Denne antagelse er ikke forankret i litteraturen, men står i kontrast til både danske og internationale registerdata, hvor kun 27 % af HCM-patienter modtager SRT i løbet af livet. En årlig eskalationsrate på 95 % gør Danmark til en ekstrem outlier i Europa og betyder i modellen, at næsten alle patienter hurtigt flyttes væk fra NYHA III.

Kombineres denne antagelse med Medicinrådets øvrige antagelse om, at 90 % af patienterne opnår NYHA-klasse I efter en SRT (jf. Tabel 16), bliver konsekvensen i praksis, at der stort set ikke vil eksistere oHCM-patienter i NYHA-klasse III over tid. Dette stemmer ikke overens med den kliniske virkelighed, hvor en betydelig andel af patienterne fortsat lever med symptomer svarende til NYHA III, uanset tilgængelig behandling. Det er derfor ikke plausibelt, at kombinationen af disse to antagelser afspejler dansk klinisk praksis.

Antagelsen er af altafgørende betydning for den sundhedsøkonomiske analyse og gør det nærmest umuligt for mavacamten at være omkostningseffektiv i Medicinrådets hovedanalyse. Det er derfor essentielt, at den underbygges med data, og at usikkerheden omkring den – herunder det urealistiske samspil med antagelsen om NYHA-klasse-forbedring efter SRT – belyses i Medicinrådets hovedanalyse.

2. Langsigtet sygdomsprogression efter mavacamten og SRT

I rapporten beskrives det, at mavacamten kan reducere den naturlige sygdomsprogression, men overfører samtidig samme lave progressionsrate til patienter efter SRT (afsnit 4.1.6, Tabel 15). Mavacamten har en dokumenteret, trial-baseret effekt på symptomer og obstruktion, mens SRT er et indgreb, hvis effekt på langsigtet sygdomsbiologi ikke er dokumenteret på samme måde. Antagelsen tildeler reelt SRT en sygdomsmodificerende effekt uden evidensgrundlag og forbedrer komparatorarmen systematisk.

Den sundhedsøkonomiske betydning af denne antagelse er markant og grundet usikkerheden bør antagelsen derfor varieres i Medicinrådets hovedanalyse.

3. Sammenligning med NICE og evidensgrundlaget

NICE's EAG behandlede de samme centrale spørgsmål i TA913 og anvendte en fælles langsigtet progressionsrate på 4,55 % årligt fra Maron et al. ens på tværs af alle behandlinger i modellen, herunder mavacamten, BB/CCB-monoterapi, disopyramid og SRT. Det betyder, at det ikke i sig selv er forskellen mellem mavacamten og SRT, der er det afgørende punkt, men derimod hvilket niveau progressionsraten for SRT sættes til. Den eneste lavere progressionsrate, som EAG overvejede, vedrørte aktiv lægemiddelbehandling og blev alene undersøgt i scenarieanalyser; EAG anvendte ikke en lavere end standardbehandlingsrate for SRT. Medicinrådets valg om at sænke den langsigtede progression efter SRT

helt ned til mavacamtens niveau går derfor længere end NICE's vurdering og afspejler en usædvanligt favorabel antagelse om SRT som procedure.

Medicinrådets antagelser er derfor ikke blot konservative justeringer. På flere punkter går man længere end det ses i registerevidensen og NICE's vurdering. Det gælder særligt den meget høje SRT-rate, den forbedrede NYHA-transition efter SRT og den lave proceduremortalitet på 0,5 %, som ligger under både ansøgers estimat og NICE's anvendte værdi.

4. NYHA II er ikke tilstrækkeligt belyst

Camzyos er ansøgt og godkendt til patienter i NYHA II–III, men Medicinrådets reelle vurdering fokuserer primært på NYHA III og sammenligningen med SRT jf. "Medicinrådet anser mavacamten som et medicinsk alternativ til SRT til patienter med betydelige daglige symptomer svarende til NYHA -klasse III, men også relevant hos patienter i NYHA-klasse II, som ikke er kandidater til SRT" Section 3.5 page 46.

Problemstillingen er ikke, at NYHA II ikke indgår i vurderingen, men at Medicinrådet ikke konkluderer selvstændigt for denne patientgruppe, bortset fra at SRT i praksis kun anses som relevant for NYHA III. Dette er inkonsistent, fordi SRT normalt ikke er relevant for NYHA II-patienter, mens mavacamten netop repræsenterer en ikke-invasiv mulighed for patienter med symptomer, før de eventuelt når et stadie, hvor SRT overvejes.

Modellen peger samtidig på, at mavacamten kan være omkostningseffektiv og klinisk relevant for NYHA II-patienter, som ikke – eller først senere – vil være kandidater til SRT, selv om det kan være forbundet med usikkerhed at identificere denne patientgruppe. At SRT begrænses til NYHA III på grund af procedurens risici, begrunder derfor ikke i sig selv, at mavacamten også afgrænses til NYHA III. Da SRT i praksis ikke er relevant for NYHA II, bør denne patientgruppe ikke implicit afgrænses væk gennem en komparatorlogik, der primært er bygget op omkring SRT.

Hvis mavacamten i Medicinrådets hovedanalyse scenarie er omkostningseffektiv, er det derfor uklart, hvorfor anbefalingen skulle begrænses til NYHA III jf. opstartskriterierne i bilag A. Medicinrådet har ikke fremlagt et selvstændigt argument for en sådan afgrænsning. Vurderingen bør derfor tydeligere adressere mavacamten som en tidlig, medicinsk og ikke-invasiv behandlingsmulighed for relevante NYHA II-patienter.

5. Konsekvensen for ICER'en

Samlet betyder ændringen fra 2 % til 95 % og antagelsen om samme lave langsigtede progression efter SRT som på mavacamten, at forværring til NYHA III får meget lille økonomisk og klinisk betydning i modellen. Næsten alle patienter antages at få SRT, mange returneres til NYHA I, risikoen ved proceduren er lav, og den efterfølgende progression antages at være lige så gunstig som ved mavacamten. Dermed udviskes mavacamtens centrale værdi: At holde patienterne velbehandlede, forsinke progression og reducere behovet for invasiv behandling.

Det er denne mekanisme, der især driver ICER'en op. Modellen bliver i praksis en model, hvor SRT fremstår som en næsten fuldstændig løsning for komparatorarmen. Det står i kontrast til både det anerkendte unmet need, den internationale anvendelse af SRT og Medicinrådets egen formulering af mavacamten som et medicinsk alternativ til SRT.

Konklusion

De centrale SRT-relaterede antagelser er ikke tilstrækkeligt underbygget. Især ændringen fra 2 % til 95 % årlig SRT-rate, identisk langsigtet progression efter SRT og mavacamten samt optimistiske antagelser om SRT-effekt og mortalitet giver samlet et billede af SRT, der er langt mere gunstigt end evidensen understøtter. Rådet opfordres til at tage dette med i betragtning, så SRT modelleres som en relevant, men begrænset og invasiv behandlingsmulighed.

Med venlig hilsen

Nicolai Fik

Market Access Direktør & Landechef

Bristol Myers Squibb, Danmark A/S

Kilder anvendt som grundlag:

1. Marstrand P, Han L, Day SM, Olivotto I, Ashley EA, Michels M, et al. Hypertrophic cardiomyopathy with left ventricular systolic dysfunction: insights from the SHaRe Registry. Circulation. 2020 Apr 28;141(17):1371-83.
2. Medicinrådets vurderingsrapport for mavacamten,
3. Ansøgers DMC-dossier,
4. National Institute for Health and Care Excellence (NICE). *Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy (TA913).* London: NICE; 2023. Available from: https://www.nice.org.uk/guidance/ta913
5. Olivotto I, et al. *EXPLORER-HCM*: Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy. N Engl J Med. 2020;383:1017-1028; and NICE Technology Appraisal TA913 including associated EAG documentation.
6. Arbelo E, Protonotarios A, Gimeno JR, et al. 2023 ESC Guidelines for the management of cardiomyopathies. *Eur Heart J.* 2023;44(37):3503-3626. doi:10.1093/eurheartj/ehad194.

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28. august, 2026

BMS' 2. notat for Camzyos *(mavacamten)* vurderingsrapport version 2.0

BMS' 1. notat er ligeledes gældende da det omfatter kommentarer til hoved- og følsomhedsanalysen.

I version 2.0 har Medicinrådet tilføjet et nyt **scenarie 2** – en "omkostningsanalyse uden ligeværdighed", hvor mavacamten sammenlignes direkte med SRT for patienter i NYHA-klasse III. **Den godkendte indikation for mavacamten omfatter i imidlertid også symptomatiske patienter i NYHA klasse II og det fremgår ikke tydeligt, hvorfor denne gruppe patienter nedprioriteres i vurderingen.**

Fra BMS' perspektiv er følsomhedsanalysen, hvor det antages, at ingen patienter modtager SRT, et væsentligt supplement til hovedanalysen. I hovedanalysen antages at næsten alle patienter i NYHA-klasse III modtager SRT inden for en kort tidshorisont (99,99 % inden for 3 år) og vender tilbage til NYHA-klasse I.

Baseret på data der findes på området er dette ikke ladsiggørligt og burde derfor ikke danne basis for beslutningstagning.

Antagelserne om SRT gør det endvidere umuligt for mavacamten at være omkostningseffektiv i Medicinrådets hovedanalyse. Følsomhedsanalysen viser dog tydeligt, at mavacamten kan være omkostningseffektiv og klinisk relevant for NYHA II-patienter, som ikke – eller først senere – vil være kandidater til SRT, selv om det kan være forbundet med usikkerhed at identificere denne patientgruppe. Scenarie 2 ser BMS som mindre relevant.

Scenarie 2 sammenligner mavacamten og SRT under antagelse om ligeværdighed. Medicinrådet nævner samtidig selv, at ligeværdighed ikke kan fastslås. I rapporten står... *"Det kan dog heller ikke entydigt siges, at de to behandlinger er ligeværdige især pga. forskellige bivirkninger og risici. Medicinrådet kan derfor ikke konkludere, om mavacamten og SRT vil være ligeværdige."*

Scenarie 2 ignorerer værdien af at undgå et invasivt indgreb. Ved kun at sammenligne omkostninger tilskrives der ingen værdi til de kvalitative forskelle, som Medicinrådet selv fremhæver andetsteds i rapporten:

- SRT medfører indlæggelse i **5-8 dage** (TASH) og længere rekonvalescens ved myektomi.
- Ca. **10 % af TASH-patienter får behov for pacemaker** pga. AV-blok, med efterfølgende livslang infektionsrisiko ved batteriskift.
- Ca. **10 % kræver genbehandling**, og enhver invasiv procedure er forbundet med en – om end lav – procedurerisiko.
- SRT er **irreversibel**, mens Mavacamten derimod er en medicinsk behandling, hvor dosis kan reduceres, behandlingen kan pauseres eller seponeres, hvis patienten oplever bivirkninger eller utilstrækkelig effekt.

- Derudover antages der behandling med Camzyos til samme pris i 15 år. Patentet for Camzyos udløber tidligere og de samlede omkostninger til behandling med Camzyos/mavacamten vil være stærkt reduceret i de sidste behandlings år grundet generiske konkurrence.

Rapporten adresserer i begrænset omfang symptomatiske NYHA klasse II-patienter, hvor SRT typisk ikke er indiceret. Samtidig efterlader vurderingen et uafklaret behandlingsbehov hos symptomatiske patienter i NYHA klasse II, som fortsat har betydende symptomer trods maksimalt tolereret behandling med betablokker og/eller calciumkanalblokker, men som typisk ikke er kandidater til SRT. **Den nuværende tilgang indebærer i praksis, at disse patienter må afvente yderligere sygdomsprogression, før de kan få adgang til en behandling, som allerede er godkendt til deres sygdomsstadie.**

Konkluderende bemærkning: Følsomhedsanalysen, hvor det antages, at 0 % modtager SRT, er et vigtigt supplement til hovedanalysen. Fra BMS' perspektiv er scenarie 2 analysen mindre relevant af de grunde, der er anført ovenfor. ***Der er en række antagelser der er ændret fra evidensbaseret artikler til behandlingspraksis igennem hele vurderingsrapporten. Nogle af disse har signifikant betydning på den sundhedsøkonomiske model. Det er derfor ekstra vigtigt at et Scenarie 2 ikke kommer til at stå alene, og at særligt følsomhedsanalysen og dens konsekvenser bliver en del af den endelige vurdering.***

Med venlig hilsen

Nicolai Fik

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07.08.2026
MBA/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	02.09.2026
Leverandør	Bristol Myers Squibb
Lægemiddel	Camzyos (mavacamten)
Ansøgt indikation	Til behandling af symptomatisk (New York Heart Association, NYHA, klasse II-III) obstruktiv hypertrofisk kardiomyopati (oHCM) hos voksne patienter
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel, revurdering

Prisinformation

Amgros har forhandlet følgende pris på Camzyos (mavacamten):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Camzyos	2,5 mg (28 stk.)	11.614,89	[redacted]	[redacted]	[redacted]	[redacted]
Camzyos	5 mg (28 stk.)	11.614,89	[redacted]	[redacted]	[redacted]	[redacted]
Camzyos	10 mg (28 stk.)	11.614,89	[redacted]	[redacted]	[redacted]	[redacted]
Camzyos	15 mg (28 stk.)	11.614,89	[redacted]	[redacted]	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

Aftaleforhold

Amgros har en eksisterende aftale på Camzyos. Aftalen gælder til den 31.03.2027. Der er inkluderet mulighed for prisregulering i aftalen.

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Der er på nuværende tidspunkt ingen direkte farmakologiske alternativer til Camzyos. Det primære behandlingsalternativ for patienter med vedvarende symptomer er septal reduktionsbehandling (SRT).

Tabel 2 viser de årlige lægemiddeludgifter ved behandling med Camzyos.

Tabel 2: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering*	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Camzyos	2,5 mg, 5 mg, 10 mg eller 15 mg (28 stk.)	1 kapsel én gang daglig, oral	[redacted]	[redacted]

Typisk startdosis er 5 mg dagligt, som titreres individuelt mellem 2,5 mg og 15 mg på baggrund af effekt og ekkokardiografisk monitorering.

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til vurdering
Sverige	Vurderes ikke nationalt	Link til vurdering
England	Anbefalet	Link til vurdering

Opsummering

[redacted]

Application for the assessment of mavacamten (Camzyos®) for the treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy

Contact information

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Table of contents

1 Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Camzyos®
Generic name	Mavacamten
Therapeutic indication as defined by EMA	Mavacamten is indicated for the treatment of symptomatic (New York Heart Association [NYHA] class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients
Marketing authorization holder in Denmark	Bristol Myers Squibb Hummeltoftevej 49 2830 Virum Denmark
ATC code	C01EB24
Combination therapy and/or co-medication	Can be used in combination with beta-blockers and calcium antagonists
(Expected) Date of EC approval	26 June 2023
Has the medicine received a conditional marketing authorization?	N/A
Accelerated assessment in the European Medicines Agency (EMA)	N/A
Orphan drug designation (include date)	N/A
Other therapeutic indications approved by EMA	None
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? Yes Is the product suitable for a joint Nordic assessment? No If no, why not? Camzyos is already reimbursed in Austria, Belgium, Bulgaria, Croatia, Czechia, Estonia, **Finland**, France, Germany, Greece, Hungary, Italy, Latvia, Luxembourg, Netherlands, **Norway**, Poland, Scotland, Slovenia, Spain, Switzerland, United Kingdom and under assessment in **Sweden** and **Denmark**.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	28 hard capsules in concentration 2.5/5/10/15 mg mavacamten

ATC = Anatomical Therapeutic Chemical Classification System; EC = ethics committee; N/A = not applicable.

2 Summary table

Summary	
Indication relevant for the assessment	Mavacamten is indicated for the treatment of symptomatic (New York Heart Association [NYHA] class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients
Dosage regiment and administration	CYP2C19 intermediate, normal, rapid, and ultra-rapid metabolizer phenotype: ▪ The recommended starting dosage is 5 mg orally once daily. The maximum dosage is 15 mg once daily. CYP2C19 poor metabolizer and unknown phenotype: The recommended starting dose is 2.5 mg orally once daily. The maximum dose is 5 mg once daily. The patient should be assessed for early clinical response by LVOT gradient with Valsalva manoeuvre 4 and 8 weeks after treatment initiation. Once an individualized maintenance dose is achieved, patients should be assessed every 6 months. If at any visit the patient's LVEF is < 50%, the treatment should be interrupted for 4 weeks and until LVEF returns to ≥ 50%.
Choice of comparator	Placebo + BB/CCB monotherapy
Prognosis with current treatment (comparator)	Many patients with oHCM experience significant symptoms such as dyspnea, chest pain, fatigue, and syncope, which can severely impact QoL. oHCM significantly affects HRQoL, including professional life, leisure time activities, mental well-being, and family planning. As a result, oHCM significantly affects a patient's social life and ability to work, with symptoms often developing gradually over the years. Consequently, patients with oHCM must adapt to severe limitations in daily life due to the burden of these symptoms.[1-4] There is an association between risk of mortality in patients with oHCM and an increased symptomatic burden, as measured by NYHA class. NYHA class III/IV has been shown to be the most important risk factor for cardiovascular death for oHCM patients (HR = 2.53, 95% CI (2.10, 3.07).[5] Further, SHaRe is an international registry that maintains longitudinal databases of clinical characteristics and outcomes data of 7,964 patients with HCM as of 2019.[6] Of these patients, 2,495 were adults with at least one definite NYHA assessment. The risks of all-cause mortality at 1 year of follow-up were estimated for NYHA classes. The HR by NYHA class for II vs. I was 1.48 and III vs. II was 3.17.
Type of evidence for the clinical evaluation	Placebo-controlled RCT.
Most important efficacy endpoints (Difference/gain compared to comparator)	A greater proportion of patients in the mavacamten group compared with the placebo group achieved the primary composite endpoint (37% vs. 17%; $P < 0.0005$). Although only 8% of placebo patients had a ≥ 3.0 mL/kg/min increase in pVO_2 and ≥ 1 NYHA class improvement, 20% of mavacamten-treated patients had both (difference, 12.5; 95% CI, 4.02-21.01). A recently published study demonstrated by Patel et al. (2026)[7].[7] The results show a reduction on all-cause mortality of mavacamten in patients with oHCM, thus supporting the assumption of a mortality benefit of mavacamten.[7] The study was a U.S. multi-center TriNetX cohort of 12,784 oHCM patients which

Summary	
	compared mavacamten (n=550) to standard medical therapy.[7] The results demonstrated a reduction in mortality risk for mavacamten compared to standard medical therapy.
Most important serious adverse events for the intervention and comparator	An LVEF ≤ 30% was a prespecified AE of special interest in EXPLORER-HCM. Nine patients (mavacamten, n = 7; placebo, n = 2) experienced a **transient LVEF < 50%.**
Impact on health-related quality of life	The EQ-5D-5L index score collected as part of EXPLORER-HCM at week 38 showed a difference of −0.026 (95% CI, −0.067 to 0.014; *P* = 0.203) between mavacamten and placebo. Health economic model: Overall utility values per health state were used for the model because health-state occupation rather than treatment was seen as the most important factor determining utility. Disutility associated with AEs was not included in the model due to the potential double counting of the impact of AEs within the underlying utilities observed in the trial.
Type of economic analysis that is submitted	Cost-utility analysis using a Markov model
Data sources used to model the clinical effects	EXPLORER-HCM
Data sources used to model the health-related quality of life	EXPLORER-HCM
Life-years gained	▪ Mavacamten + BB/CCB: 13.82 years ▪ BB/CCB monotherapy: 12.26 years
QALYs gained	▪ Mavacamten + BB/CCB: 12.53 QALYs ▪ BB/CCB monotherapy: 10.79 QALYs
Incremental costs	985,737 DKK
ICER (DKK/QALY)	568,103 DKK/QALY
Uncertainty associated with the ICER estimate	Based on the sensitivity analyses for the model, excess mortality related to NYHA class has the biggest impact on the results; however, the uncertainty is reduced by the new data demonstrating a beneficial effect on mortality for mavacamten and also a correlation between increased mortality risk and NYHA class. Further, a recently published study confirms the health benefits of mavacamten compared to standard of care.[8]
Number of eligible patients in Denmark	**Year 1**: 244 **Year 2**: 270 **Year 3**: 296 **Year 4**: 322 **Year 5**: 348
Budget impact (in year 5)	DKK 22,645,911

AE = adverse event; BB/CCB = beta-blocker/calcium channel blocker; CI = confidence interval; HCM = hypertrophic cardiomyopathy; HR = hazard ratio; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; pVO_2 = peak oxygen consumption; QALY = quality-adjusted life-year; QoL = quality of life; RCT = randomized controlled trial.

3 The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

3.1.1 Pathophysiology

Hypertrophic cardiomyopathy (HCM) is the most common hereditary heart disease caused by a multitude of integral changes to the structure and the function of the heart. HCM is characterized by thickening (hypertrophy) of the heart muscle, particularly the left ventricle, which cannot be explained by another cardiac or systemic disease.[9] This thickening can impair normal heart function, leading to various clinical symptoms and complications. The condition is chronic and progressive with a diverse clinical presentation and course. HCM is primarily caused by mutations in genes encoding sarcomeric proteins, the contractile unit of the heart muscle. These mutations disrupt sarcomere structure and function, resulting in abnormal myocyte growth and hypertrophy; disorganized cardiomyocytes (disarray); increased myocardial fibrosis; and a small, stiff ventricle with excessive contractility, impaired relaxation, and poor left ventricular compliance, which can lead to heart failure.[9-13] These structural abnormalities predispose patients to arrhythmias, such as atrial fibrillation (AF), ventricular tachycardia, and ventricular fibrillation, increasing the risk of heart failure and sudden death in HCM. Patients with HCM and AF have an increased risk of thromboembolic events, such as stroke, compared with HCM patients without AF.[9,14]

3.1.2 Clinical presentation and symptoms

The clinical presentation and course of HCM may vary widely and symptoms can be deceivingly mild and hinder the fact that disease progression has begun.[15] Symptoms can be debilitating, life-changing, and result in impaired functionality and lower quality of life (QoL). The most common symptoms include shortness of breath (dyspnea), fatigue, palpitations, light-headedness, chest pain, and syncope.[1,16] Approximately 50% of patients with HCM will experience some degree of heart failure, which is expressed by exertional dyspnea due to different pathological mechanisms, in the presence of preserved systolic function.[17] However, for some patients, the first symptom is sudden cardiac death (SCD). To mitigate the risk of SCD, 5-year risk is assessed for each patient using the European Society of Cardiology (ESC) HCM risk-SCD calculator, and patients at risk of SCD are offered an implantable cardioverter-defibrillator (ICD) as preventive measure.[9,12,18,19] Note, the risk of sudden death is independent from the risk of developing end-stage HCM with disease progression, and the risk of sudden death is higher for patients below 60 years of age.[17,20] Long-term outcomes for patients with HCM have improved with advances in diagnosis, risk stratification, and treatment.

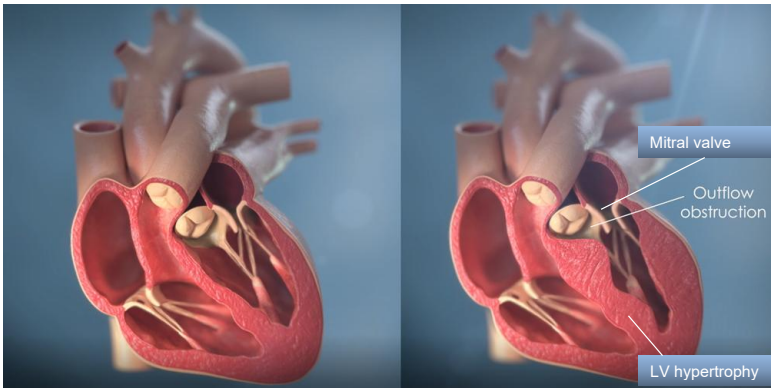
However, HCM remains associated with significant risks, and ongoing monitoring and management are essential to optimize outcomes and reduce the risk of complications.[12]

HCM is classified into 2 subtypes: obstructive and non-obstructive. The focus here is solely on obstructive HCM (oHCM), and non-obstructive HCM is not discussed.

3.1.3 Definition of obstructive HCM (oHCM)

In oHCM, the thickened septum can dynamically narrow the left ventricular outflow tract (LVOT), obstructing blood flow to the aorta, which can occur at rest or during provocation.

Figure 1. Obstructive HCM



A. Normal heart **B.** oHCM

HCM = hypertrophic cardiomyopathy; LV = left ventricular; oHCM = obstructive hypertrophic cardiomyopathy. Adapted from Mayo Clinic (2020)[21]

It is estimated that approximately 30% of patients present with LVOT obstruction at rest, and another 30% present with LVOT obstruction during stress.[18] LVOT obstruction is a strong independent predictor of severe symptoms and death.[22-25] Dynamic narrowing can also involve systolic anterior motion (SAM) of the mitral valve, leading to mitral regurgitation and further hemodynamic instability. Obstructive HCM is defined by unexplained left ventricular hypertrophy (wall thickness ≥ 15 mm, or 13 mm if familial) and an LVOT obstruction (peak gradient ≥ 30 mmHg at rest or with provocation).[12,26]

3.1.3.1 Obstructive HCM and its complications

Many patients with oHCM experience significant symptoms such as dyspnea, chest pain, fatigue, and syncope, which can severely impact QoL. oHCM significantly affects health-related QoL (HRQoL), including professional life, leisure time activities, mental well-being, and family planning. As a result, oHCM significantly affects a patient's social life and ability to work, with symptoms often developing gradually over the years. Consequently, patients with oHCM must adapt to severe limitations in daily life due to the burden of these symptoms.[1-4]

Obstructive HCM is associated with an increased risk of long-term cardiovascular (CV) complications.[22] The majority of patients with oHCM will have progressive left ventricular remodelling, leading to cardiac dysfunction and development of the clinical syndrome of heart failure (end-stage HCM), which is associated with substantial cardiac morbidity and mortality.[12,16,22,23,27-29] Other common complications include stroke and arrhythmias, such as AF or non-sustained ventricular tachycardia in up to 30%-33% of patients. Patients with oHCM must adapt and accept severe limitations due to burden of symptoms. A

recent Danish nationwide study has also found that a diagnosis of HCM was associated with a significant increase in heart failure and mortality rates compared with matched controls from the background population.[30] Obstructive HCM-related complications generally occur from 50 through 70 years of age, but they can happen at any age. According to the Sarcomeric Human Cardiomyopathy Registry (SHaRe), the risk of these adverse outcomes is higher in patients diagnosed early in life (aged < 40 years) and in those with pathogenic sarcomeric variations, with the exception of ventricular arrhythmias (see Table 80).[22,27]

3.1.3.2 LVOT obstruction and risk of heart failure

The primary factor contributing to heart failure symptoms in oHCM is LVOT obstruction, which independently influences the progression of heart failure and increases the risk of stroke-related or heart failure-related mortality.[22] Several studies show that progressive left ventricular remodelling and fibrosis in oHCM can also lead to heart failure. Hence, reduced cardiac functioning and the presence and severity of LVOT obstruction are significant predictors of adverse outcomes. Patients with severe obstruction are also more likely to experience progressive symptoms, heart failure, and increased mortality.[13,22,25] Those with severe symptoms and significant LVOT obstruction are at higher risk of developing heart failure, which is associated with increased morbidity and mortality.[12,22]

For patients with oHCM the LVOT obstruction is dynamic and with spontaneous variability due to the altered myocardial contractility and loading conditions.[17] Due to the dynamic nature of the LVOT obstruction, it can be present and significant irrespective of perceived cardiac symptoms. Even in the absence of severe symptoms, the magnitude of the resting LVOT gradient is directly and independently associated with increased risk of severe adverse outcomes, and patients who are asymptomatic or mildly symptomatic but presents with high LVOT gradients at rest, have higher risk of severe heart failure and have poorer expected survival.[22,23,25]

Another study has shown that in asymptomatic or mildly symptomatic oHCM patients, the LVOT is the primary predictor of CV death, whereas, after development of more severe symptoms, the New York Heart Association (NYHA) functional class becomes the predominant marker of prognosis.[23]

This underscores the importance of proper clinical assessment and detection of LVOT gradients during rest and provocation. In addition, it is critical to establish the patient's correct level of symptoms and functional limitations. Consequently, the most current treatment guidelines emphasizes that effective treatment of oHCM is not only focusing on reducing the level of symptoms but importantly, on reducing the LVOT obstruction irrespective of the perceived level of symptoms.[9]

The patient's degree of heart failure symptoms in oHCM is traditionally described based on the NYHA functional classes I-IV. The NYHA functional classification system is widely used to categorize risk of heart failure according to the severity of symptoms while an individual is performing physical activity (Figure 27); worse symptoms equate to higher NYHA classes and correlate proportionally to a greater risk of all-cause mortality.[31,32] NYHA classification is not an exact measure, as it is often based on a subjective assessment of symptoms in routine clinical practice.

The presence and level of LVOT obstruction is assessed in clinical practice, at rest, or during provocation by echocardiography. For guiding treatment in clinical practice, an LVOT > 50 mmHg is considered severe obstruction requiring guideline-directed treatment.[9]

3.1.3.3 oHCM mortality and NYHA class

Association between risk of mortality in patients with oHCM and an increased symptomatic burden, as measured by NYHA class, has been demonstrated in several studies[23-25] and large register-based studies.[6,33-35]

A meta-analysis of 12,146 HCM patients shows LVOT/mid-ventricular obstruction is a strong predictor of sudden cardiac death (population-attributable risk ~16.4%) and all-cause death (~10.1%), with NYHA III/IV status also strongly prognostic.[5]

Further evidence for the effect of mavacamten on mortality has been shown in a recently published study by Patel et al. (2026)[7].[7] The results show a reduction on all-cause mortality of mavacamten in patients with oHCM, thus supporting the assumption of a mortality benefit of mavacamten.[7] The study was a U.S. multi-center TriNetX cohort of 12,784 oHCM patients which compared mavacamten (n=550) to standard medical therapy.[7] The results demonstrated a reduction in mortality risk for mavacamten compared to standard medical therapy:

Relative risk for mortality (median follow up 19 months):

- All-cause mortality in the mavacamten group after 19 months: 5/550 =0.9%
- All-cause mortality in the comparator group: 393/12 234 =3.2%
- Absolute risk reduction, all-cause mortality: 3.2-0.9 =2.3%
- Relative risk reduction, all-cause mortality, 72% (2.3/3.2).

Wang et al. (2023)[34] conducted an analysis of oHCM mortality using a cardiac cohort of the Optum Market Clarity database with linked claims and electronic health records in a United States (US) setting. The study included 4,631 adults with oHCM (NYHA class I: 23.9%; II: 38.8%; III: 32.4%; IV: 5.0%) who had a NYHA class ≥ I after first observed oHCM diagnosis. This study provided hazard ratio (HR) estimates for all-cause mortality adjusted by age, gender, and race. Mean age was 59 years at first observed diagnosis, 47% of the population was female, and 77% of the patient population was white.[34] Table 81 presents the HRs by NYHA class.

SHaRe is an international registry that maintains longitudinal databases of clinical characteristics and outcomes data of 7,964 patients with HCM as of 2019.[6,34,35] Of these patients, 2,495 were adults (aged ≥ 18 years) with at least one definite NYHA assessment (NYHA I: 38%; II: 41%; III-IV: 21%). The mean age for these patients was 52 years, 42% of the population was female, and 89% of the patient population was white. Based on these data, the risks of all-cause mortality at 1 year of follow-up were estimated for NYHA classes I, II, and III-IV, respectively. An adjusted analysis (i.e., adjusted for age at diagnosis, gender, race, family history, LVOT at rest, left ventricular ejection fraction [LVEF], and maximal ventricular wall thickness) using multivariate analysis reported HR by NYHA class.[6,34,35] Table 81 presents the HRs by NYHA class.

3.2 Patient population

Mavacamten is indicated for the treatment of symptomatic (NYHA class II-III) oHCM in adult patients.

Mavacamten has been investigated in the pivotal EXPLORER-HCM study as an add-on treatment to first-line therapy with beta-blocker (BB) or calcium channel blocker (CCB).

The target population is patients with mild to moderate symptoms (NYHA II-III) who continue to experience symptoms, functional impairment, or reduced QoL despite first-line medical treatment with BB or CCB and/or continue to have obstruction at rest and/or with provocation (LVOT ≥ 30 mmHg) but who do not yet have significant or severe symptoms that indicate invasive irreversible surgical treatment with either myectomy or alcohol septal ablation (ASA). Patients with mild to moderate symptoms (NYHA II-III) who are intolerant to or have contraindications for first-line treatment with BB or CCB would also be eligible for mavacamten.

3.2.1 Incidence and prevalence in Denmark

Epidemiology data specifically related to oHCM are limited. Instead, there are data on the epidemiology of HCM in general. The overall global prevalence of HCM is estimated to be 1 in 500 people,[36-38] whereas diagnosed prevalence of symptomatic HCM is estimated to be 1 in 1,500 people.[12,31,39-45] Approximately 1 in 3 patients with symptomatic HCM is estimated to have oHCM at rest and 1 in 3 patients at stress; 1 in 3 patients have non-obstructive HCM.[12,31] However, it is unknown how these global estimates correlate with the Danish population; therefore, we used Danish registries to inform about the actual incidence of oHCM in Denmark. The Danish registry-based study investigated temporal trends in HCM and oHCM and patient characteristics during the years 2005--2018.[46,47] In the study, all Danish residents aged 18 years or older with a hospitalization or ambulatory first-time diagnosis for HCM were identified through The Danish National Patient Register and run in conjunction with The Danish National Prescription Registry. A total of 3,856 patients were diagnosed with HCM in Denmark from 1 January 2005 through 31 December 2018, with a median age at diagnosis of 67.8 years. Overall, 2,139 patients (55.47%) were diagnosed with non-obstructive HCM and 1,717 (44.53%) with oHCM. Over the observation period, mortality remained high; at the end of the study, 1,154 patients with oHCM (67.2%) were alive, while 563 (32.8%) had died.[48] Table 1 presents the incidence of oHCM in Denmark from 2014--2018.

Table 1. Incidence and prevalence of oHCM in Denmark (2014-2018)

Year	2014	2015	2016	2017	2018
Incidence in Denmark	138	128	139	133	103
Prevalence in Denmark	NA	NA	NA	NA	NA
Global prevalence	NA	NA	NA	NA	NA

NA = not available; oHCM = obstructive hypertrophic cardiomyopathy.
Source: Zoerner et al. (2022)[48]

To estimate the number of patients eligible for mavacamten, several assumptions were needed, as the registries do not capture symptom severity or NYHA class. Overall, 1,154 patients were diagnosed with oHCM in Denmark during the period of 2005-2018 and were still alive in 2018.[48] An assumption was needed to account for any patients diagnosed before 2005 who were still alive in 2018. Because the lower quartile of this patient population had a median age of 58 years,[48] it was assumed that most patients

would still be alive in 2018; hence, 25% was estimated and added on to represent patients diagnosed before 2005 and still alive in 2018.

As only NYHA class II-III patients are eligible for mavacamten, another assumption is needed. Thus, it was assumed that all NYHA class II-III patients are treated with either BB and/or CCB. Of the 1,717 patients diagnosed with oHCM, 675 were treated with BB at baseline and 500 were treated with CCB at baseline.[48] Based on an expert elicitation study from the United Kingdom (UK),[49] it was assumed that 10% of patients with oHCM are treated with CCB alone and the rest with CCB in combination with BB. Therefore, it was estimated that 725 patients are being treated with BB and/or CCB, corresponding to 42.2% of the patients. With no data on the number of patients with insufficient relief of symptoms after treatment with BB and/or CCB, Bristol Myers Squibb (BMS) estimated this number to be 40%. For simplicity, it is assumed that the number of patients based on the 2018 figure is representative of today. Based on these assumptions, it is anticipated that 244 patients in Denmark could be considered eligible for treatment with mavacamten today. Table 2 presents the calculations and assumptions.

Table 2. Eligible patient calculations

Population	Proportion	No. of patients	Source	Calculation
Number of patients with oHCM from 2005-2018 and still alive in 2018		1,154	Zoerner et al. (2022)[48]	
Number of patients with oHCM and still alive in 2018, including patients diagnosed before 2005	+25%	1,443	Zoerner et al. (2022)[48]	1,154 patients + 25% (diagnosed before 2005 and still alive in 2018)
Number of patients with oHCM and NYHA class II-III	42.2%	609	Zoerner et al. (2022)[48] and assumption	1,443 patients × 42.2% (patients with oHCM treated with BB and/or CCB)
Number of patients with insufficient relief of symptoms after treatment with BB and/or CCB	40%	244	BMS estimate	40% of 609 patients

BB = beta-blocker; CCB = calcium channel blocker; NYHA = New York Heart Association; oHCM = obstructive hypertrophic cardiomyopathy.

Because a stable number of patients with oHCM were diagnosed each year from 2005-2018, we assumed a stable incidence of 128 patients per year calculated based on the most recent 5-year incidence rate (see Table 1). The same assumptions for the prevalence number were used to estimate a yearly incidence of 26 patients with NYHA class II-III and insufficient relief of symptoms on BB and/or CCB. The prevalence and incidence estimates were used to estimate the number of eligible patients over the next 5 years. The numbers presented in Table 3 consider mortality as described in Section 8.2 mortality has only a minor impact on the 5-year period.

Although the patient numbers are uncertain due to the number of assumptions needed in the estimation, to the best of our knowledge, they do represent the most realistic numbers for the Danish patients eligible for mavacamten.

Table 3. Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients with oHCM in Denmark who are eligible for mavacamten	244	270	296	322	348

oHCM = obstructive hypertrophic myocardiopathy.

3.2.2 Age group of population affected and patient group currently eligible for treatment in Denmark

Specific information for oHCM has not been identified in the literature; therefore, the age group data are presented for HCM instead.

Although HCM can present symptomatically at any age, the prevalence of HCM is shown to increase with age. Most patients are diagnosed in their 50s.[29,50] Although the incidence of HCM is slightly greater in men than women (55% vs. 45%), women are often diagnosed later in life, have more symptoms, and have a worse prognosis than men.[51] In SHaRe, a global registry, the median age of diagnosis was 45.8 years.[27] In the Cardiomyopathy Registry of the EURObservational Research Programme, the mean age of diagnosis was 47 years, with the 25th and 75th percentiles at 33 and 59 years of age, respectively.[52] According to a recent Danish nationwide study of HCM, the average age of diagnosis was 63 years, and women were 7 years older than men at time of diagnosis. Although this study reported significantly higher mortality rates among patients with HCM compared with matched controls, it did not find that gender was significantly associated with mortality.[30] The Danish registry study reported a median age of 68.4 years at the time of diagnosis for all patients with oHCM.[48] In the EXPLORER-HCM trial, the mean age was 58.5 years in both the mavacamten group and the placebo group.[52,53] Most patients had NYHA class II symptoms (73%) and were taking BBs or CCBs (92%).[53] In the absence of more specific data on mean age for oHCM specifically, EXPLORER-HCM is considered to reflect the general oHCM population in Denmark.

3.3 Current treatment options

The current treatment algorithm for oHCM in Danish clinical practice is described in the NBV, National treatment guideline by the Danish Cardiologic Society and based on ESC 2023 guidelines.[9,18] Patients in Denmark are offered genetic testing as part of their diagnosis of oHCM; based on family history, it is possible to refer the patient and relatives for family screening. Patients who are asymptomatic (NYHA class I) and carriers of specific pathogenic genes are not offered pharmacological treatment but are routinely called in for echocardiographic checkup at certain intervals.

When patients start to develop symptoms (NYHA class II), such as dyspnea or chest pain, and/or present with an LVOT gradient, patients are offered treatment with a negative inotropic agent, such as a non-vasodilating BB. Second-line treatment is CCB, such as verapamil or diltiazem. These pharmacological treatments work by reducing heart rate and force of contraction, and can help improve symptoms of oHCM, but do not target the underlying pathophysiology or etiology of the disease or disease progression.[10,12] Patients with oHCM are often treated with drugs indicated for other CV disorders, such as heart failure (e.g., BBs and CCBs), that have not been systematically investigated for oHCM specifically in large, randomized controlled trials (RCTs).[12] Beta-blockers and non-dihydropyridine CCBs have been the mainstay of treatment for decades but only offer

limited and variable relief from symptoms and/or functional status.[1,54] In addition to inadequate symptom relief, these treatments are often poorly tolerated.[55] Potential side effects of BBs that may affect daily life include fatigue, chronotropic incompetence, and asthma; potential side effects of CCBs are atrioventricular (AV) conduction decrease and ankle edema.[55]

For patients who continue to experience decreased functionality, or who are mildly to moderately symptomatic despite optimally dosed treatment with either BB or CCB (NYHA II-III), there is currently no other treatments available until patients progress to severe symptoms or severely decreased functionality. Patients who continue to progress, who have high LVOT gradients (> 50 mmHg), and experience severe and limiting symptoms (NYHA class III-IV) and/or exertional or unexplained recurrent syncope in spite of maximally tolerated drug therapy are candidates for invasive treatments, such as septal reduction therapy (SRT).[9,18] According to the guidelines, patients who have another surgical indication, such as mitral valve regurgitation, SAM, or left atrial dilatation, can also be considered as candidates for SRT.[9]

In the international SHaRe registry, 18% of patients with HCM underwent SRT at any time (27.3% of patients with HCM–left ventricular systolic dysfunction [LVSD] and 17.5% of patients without LVSD).[56] In Denmark, ASA[i,57] is the preferred treatment in comparison to ventricular septal myectomy. [ii,57] The annual rate of ASA procedures in Denmark is approximately 40 cases (per year). [57] Septal reduction therapy can treat cardiac structural changes by physically removing the obstruction to relieve the gradient caused by the disease but does not alter the underlying pathophysiology of oHCM.[12,31,56,58,59] The procedure is associated with peri-procedural and potentially severe post-surgery complications, as well as the potential need for pacemaker implantation and re-intervention.[60] Additionally, approximately 20% to 30% of patients still require treatment following invasive therapy.[12,61] The main non-fatal complication of ASA is AV block in 7% to 20% of patients.[9] For patients who refuse to receive, or are ineligible for, SRT due to their overall condition or morphology of the heart, there is currently no further treatments available. In cases where patients remain severely symptomatic and have poor QoL, heart transplant is the final resort.[18,61]

3.4 The intervention

Mavacamten is a first-in-class, selective, allosteric, and reversible cardiac myosin inhibitor developed to target the underlying pathophysiology (exaggerated myosin–actin interaction) of oHCM. The mode of action of mavacamten is multifactional.

Mavacamten binds to cardiac myosin, a motor protein responsible for cardiac muscle contraction. By inhibiting the ATPase activity of myosin, mavacamten reduces the number of myosin–actin cross-bridges that form during the cardiac cycle. This leads to a decrease in the force of cardiac muscle contraction. By reducing the hypercontractility

[i] Alcohol septal ablation is a non-surgical procedure in which pure alcohol is injected into an artery to target the area of thickened heart tissue; this damages the tissues, which results in shrinkage, removing the outflow obstruction.
[ii] Myectomy is open heart surgery to remove a section of the thickened heart tissue and, therefore, reduce outflow obstruction.

and the number of active myosin heads, mavacamten decreases the obstruction in the LVOT. This helps to improve blood flow from the left ventricle to the aorta and reduces the pressure gradient across the LVOT. Ultimately, the reduction in LVOT obstruction and normalization of cardiac muscle contraction help to alleviate symptoms associated with oHCM, such as shortness of breath, chest pain, and exercise intolerance. This can lead to an improvement in overall functional capacity and QoL for patients.[53,62,63]

Overall, the targeted inhibition of cardiac myosin by mavacamten addresses the underlying pathophysiology of oHCM, in contrast to the current, established treatments in Denmark. Mavacamten provides a novel therapeutic approach for managing symptomatic oHCM and constitutes an effective and safe, once-daily oral therapy.

Table 4 provides an overview of mavacamten. Full details of the prescribing information for mavacamten are available from the summary of product characteristics (SmPC).[64]

Table 4. Summary of intervention

Overview of intervention	
Indication relevant for the assessment	Mavacamten is indicated for the treatment of symptomatic (New York Heart Association [NYHA] class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients
ATMP	N/A
Method of administration	Oral use (capsule), once daily
Dosing	CYP2C19 intermediate, normal, rapid, and ultra-rapid metabolizer phenotype: The recommended starting dosage is 5 mg orally once daily. The maximum dosage is 15 mg once daily. CYP2C19 poor metabolizer and unknown phenotype: ▪ The recommended starting dose is 2.5 mg orally once daily. The maximum dose is 5 mg once daily. The patient should be assessed for early clinical response by LVOT gradient with Valsalva manoeuvre 4 and 8 weeks after treatment initiation. Once an individualized maintenance dose is achieved, patients should be assessed every 6 months. If at any visit the patient's LVEF is < 50%, the treatment should be interrupted for 4 weeks and until LVEF returns to ≥ 50%.
Dosing in the health economic model (including relative dose intensity)	▪ Mavacamten: 2.5 mg once daily ▪ BB/CCB ▪ Metoprolol: 50 mg once daily ▪ Verapamil: 120 mg once daily ▪ Relative dose intensity: 100% for all treatments
Should the medicine be administered with other medicines?	Can be used in combination with BBs and CCBs
Treatment duration / criteria for end of treatment	Consideration should be given to discontinuing treatment in patients who have shown no response (e.g., no improvement in symptoms, QoL, exercise capacity, LVOT gradient) after 4-6 months on the maximum tolerated dose. Discontinue treatment if LVEF < 50% on 2 occasions at 2.5 mg daily.
Necessary monitoring, both during administration and during the treatment period	Before treatment initiation, patients' LVEF should be assessed by echocardiography. If LVEF is < 55%, treatment should not be initiated. Four to 8 weeks after treatment initiation, the patient should be assessed for early clinical response. If LVOT gradient with Valsalva manoeuvre is < 20 mmHg, the daily dose should be reduced by 1 dose level. Otherwise, if LVEF remains > 50%, the current once-daily dose should be maintained. If LVEF ≥ 55% and LVOT ≥ 30 mmHg, the dose should be increased to the next highest daily dose level. The maximum daily dose is 15 mg. Dose increases should not occur more frequently than every 12 weeks. Following any dose increase, LVEF should be assessed after 4 to 8 weeks, and then the patient

Overview of intervention	
	should return to monitoring every 12 weeks. Once an individualized maintenance dose is achieved, patients should be monitored every 6 months.
Need for diagnostics or other tests (e.g., companion diagnostics). How are these included in the model?	Before initiation of treatment, women of childbearing potential must have a negative pregnancy test. Patients should be cytochrome P450 (CYP) 2C19 (CYP2C19) genotype tested to determine their CYP2C19 phenotype before starting treatment. Patients with CYP2C19 poor metabolizer phenotype have increased mavacamten exposures (up to 3 times) that can lead to an increased risk of systolic dysfunction compared with normal metabolizers.[64]
Package size(s)	28 hard capsules in concentration 2.5/5/10/15 mg mavacamten

ATMP = Advanced Therapy Medicinal Products; BB = beta-blocker; CCB = calcium channel blocker; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; N/A = not applicable; QoL = quality of life.

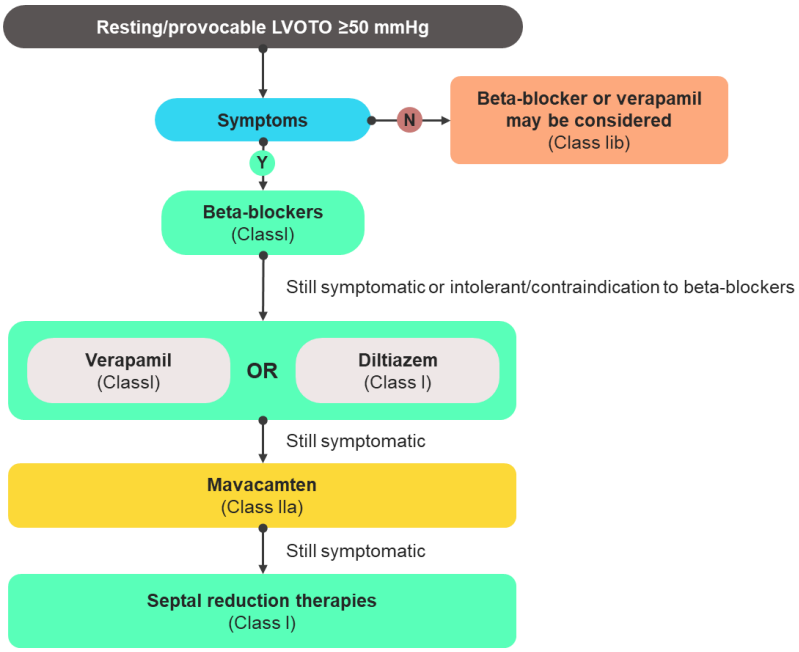
3.4.1 Description of ATMP

Not applicable.

3.4.2 The intervention in relation to Danish clinical practice

The current clinical treatment pathway for patients with oHCM in Denmark is shown in Figure 2, which includes the proposed placement of mavacamten. The estimates for patient numbers are presented and explained in Section 3.2.1.

Figure 2. Overview of the oHCM treatment pathway in Denmark and mavacamten's anticipated position



LVOTO = left ventricular outflow tract obstruction; NYHA = New York Heart Association; oHCM = obstructive hypertrophic cardiomyopathy.
Adapted from : Arbelo et al. (2023)[9]

During the European Medicines Agency (EMA) process the CYP2C19 genotype testing was introduced to the label, although the test and starting dose have not been part of the clinical program for mavacamten (Table 4). The incidence of CYP2C19 poor metabolizer phenotype ranges from approximately 2% in Caucasian to 18% in Asian populations.[64]

As genetic testing of patients as well as relatives has been part of standard clinical care in Denmark for several years[18,30], it is unlikely that genetic testing will increase the patient pool eligible for treatment with mavacamten because only patients presenting with symptoms require pharmacological intervention and only patients on standard of care medication with persisting NYHA class II-III symptoms are indicated for treatment with mavacamten.

3.5 Choice of comparator(s)

Based on current practice in Denmark, mavacamten is intended for adult patients in NYHA class II-III with insufficient symptomatic relief from BBs and CCBs. Mavacamten offers a novel treatment option of symptomatic oHCM that will be added to current treatment regimens and is not expected to replace any other therapy. Therefore, the relevant comparator in efficacy and safety studies is placebo + BBs/CCBs. For the health economic analysis, the relevant comparator is BBs/CCBs. SRT is not a relevant comparator for mavacamten, as mavacamten is intended for symptomatic patients with obstructive HCM (NYHA II–III) who remain symptomatic despite optimal medical therapy and is positioned before invasive interventions. In contrast, SRT is reserved for a selected subgroup (still symptomatic NYHA class III–IV, or class II with syncope, and resting or maximum provoked gradient of ≥50 mmHg) of patients with severe, refractory symptoms and represents an invasive treatment strategy.

3.6 Cost-effectiveness of the comparator(s)

Based on current practice in Denmark, mavacamten is intended for adult patients in NYHA class II-III with insufficient symptomatic relief from BBs and CCBs. Mavacamten offers a novel treatment option for symptomatic oHCM that will be added to current treatment regimens; it is not expected to replace any other therapy. Therefore, the relevant comparator in efficacy and safety studies is placebo + BBs/CCBs. For the health economic analysis, the relevant comparator is BBs/CCBs.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The definition, validity, and clinical relevance of all efficacy outcome measures included in the submission are included in Table 5 and Table 6.

Table 5. EXPLORER-HCM outcome, definition, validity, and clinical relevance

Outcome measure	Definition	Validity	Clinical relevance
Primary endpoints			
Composite endpoint 1	Change from baseline to week 30, increase in pVO_2 of ≥ 1.5 mL/kg/min and improvement of ≥ 1 NYHA class	The NYHA functional classification system is widely used to categorize heart failure. Higher NYHA classes correlate to a greater risk of all-cause mortality.[5,7,27,31,32,34,35] pVO_2 is a direct, objective, and reproducible measure that has been shown to correlate with NYHA functional class, PROs, and QoL in HCM.[65]	After discussions with HCM experts and patients, as well as regulatory authorities, the primary endpoint in the pivotal phase 3 EXPLORER-HCM clinical trial was designed to comprehensively evaluate clinically meaningful treatment benefits for oHCM by using both objective assessments of exercise capacity (pVO_2 measured by CPET) and subjective assessments of symptom burden (NYHA class).[53,66]
Composite endpoint 2	Change from baseline to week 30, increase in pVO_2 of ≥ 3.0 mL/kg/min and no worsening in NYHA class		
Secondary endpoints			
Post-exercise LVOT gradient	Post-exercise LVOT gradient, from baseline to week 30	Exercise typically elicits maximal levels of obstruction in oHCM and is an objective and reproducible measure.[12]	Reduction of LVOT gradient is one of the main goals of oHCM treatment.[12] LVOT gradient is used in clinical practice and LVOT gradient > 50 mmHg is one criterion for considering SRT.[12] LVOT obstruction is also associated with an increased risk of death related to HCM, death from heart failure or stroke, and progression to NYHA functional class III or IV.[22]
pVO_2	pVO_2, from baseline to week 30	Peak VO_2 measured by CPET is a direct, objective, and reproducible measure of exercise capacity. It has been endorsed for the clinical evaluation of the efficacy of therapeutic intervention in patients with HCM because of its high reproducibility, low variance, and narrow dynamic range at maximal effort.[67]	In HCM, pVO_2 has been shown to correlate with NYHA functional class, PROs, and QoL and to be associated with clinical prognosis.[65,67,68] Data from the large, multi-center registry SHaRe indicated that pVO_2 is an independent predictor of clinically significant cardiac events and death in patients with HCM.[43]
NYHA class change	Proportion of patients with ≥ 1 NYHA class improvement, from baseline to week 30	The NYHA functional classification system is widely used to categorize heart failure. Higher NYHA classes correlate to a greater risk of all-cause mortality.[5,7,27,31,32,34,35]	This endpoint is aligned with CHMP guideline on CHF, which notes that exercise testing may be considered as a primary endpoint in selected patient populations with high unmet medical need (including HCM) if the effect size is clinically meaningful and consistent with an improvement in PROs and the CV safety profile of the product is adequately characterized. Reduction in NYHA class of 1 or more represents a clinically meaningful improvement.[69]

Outcome measure	Definition	Validity	Clinical relevance
HRQoL	Assessed by several PRO questionnaires: KCCQ-CSS and KCCQ-OS, from baseline to week 30 HCMSQ-SoB subscore, specifically designed to evaluate symptomatic burden in patients with HCM, from baseline to week 30	KCCQ is a valid tool for use in studies of patients with heart failure[70] The HCMSQ was developed by the sponsor in line with FDA guidance for industry.[71]	The measures assess HRQoL concepts that are specific to HCM. KCCQ is used to assess the impact of HCM on health status and work productivity and activity.[72-75] The HCMSQ is a novel PRO developed by MyoKardia in line with FDA guidance (US Department of Health and Human Services 2009).[70,76]
Exploratory endpoints			
EQ-5D-5L index score and EQ VAS score,	EQ-5D-5L index score and EQ VAS score, from baseline to week 30		The measures assess the impact of HCM on health status and work productivity and activity, with the possibility to compare across disease categories.[70,76]
Proportion of patients with a complete response	Proportion of patients with a complete response (all LVOT gradients < 30 mmHg and NYHA I status), from baseline to week 30	Exercise typically elicits maximal levels of obstruction in oHCM and is an objective and reproducible measure. The NYHA functional classification system is widely used to categorize heart failure. Higher NYHA classes correlate to a greater risk of all-cause mortality.[5,7,27,31,32,34,35]	Reduction of LVOT gradient is one of the main goals of oHCM treatment.[12] LVOT gradient is used in clinical practice and LVOT gradient > 50 mmHg is one criterion for considering SRT.[12] LVOT obstruction is also associated with an increased risk of death related to HCM, death from heart failure or stroke, and progression to NYHA functional class III or IV.[22] This endpoint is aligned with CHMP guideline on CHF, which notes that exercise testing may be considered as a primary endpoint in selected patient populations with high unmet medical need (including HCM) if the effect size is clinically meaningful and consistent with an improvement in PROs and the CV safety profile of the product is adequately characterized. Reduction in NYHA class of 1 or more represents a clinically meaningful improvement.[69]
Improvement in LVOT gradients	Proportion of patients with improvement in LVOT gradients, from baseline to week 30	Exercise typically elicits maximal levels of obstruction in oHCM and is an objective and reproducible measure.	Reduction of LVOT gradient is one of the main goals of oHCM treatment.[12] LVOT gradient is used in clinical practice and LVOT gradient > 50 mmHg is one criterion for considering SRT.[12] LVOT obstruction is also associated with an increased risk of death related to HCM, death from heart failure or stroke, and progression to NYHA functional class III or IV.[22]
Cardiac biomarkers	Serum concentrations of cardiac biomarkers (NT-proBNP, hs-cTnI), from baseline to week 30	Previous studies in heart failure demonstrated that screening levels of NT-proBNP were strongly associated with the total heart failure hospitalizations and CV death (PARAGON-HF study of heart failure with preserved ejection fraction).[77]	In a large cohort of patients with HCM, NT-proBNP was an independent predictor of morbidity and mortality.[79] Furthermore, decreases in NT-proBNP predicted a lower subsequent risk of these outcomes and were associated with significant decreases in left atrium size.[80] Among patients with HCM, an abnormal serum concentration of cardiac troponin is an independent predictor of adverse outcome, and a higher degree of troponin abnormality has been associated with a greater risk of CV events. Serum hs-cTnT was higher in patients with HCM

Outcome measure	Definition	Validity	Clinical relevance
		A retrospective study demonstrated that elevated hs-cTnT is associated with a greater risk of end-stage HCM.[78]	with AF, LVSD, in patients with NYHA class III-IV, LV outflow obstruction, and presence of gadolinium enhancement.[81,82]
Echocardiogram parameters of left ventricular structure and function, including systolic and diastolic function	Echocardiogram parameters of left ventricular structure and function, including systolic and diastolic function (left ventricular mass index, left atrial volume index, lateral early diastolic mitral annular velocity [e'], septal e', lateral ratio between early mitral inflow velocity and mitral annular early diastolic velocity [E/e'], and septal E/e'), from baseline to week 30		

AF = atrial fibrillation; CHF = congestive heart failure; CHMP = Committee for Medicinal Products for Human Use; CPET = cardiopulmonary exercise test; hs-cTnI = high-sensitivity cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T; CV = cardiovascular; FDA = Food and Drug Administration; HRQoL = health-related quality of life; LVOT = left ventricular outflow tract; LVSD = left ventricular systolic dysfunction; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; oHCM = obstructive hypertrophic cardiomyopathy; PRO = patient-reported outcome; pVO_2 = peak oxygen consumption; SRT = septal reduction therapy.

Table 6. EXPLORER-LTE outcome, definition, validity and clinical relevance

Outcome measure	Definition	Validity	Clinical relevance
Efficacy and pharmacodynamic endpoints			
Echocardiogram parameters systolic and diastolic function	Change from baseline in echocardiographic parameters of systolic function (e.g., LVEF) and diastolic function (e.g., peak velocity of early diastolic septal and lateral mitral annular motion [e'], ratio of peak velocity of early diastolic transmitral flow [E] to e' [E/e'], ratio of E to peak velocity of late transmitral flow [A] [E/A], pulmonary artery systolic pressure, left atrium size) over time		

Outcome measure	Definition	Validity	Clinical relevance
LVOT gradient	Change from baseline in resting and Valsalva manoeuvre LVOT gradient		Reduction of LVOT gradient is one of the main goals of oHCM treatment.[12] LVOT gradient is used in clinical practice and LVOT gradient > 50 mmHg is one criterion for considering SRT.[12] LVOT obstruction is also associated with an increased risk of death related to HCM, death from heart failure or stroke, and progression to NYHA functional class III or IV.[22]
NYHA class change	Change from baseline in NYHA class over time	The NYHA functional classification system is widely used to categorize heart failure. Higher NYHA classes correlate to a greater risk of all-cause mortality.[5,7,27,31,32,34,35]	This endpoint is aligned with CHMP guideline on CHF, which notes that exercise testing may be considered as a primary endpoint in selected patient populations with high unmet medical need (including HCM) if the effect size is clinically meaningful and consistent with an improvement in PROs and the CV safety profile of the product is adequately characterized. Reduction in NYHA class of 1 or more represents a clinically meaningful improvement.[69]
Cardiac biomarkers	Change from baseline in NT-proBNP over time	Previous studies in heart failure demonstrated that screening levels of NT-proBNP were strongly associated with the total heart failure hospitalizations and CV death (PARAGON-HF study of heart failure with preserved ejection fraction).[77]	In a large cohort of patients with HCM, NT-proBNP was an independent predictor of morbidity and mortality.[79] Furthermore, decreases in NT-proBNP predicted a lower subsequent risk of these outcomes and were associated with significant decreases in left atrium size.[80]
Cardiac transplant	Frequency of cardiac transplant		
Exploratory endpoints			
Patient-reported severity	Change from baseline over time in participant-reported severity of HCM symptoms as assessed by the HCMSQ score		The measures assess HRQoL concepts that are specific to HCM. The HCMSQ is a novel PRO developed by MyoKardia in line with FDA guidance.[70,76]
Health status	Change from baseline in health status as assessed by the EQ-5D scores		The measure assess the impact of HCM on health status and work productivity and activity, with the possibility to compare across disease categories.[70,76]

CHF = congestive heart failure; CHMP = Committee for Medicinal Products for Human Use; CV = cardiovascular; FDA = Food and Drug Administration; HCMSQ = Hypertrophic Cardiomyopathy Symptom Questionnaire; HR = heart failure; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; oHCM = obstructive hypertrophic cardiomyopathy; PRO = patient-reported outcome; SRT = septal reduction therapy.

4 Health economic analysis

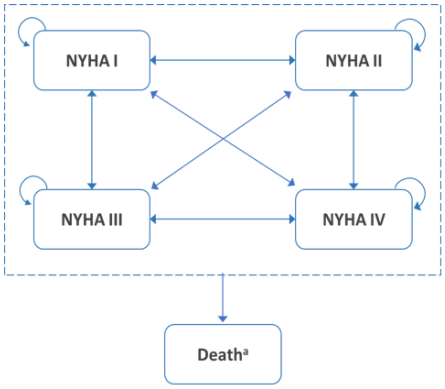
The model was constructed to estimate the health economic value of mavacamten by calculating the costs and health outcomes (i.e., life-years [LYs] and quality-adjusted life-years [QALYs]) associated with mavacamten + BB/CCB versus the comparator of interest.

A Markov model was chosen due to the chronic nature of oHCM, with possible and recurrent transitions among various health states representing varying levels of disease severity. The use of a Markov model was deemed appropriate because it can capture disease progression and patient heterogeneity among patients with oHCM with a manageable number of mutually exclusive and collectively exhaustive health states. Furthermore, a Markov model was the most often used framework for assessing the cost-effectiveness of treatment options in various CV diseases, including heart failure and myocardial infarction.[83]

4.1 Model structure

Figure 3 presents a simplified model structure. It is classified based on mutually exclusive and jointly exhaustive NYHA-based health states (NYHA I, II, III, IV) and Death. All patients enter the model in either NYHA II or III health states, which reflects the baseline population of EXPLORER-HCM and aligns with the EMA regulatory label. At initiation of EXPLORER-HCM, 72.9% and 27.1% of patients were NYHA II and III, respectively. During the trial, a significant proportion of patients moved to NYHA class I from NYHA II or III. However, the number of patients moving to NYHA class IV was small, irrespective of the treatment arm.

Figure 3. Simplified model schematic



NYHA = New York Heart Association.
[a] Death state is accessible from all non-Death health states.

At each cycle/assessment period, patients can transition to any other NYHA health state or stay in the same state based on the probability of experiencing improvement or worsening of NYHA class; this is driven by transition probabilities (TPs) implemented in the model. Furthermore, all patients are considered at risk of death in each model cycle.

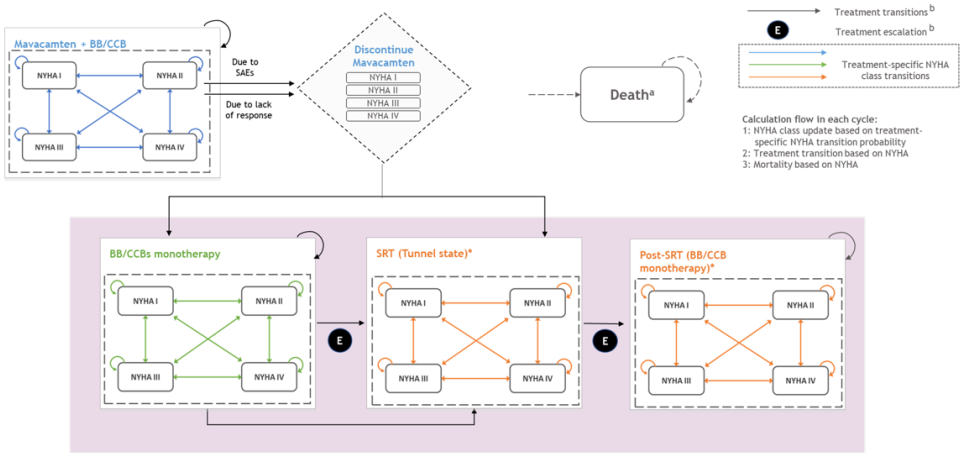
NYHA class is a component of the primary endpoint and a key standalone secondary endpoint in EXPLORER-HCM. NYHA class is commonly used in treatment guidelines and clinical practice.[10]

A systematic literature review (SLR) of cost-effectiveness models (CEMs) in patients with heart failure found that, among 64 studies identified, 40 studies used NYHA class–based Markov health states.[83]

In addition, NYHA class correlates well with patient utility and mortality and is commonplace within published literature for both heart failure and cardiomyopathy.[84] The correlation between increased mortality risk with increased NYHA class is confirmed in Liu et al. (2017)[5], demonstrating that patients in higher NYHA classes have a higher risk for all-cause death and cardiovascular death.[5] Further, direct evidence of a reduction of all-cause mortality of mavacamten compared to standard medication in oHCM patients has been shown.[7] Where data were collected, this model is informed by clinical trial data for mavacamten, with published literature used to supplement when appropriate, especially in areas where the clinical trial data do not inform certain inputs. Other CV outcomes, such as heart failure, transplant, stroke, and myocardial infarction, are not modelled separately in the present model structure because they are assumed to be captured by the overarching NYHA-based health states. If mavacamten were to potentially reduce the incidence of these CV outcomes, not modelling them explicitly would likely be a conservative approach, considering these events may lead to a higher utilization of healthcare services.

Although Figure 3 depicts a simplification of the model and stages, Figure 4 presents the full model, including its structure and stages.

Figure 4. Stages and structure of the model



BB = beta-blocker; CCB = calcium channel blocker; NYHA = New York Heart Association; SAE = serious adverse event; SRT = septal reduction therapy.
Note: Treatment with SRT was modelled as an event (tracked using tunnel state). Hence, patients treated with SRT were moved to post-SRT state after 1 cycle. Pink shaded box highlights the treatment pathway as outlined in the European Society of Cardiology guidelines.
[a] Death state is accessible from all non-Death health states.
[b] Treatment transitions are based on NYHA classes.

4.1.1 Treatment pathways

The CEM is designed to allow inclusion of various subsequent treatments (i.e., BB/CCB monotherapy, SRT + BB/CCB) that patients can switch to or escalate to. Alcohol septal ablation therapy and myectomy were included as eligible procedures for SRT.

During the first 30 weeks (i.e., EXPLORER-HCM trial period), all patients remained on their initial treatment; however, patients were allowed to discontinue or escalate from their initial therapy at the end of week 30 and at each model cycle thereafter throughout the time horizon. Sections 8.3 and 8.4 describe the reasons for discontinuation or escalation from initial therapy, as well as the inputs.

Details of each treatment pathway for patients in the intervention and comparator arms are described in subsequent sections and depicted in Figure 4.

4.1.1.1 Treatment pathways in comparator arm

In the comparator arm, patients initially received BB/CCB monotherapy, reflecting the comparator/placebo arm of EXPLORER-HCM. Patients were able to escalate along the treatment pathway (as per the ESC guidelines[12]) at week 30 and beyond to a subsequent treatment (i.e., SRT + BB/CCB). Escalation was undertaken on a per-cycle basis, with a defined proportion of patients escalating based on the NYHA class they were in at the time of escalation.

Septal reduction therapy was modelled as an incident event. Hence, patients undergoing SRT were moved to a post-SRT state after 1 cycle. The SRT tunnel state was included to allow for the modelling of incident costs, disutility, and mortality associated with the procedure and to model an incident transition of NYHA health state as a consequence of the procedure. During the post-SRT state, patients reverted to BB/CCB monotherapy based on internal clinical insight. In addition, the inclusion of a post-SRT state allowed for incorporating different TPs and other key inputs before and after SRT; this, in turn, reflected the differences in clinical profiles of the patients more accurately.

4.1.1.2 Treatment pathways in the intervention arm

In the intervention arm, patients received mavacamten in combination with BB/CCB monotherapy, reflecting the treatment regimen of EXPLORER-HCM's intervention arm, which is based on the intended positioning of the therapy (i.e., mavacamten + BB/CCB). Patients were allowed to discontinue mavacamten due to serious adverse events (SAEs) or lack of response (discussed further in Section 8.4). After discontinuation of mavacamten, patients in the base case were distributed to the start of standard of care (BB/CCB monotherapy). Once patients transitioned and commenced BB/CCB monotherapy, the same assumptions were considered as patients in the comparator arm (detailed in Section 0) (Figure 4).

4.2 Model features

Table 7. Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with symptomatic (NYHA II-III) oHCM	In line with the EMA label and anticipated use in Denmark
Perspective	Limited societal perspective	According to DMC guidelines
Analytical method	Markov model	Can capture disease progression and patient heterogeneity among patients with oHCM with a manageable number of mutually exclusive and collectively exhaustive health states

Model features	Description	Justification
Time horizon	Lifetime (40 years)	As the mean age of EXPLORER-HCM is 59 years, a 40-year time horizon was considered adequate to capture all health benefits and costs in line with DMC guidelines.
Cycle length	First 30 weeks: variable cycle lengths (i.e., weeks 4, 8, 10, 14, 16, 18, 22, 26, 30) After week 30: 28 days	First 30 weeks: clinical assessment timepoints from EXPLORER-HCM were used as cycle lengths, which allowed for the transition rates observed in the trial to be directly applied in the model. After week 30: to align with the anticipated dosage of mavacamten (i.e., 28-day cycles, each pack with 28 capsules; 1 capsule per day).
Half-cycle correction	Yes	According to DMC guidelines.
Discount rate	3.5 %	The DMC applies a discount rate of 3.5% for all years.
Intervention	Mavacamten + BB/CCB	
Comparator(s)	BBs/CCB monotherapy	According to national treatment guidelines. Validated by Danish clinical expert.
Outcomes	▪ Incremental costs per QALY gained ▪ Incremental costs per LY gained	
Costs	▪ Treatment acquisition costs ▪ Monitoring cost ▪ One-off CYP test cost ▪ HCRU cost ▪ AE cost ▪ Patient time costs ▪ Transportation costs	Standard costs for patients with oHCM
Utilities	Overall health-state utilities derived from EXPLORER-HCM	Health-state utility values obtained from EXPLORER-HCM in which patients completed the EQ-5D-5L. Disutility associated with AEs was not included in the model due to the potential double counting of the impact of AEs within the underlying utilities observed in the trial.

AE = adverse event; BB/CCB = beta-blocker/calcium channel blocker; CYP = cytochrome P450; EMA = European Medicines Agency; HCM = hypertrophic cardiomyopathy; HCRU = healthcare resource utilization; LY = life-year; NYHA = New York Heart Association; oHCM = obstructive hypertrophic cardiomyopathy; QALY = quality-adjusted life-year.

5 Overview of literature

5.1 Literature used for the clinical assessment

The intervention (mavacamten in combination with standard of care) and comparators (placebo in combination with standard of care comprising BBs and/or CCBs) being considered have been evaluated within a single RCT. Therefore, an SLR has not been conducted, and this dossier is based on the available head-to-head trials. Two key

studies included the intervention in the population relevant to the scope of this submission:

- The phase 3 trial, EXPLORER-HCM, investigated the safety and efficacy of mavacamten in patients with symptomatic oHCM. To date, this is the largest RCT conducted specifically for the treatment of oHCM.[53]
- The phase 2 trial, PIONEER-HCM, investigated the safety, tolerability, and dosing of mavacamten in patients with oHCM.[85]

There are 3 ongoing studies assessing mavacamten in patients with oHCM: MAVA-LTE (NCT03723655), PIONEER-OLE (NCT03496168), and VALOR-HCM (NCT04349072). These are open-label extension studies that provide long-term data for patients previously enrolled in the pivotal phase 3 study (EXPLORER-HCM), the phase 2 exploratory study (MAVERICK-HCM), the phase 2 proof-of-concept study (PIONEER-HCM), and the phase 3 study (VALOR-HCM). VALOR-HCM evaluated mavacamten for its effect on guideline eligibility for SRT procedures or a patient decision to proceed with SRT after 16 weeks of treatment in patients with symptomatic NYHA II-IV oHCM. This does not reflect the correct per label patient population, hence VALOR-HCM is considered only for safety data. MAVERICK-HCM was conducted in patients with non-obstructive HCM and therefore is not described further in the main submission.

PIONEER-HCM was a phase 2, open-label study[85] and was not considered to represent the best available evidence, given that data are available from the pivotal phase 3 EXPLORER-HCM trial.[53] PIONEER-HCM[86] and the associated long-term extension (LTE) study, PIONEER-OLE,[86] are therefore not described further in the main submission.

In addition, real-world evidence (RWE) was available for 22 months of results from the mavacamten Risk Evaluation and Mitigation Strategy (REMS) program.[87] Results from the REMS program have been presented in the submission as supporting evidence, although these results were not considered the best available evidence because data are available from the pivotal phase 3 EXPLORER-HCM trial.[53]

5.1.1 List of relevant studies

Table 8. Summary of RCTs included in the assessment

Trial name	NCT number	Phase	Dates of study	Used in comparison with	Reference
EXPLORER-HCM	NCT03470545	3	May 2018 to May 2020	Placebo	Olivotto et al. (2020)[53]
					Spertus et al. (2021)[63]
					Xie et al. (2021)[88]
					Ho et al. (2020)[66]
					Saberi et al. (2020)[89]
					Hegde et al. (2021)[90]
MAVA-LTE (EXPLORER-HCM cohort)	NCT03723655	2/3	October 2018 to April 2026	None	Rader et al. (2022)[91]
					Garcia-Pavia et al. (2024)[92]
VALOR-HCM	NCT04349072	3	July 2020 to June 2024	Placebo	Desai et al. (2021)[93]
					Desai et al. (2022)[94]
					Desai et al. (2025)[95]

NCT = National Clinical Trial; RCT = randomized controlled trial.

[a] Included for safety results only.

Table 9. Summary of ongoing RCTs

Trial name	NCT number	Phase	Dates of study	Used in comparison with	Reference
MAVA-LTE: EXPLORER-HCM cohort	NCT03723655	2/3	October 2018 to April 2026	None	Rader et al. (2022)[91] Garcia-Pavia et al. (2024)[92]
PIONEER-OLE	NCT03496168	2	April 2018 to November 2023	None	Heitner et al. (2019)[85]

NCT = National Clinical Trial; RCT = randomized controlled trial.

Table 10. Summary of real-world study (supporting evidence)

Study name	NCT number	Phase	Dates of study	Used in comparison with	Reference
Risk Evaluation and Mitigation Strategy program	N/A	N/A	April 2022 to February 2024	None	Desai et al. (2025)[87]

N/A = not applicable; RCT = randomized controlled trial.

For detailed information about included studies, see Appendix A.

5.2 Literature used for the assessment of health-related quality of life

An SLR was undertaken to identify HRQoL studies relevant to this submission from the published literature. Appendix I reports the methods and findings.

Table 11. Relevant literature included for (documentation of) HRQoL (see Section 10)

Trial name	Country	Reference	Title	Objective	Intervention/comparator	Instruments
EXPLORER-HCM NCT03470545	13 countries: US, Spain, Poland, Israel, Germany, France, Czech Republic, Denmark, Netherlands, Portugal, Italy, Belgium, UK	Olivotto et al. (2020)[53]	Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial	To assess the efficacy and safety of mavacamten, a first-in-class cardiac myosin inhibitor, in symptomatic oHCM	I: Mavacamten C: Placebo	KCCQ-CSS HCMSQ-SoB
		Spertus et al. (2021)[63]	Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): health status analysis of a randomised, double-blind, placebo-controlled, phase 3 trial	To assess the effect of mavacamten, a first-in-class cardiac myosin inhibitor, on patients' health status—i.e., symptoms, physical and social function, and QoL	I: Mavacamten C: Placebo	KCCQ-CSS KCCQ-OS
		Xie et al. (2021)[96]	Health utilities among patients with obstructive hypertrophic cardiomyopathy (obstructive HCM): an analysis of patient health-related quality of life in the EXPLORER-HCM trial	To assess the effects of mavacamten on patient HRQoL and estimate the utilities for health states defined by NYHA class for these patients	I: Mavacamten C: Placebo	EQ-5D-5L (US value set) EQ VAS
		Naidu et al. (2021)[97]	Mavacamten improves symptoms of shortness of breath in patients with obstructive hypertrophic cardiomyopathy (HCM): analysis of the HCM Symptom Questionnaire in the phase 3 EXPLORER trial	To assess the efficacy and safety of mavacamten, a first-in-class cardiac myosin inhibitor, in symptomatic oHCM	I: Mavacamten C: Placebo	HCMSQ-SoB
		Jacoby et al. (2021)[98]	Efficacy of mavacamten in patients with symptomatic hypertrophic cardiomyopathy: subgroup analyses by background beta-blocker use from the EXPLORER-HCM and MAVA-LTE studies	To examine the effects of mavacamten with and without BB use in patients with symptomatic oHCM	I: Mavacamten +/- BB C: Placebo	KCCQ-CSS
-	US	Serber et al. (2007)[99]	Depression, anxiety, and quality of life in patients with obstructive hypertrophic	To examine the changes in psychosocial parameters (i.e., depression, anxiety, satisfaction with life, and optimism) and QoL in	I: ASA C: -	SF-12

Trial name	Country	Reference	Title	Objective	Intervention/comparator	Instruments
			cardiomyopathy three months after alcohol septal ablation	patients with oHCM from before to 3 months after ASA		Minnesota Living with Heart Failure Questionnaire
-	US	Balaram et al. (2012)[100]	Role of mitral valve plication in the surgical management of hypertrophic cardiomyopathy	To demonstrate the role of mitral valve plication in selected patients through evaluation of clinical outcomes and survival	Mitral valve plication (with or without)	Minnesota QoL score
-	US	Shalen et al. (2021)[101]	Perioperative amiodarone to prevent atrial fibrillation after septal myectomy in obstructive hypertrophic cardiomyopathy	To hypothesize that prophylactic amiodarone would reduce the incidence of post-operative AF following septal myectomy for oHCM.	I: Myectomy C: -	KCCQ score
-	European	Linde et al. (1999)[102]	Placebo effect of pacemaker implantation in obstructive hypertrophic cardiomyopathy	To compare the effects of AV synchronous pacing with an optimal AV delay to inactive pacing in patients with oHCM	I: Inactive Pacing C: Active Pacing	Karolinska questionnaire VAS
-	Germany	Boekstegers et al. (2001)[103]	Pressure-guided non-surgical myocardial reduction induced by small septal infarctions in hypertrophic obstructive cardiomyopathy	To assess the safety and efficacy of pressure-guided NSMR with the induction of small septal infarctions in patients with oHCM	I: Pressure-guided NSMR by small septal infarction C: -	SF-12
-	Spain	Galve et al. (2010)[104]	Late benefits of dual-chamber pacing in obstructive hypertrophic cardiomyopathy: a 10-year follow-up study	To examine the mid-term and long-term outcomes in patients with oHCM submitted to pacing	I: DDD or VDD pacemaker C: -	SF-36
-	Spain	Berruezo et al. (2011)[105]	Biventricular pacing in hypertrophic obstructive cardiomyopathy: a pilot study	To assess the feasibility and effectiveness of LV/biventricular pacing in patients with oHCM and severe LVOT obstruction	I: (Atrio-) biventricular pacing C: -	Minnesota Living with Heart Failure Questionnaire
-	Sweden	Gadler et al. (1999)[106]	Rapid return of left ventricular outflow tract obstruction and symptoms following cessation of long-term atrioventricular synchronous	To explore the long-term efficacy of cardiac pacing in oHCM	I: Pacemaker C: -	VAS

Trial name	Country	Reference	Title	Objective	Intervention/comparator	Instruments
			pacing for obstructive hypertrophic cardiomyopathy			
-	Japan	Akita et al. (2018)[107]	Prognostic significance of repeated brain natriuretic peptide measurements after percutaneous transluminal septal myocardial ablation in patients with drug-refractory hypertrophic obstructive cardiomyopathy	To evaluate whether repeated BNP measurements after PTSMA provide prognostic information regarding the response to PTSMA in patients with drug-refractory oHCM	I: PTSMA C: -	KCCQ score
-	US	Lin et al. (2019)[108]	Papillary muscle realignment and septal myectomy for obstructive hypertrophic cardiomyopathy: 1-year outcomes experienced at a single centre	To report the long-term results of combined septal myectomy and PMR and its effects on symptoms, functional capacity, and LV filling pressure	I: Septal myectomy + routine PMR C: -	KCCQ score
NCT03532802	Denmark	Dybro et al. (2021)[54]	Randomised trial of metoprolol in patients with obstructive hypertrophic cardiomyopathy	To investigate the effects of metoprolol on LVOT obstruction, symptoms, and exercise capacity in patients with oHCM.	I: Metoprolol C: Placebo	KCCQ score

ASA = alcohol septal ablation; AV = atrioventricular; BB = beta-blocker; BNP = brain natriuretic peptide; HCMSQ-SoB = Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath; HCM = hypertrophic cardiomyopathy; HRQoL = health-related quality of life; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score; LV = left ventricular; LVOT = left ventricular outflow tract; NSMR = non-surgical myocardial reduction; NYHA = New York Heart Association; oHCM = obstructive hypertrophic cardiomyopathy; PMR = papillary muscle realignment; PTSMA = percutaneous transluminal septal myocardial ablation; QoL = quality of life; SF-12 = SF-12 Health Survey; SF-36 = SF-36 Health Survey; UK = United Kingdom; US = United States; VAS = visual analog scale.

5.3 Literature used for inputs for the health economic model

Table 12. Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data are described/applied
Altibi AM, et al. Hospital procedural volume and clinical outcomes following septal reduction therapy in obstructive hypertrophic cardiomyopathy. J Am Heart Assoc 12, e028693 (2023).[109]	SRT complication rates	Targeted literature review	Section 11.6.3; Table 52
Mentias A, et al. Survival after septal reduction in patients >65 years old with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol 81, 105-15 (2023).[110]			
Kim LK, et al. Hospital volume outcomes after septal myectomy and alcohol septal ablation for treatment of obstructive hypertrophic cardiomyopathy: US Nationwide Inpatient Database, 2003-2011. JAMA Cardiol 1, 324-32 (2016).[111]			
Maksabedian Hernandez E, et al. Association between hospital volume, clinical events, resource utilization, and costs of septal myectomy and alcohol septal ablation procedures in US patients with hypertrophic cardiomyopathy. Eur Heart J; 44 (2023).[112]			
Mutlak,D, et al. Non-surgical myocardial reduction in hypertrophic obstructive cardiomyopathy. Isr Med Assoc. J 4, 86-90 (2002).[113]			
Pedernera. Clinical and functional outcome of percutaneous alcohol septal ablation in obstructive hypertrophic cardiomyopathy. Revista Argentina de Cardiología (RAC). 83(3). 217-22 (2015).[114]			
Rigopoulos AG, et al. Cardiopulmonary exercise test parameters at three months after alcohol septal ablation in hypertrophic obstructive cardiomyopathy are associated with late clinical outcome. Heart Lung Circ. 29;202-10 (2020).[115]			
Ullah W, et al. Septal myectomy or alcohol ablation for hypertrophic cardiomyopathy: a Nationwide Inpatient Sample (NIS) database analysis. Cardiovasc Revasc Med. 50;54-8 (2023).[116]			
Mazine A, et al. A novel minimally invasive approach for surgical septal myectomy. Can J Cardiol. 32, 1340-47 (2016).[117]			

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data are described/applied
Bogachev-Prokophiev AV, et al. Concomitant ablation for atrial fibrillation during septal myectomy in patients with hypertrophic obstructive cardiomyopathy. J Thorac Cardiovasc Surg. 155;1536-1542.e1532 (2018).[118] Güçlü A, et al. Disease stage-dependent changes in cardiac contractile performance and oxygen utilization underlie reduced myocardial efficiency in human inherited hypertrophic cardiomyopathy. Circ Cardiovasc Imaging. 10 (2017).[119] Hadaya J, et al. Volume-outcome relationship in septal myectomy for hypertrophic obstructive cardiomyopathy. Surgery. 174;166-71 (2023).[120] Holst KA, et al. Impact of hospital volume on outcomes of septal myectomy for hypertrophic cardiomyopathy. Ann Thorac Surg. 114;2131-8 (2022).[121] Holst KA, et al. Septal Myectomy in hypertrophic cardiomyopathy: national outcomes of concomitant mitral surgery. Mayo Clin Proc. 94;66-73 (2019).[122] Panaich SS, et al. Results of ventricular septal myectomy and hypertrophic cardiomyopathy (from Nationwide Inpatient Sample [1998-2010]). Am J Cardiol. 114;1390-5 (2014).[123]			
Tower-Rader A, et al. Patient reported outcomes in obstructive hypertrophic cardiomyopathy undergoing myectomy: Results from SPIRIT-HCM study. Prog Cardiovasc Dis. 80;66-73 (2023).[124]	Cardiac rehabilitation (percentage of patients completed phase 2 session)		Section 11.6.2; Table 51

6 Efficacy

The pivotal trial for this application is EXPLORER-HCM (MYK-461-005) (see Table 13). Long-term supporting evidence is also presented from MAVA-LTE (MYK-461-007), a long-term safety extension study of mavacamten in adults with HCM who have completed MAVERICK-HCM or EXPLORER-HCM.[91,125] Data from patients with non-obstructive HCM (i.e., those from MAVERICK-HCM) are not relevant for the indication of this submission. Consequently, the subsequent sections present data from the EXPLORER-LTE cohort of MAVA-LTE (i.e., only those patients who were previously enrolled in EXPLORER-HCM). Hereafter, this is referred to as *the EXPLORER-LTE cohort*. The data presented from the EXPLORER-LTE cohort are from the August 2023 database lock.[92] Real-world evidence data are presented to support this submission, providing 22 months of results from the mavacamten REMS database from 28 April 2022 through 27 February 2024 (see Section 6.1.1.6).[87] For detailed study characteristics, see Appendix A. For baseline characteristics of patients included in each study, see Table 14.

6.1 Efficacy of mavacamten compared to placebo for oHCM

6.1.1 Relevant studies

The 3 studies included in this submission are the phase 3 trial, EXPLORER-HCM, which investigated the safety and efficacy of mavacamten in patients with symptomatic oHCM compared with placebo, and the 2 single arm studies the EXPLORER-LTE [92] and the RWE from the mavacamten REMS program.[87] The intervention (mavacamten in combination with standard of care) and comparators (placebo in combination with individually optimized standard of care comprising BBs and/or CCBs) that are being considered have been evaluated within a single RCT; therefore, no comparative analyses were required. Details of the 3 studies are outlined below.

6.1.1.1 EXPLORER-HCM

Table 13. EXPLORER-HCM: summary of trial methodology

Study 1	EXPLORER-HCM[53,63,88]
Sample size (n)	251
Study design	Double-blind, multi-center, randomized, placebo-controlled, phase 3 trial
Patient population	Adults with symptomatic oHCM (NYHA II-III)
Intervention(s)	Mavacamten (2.5 mg/5 mg/10 mg/15 mg) per day + BB/CCB monotherapy, (n = 123)
Comparator(s)	Placebo + BB/CCB monotherapy (n = 128)
Follow-up period	Study duration: 30 weeks Follow-up: 38 weeks
Is the study used in the health economic model?	Yes

Study 1	EXPLORER-HCM[53,63,88]
Reasons for use/non-use of the study in the model	Pivotal phase 3 trial describing the efficacy and safety of mavacamten in the relevant population
Primary endpoints reported include results	Change from baseline to week 30 in symptoms measured by a composite of the change in pVO_2 and NYHA classification system
Other outcomes reported and included results	Change from baseline to week 30 in post-exercise LVOT and pVO_2. Proportion of patients with improvements in LVOT and number of patients with complete response. Change from baseline to week 30 in HRQoL measured by EQ-5D-5L index score and EQ VAS score. Change in NYHA class from baseline to week 30. Change from baseline to week 30 in patient-reported outcomes.

BB = beta-blocker; CCB = calcium channel blocker; HRQoL = health-related quality of life; LVOT = left ventricular outflow tract; NYHA = New York Heart Association; oHCM = obstructive hypertrophic cardiomyopathy; pVO_2 = peak oxygen consumption.

6.1.1.2 EXPLORER-HCM: study design

The primary objective of EXPLORER-HCM was to evaluate the efficacy and safety of mavacamten compared with placebo in patients with symptomatic oHCM (NYHA class II-III).[53] The study was an international, parallel-group, multi-center study conducted at 68 sites, including 31 sites in Europe, of which 3 sites were in Denmark.[126] Figure 29 presents the study design for EXPLORER-HCM. Patients were randomly assigned to 2 treatment groups in a 1:1 ratio and were stratified by the following:

- NYHA class (II or III)
- Current BB use (yes or no)
- Ergometer type (treadmill or bicycle)
- Consent for CV magnetic resonance imaging (MRI) substudy (yes or no)

The starting dose for mavacamten was 5 mg, with dose adjustments occurring at weeks 8 and 14, until a target reduction in LVOT gradient < 30 mmHg and a mavacamten plasma concentration between 350 ng/mL and 700 ng/mL were achieved. Prespecified criteria, such as LVEF < 50%, were used for the temporary discontinuation of study medication. Except for disopyramide treatment (for safety reasons), patients were permitted to continue oHCM treatment, such as monotherapy with BBs or non-dihydropyridine CCBs, if dosing was stable for ≥ 2 weeks before screening and no dosing changes were expected.[53] The inclusion and exclusion criteria for this study were designed not only to prioritize safety, including the ability of patients to safely perform the cardiopulmonary exercise test (CPET) but also to represent patients with real-world, symptomatic oHCM.[53]

6.1.1.3 EXPLORER-HCM: endpoints

After discussions with HCM experts and patients, as well as regulatory authorities, the primary endpoint in the pivotal phase 3 EXPLORER-HCM clinical trial was designed to comprehensively evaluate clinically meaningful treatment benefits for oHCM by using both objective assessments of exercise capacity (peak oxygen consumption [pVO_2] measured by CPET) and subjective assessments of symptom burden (NYHA class).[53] Reduced functional capacity with exercise limitation (measured by pVO_2) is common in oHCM and reflects the consequences of dynamic obstruction, diastolic abnormalities and impaired myocardial energetics.[66] In addition, pVO_2 has been shown to correlate with NYHA functional class, patient-reported outcomes (PROs), and QoL.[66]

Hence, the goal of the trial was to investigate both improvement in functional capacity and symptom burden.[66] The primary efficacy endpoint was a composite functional endpoint, which could be achieved through either composite 1 or composite 2 (see definition below).[53] It is not possible to power randomized trials in HCM to identify benefit for hard endpoints because of the low rates of mortality, stroke, transplant, and hospitalization. The primary goal of EXPLORER-HCM was to test whether mavacamten can improve symptom burden and functional capacity, as these are issues of great importance to patients.[66]

Primary composite endpoint

- Composite 1: change from baseline to week 30, increase in pVO_2 of ≥ 1.5 mL/kg/min and improvement of ≥ 1 NYHA class
- Composite 2: change from baseline to week 30, increase in pVO_2 of ≥ 3.0 mL/kg/min and no worsening in NYHA class

Secondary endpoints

- Post-exercise LVOT gradient, from baseline to week 30
- pVO_2, from baseline to week 30
- Proportion of patients with ≥ 1 NYHA class improvement, from baseline to week 30
- HRQoL, which was assessed by 2 PRO questionnaires:
  - Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS) and KCCQ–Overall Summary (KCCQ-OS), from baseline to week 30
  - Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath (HCMSQ-SoB) subscore, specifically designed to evaluate symptomatic burden in patients with HCM, from baseline to week 30

6.1.1.4 EXPLORER-LTE: study design

The primary objective of EXPLORER-LTE was to assess the long-term safety and tolerability of mavacamten in patients with oHCM who were previously enrolled in EXPLORER-HCM.[92] All patients in EXPLORER-LTE started mavacamten treatment at 5 mg once daily, with dose adjustments at weeks 4, 8, and 12 based on site-read echocardiography measures only of LVOT, Valsalva manoeuvre gradient, and LVEF. Dose adjustment was also possible at week 24 following site-read echocardiography assessment of post-exercise LVOT gradient. Temporary discontinuation criteria included LVEF < 50%, mavacamten plasma through concentration ≥ 1,000 ng/mL, or QTcF > 15%.[91,92] This multi-center study enrolled participants who completed EXPLORER-HCM through week 38 (n = 244), following the same randomization, assessment, and visit schedule as the parent study. A total of 231 participants (116 from the EXPLORER-HCM placebo arm and 115 from the mavacamten arm) were enrolled and received active study drug (mavacamten) once daily for a duration of 252 weeks (Figure 30).[92] Because patients in EXPLORER-LTE were previously enrolled in EXPLORER-HCM, the inclusion and exclusion criteria were the same for both trials (see Section 6.1.1.2).[53]

6.1.1.5 EXPLORER-LTE: endpoints

Efficacy and pharmacodynamic endpoints

- Change from baseline in echocardiographic parameters of systolic function (e.g., LVEF) and diastolic function (e.g., peak velocity of early diastolic septal and lateral mitral annular motion [e'], ratio of peak velocity of early diastolic transmitral flow [E] to e' [E/e'], ratio of E to peak velocity of late transmitral flow [A] [E/A], pulmonary artery systolic pressure, left atrium size) over time
- Change from baseline in resting and Valsalva manoeuvre LVOT (vLVOT) gradient
- Change from baseline in NYHA class over time
- Change from baseline in NT-proBNP over time
- Frequency of cardiac transplant

Exploratory endpoints

- Change from baseline over time in participant-reported severity of HCM symptoms as assessed by the HCMSQ score
- Change from baseline in health status as assessed by the EQ-5D scores

6.1.1.6 REMS program (RWE): study design

The objective was to report the cumulative results of the first 22 months of real-world, post-approval use of mavacamten in patients with oHCM in the US from the REMS program.[87] All patients had at least 1 dose of mavacamten from 28 April 2022 through 27 February 2024. Mavacamten was dosed at 2.5, 5, 10, or 15 mg/day. Patients were required to have a clinical and echocardiographic assessment at baseline and at 4, 8, and 12 weeks after treatment initiation and every 12 weeks thereafter (unless there was a dose change or initiation of a weak CYP2C19 inhibitor or moderate CYP3A4 inhibitor).[87]

In this RWE study, 6,299 participants were enrolled and received at least 1 dose of mavacamten during the recorded period of 22 months. The study had no comparator.

6.1.1.7 REMS program (RWE): analysis

Analysis was limited to summary statistics from patients enrolled from 28 April 2022 through 27 February 2024. For the dosage and vLVOT analyses, the period of data collection was extended by 2 days (from 28 April 2022 through 29 February 2024), and data for patients with ≥ 1 year of follow-up data were collected.

The reported endpoints included:

- Incidence of LVEF < 50%
- Incidence of clinical heart failure requiring hospitalization
- Incidence of LVEF < 50% and clinical heart failure requiring hospitalization
- Dosage analysis, record of dispensed doses at the end of the month
- Post-vLVOT
- Drug interactions and counselling checklists, including concurrent medicines
- The compliance to REMS database

6.1.2 Comparability of studies

EXPLORER-HCM and EXPLORER-MAVA are very similar, as the patient cohort is the same. No baseline characteristics were reported in the RWE study by Desai et al. (2025)[87]; patients in the REMS program are treated on label; therefore, it is not possible to draw comparisons.

6.1.2.1 Comparability of patients across studies

The 3 included studies were considered comparable to each other, although no formal analysis comparing demographics across studies was performed.

Table 14. Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	EXPLORER-HCM		EXPLORER-LTE		VALOR-HCM	
	Mavacamten (n = 123)	Placebo (n = 128)	Mavacamten (n = 231)	No comparator group	Mavacamten (n = 56)	Placebo (n = 56)
Age (years), mean (SD)	58.5 (12.2)	58.5 (11.8)	60.0 (11.9)	-	59.8 (14.2)	60.9 (10.5)
Male sex, n (%)	66 (54)	83 (65)	140 (60.6)	-	29 (51.8)	28 (50)
Female sex, n (%)	57 (46)	45 (35)	91 (39.4)	-	27 (48.2)	28 (50)
NYHA class I, n (%)	NA	NA	14 (6.1)	-	NA	NA
NYHA class II, n (%)	88 (72)	95 (74)	152 (65.8)	-	4 (7.1)[a]	4 (7.1)[a]
NYHA class III, n (%)	35 (28)	33 (26)	65 (28.1)	-	52 (92.9)[b]	52 (92.9)[b]
Family history of HCM	33 (27)	36 (28)	NA	-	17 (30.4)	15 (26.8)
AF	12 (10)	23 (18)	NA	-	11 (19.6)	8 (14.3)
Hypertension	NA	NA	NA	-	36 (64.3)	34 (60.7)
Syncope or presyncope	NA	NA	NA	-	29 (51.8)	30 (53.6)
Implantable cardioverter-defibrillator	NA	NA	NA	-	9 (16.1)	10 (17.9)
Septal reduction therapy	11 (9)	8 (6)	NA	-	11 (9)	8 (6)
Type of SRT ASA (%)	NA	NA	NA	-	8 (14.3)	7 (12.5)
Type of SRT myectomy (%)	NA	NA	NA	-	48 (85.7)	49 (87.5)
pVO_2, mL/kg/min, mean (SD)	18.9 (4.9)	19.9 (4.9)	NA	-	NA	NA
NT-proBNP, ng/L, geometric mean (coefficient of variation %)	777 (136)	616 (108)	783 (326-1593)	-	724 (291-1913)	743 (275-1196)
BB, n (%)	94 (76)	95 (74)	175 (75.8)	-	26 (46.4)	25 (44.6)
CCB, n (%)	25 (20)	17 (13)	38 (16.5)	-	7 (12.5)	10 (17.9)
BB/CCB, n (%)	NA	NA	NA	-	6 (10.7)	10 (17.9)

	EXPLORER-HCM		EXPLORER-LTE		VALOR-HCM	
	Mavacamten (n = 123)	Placebo (n = 128)	Mavacamten (n = 231)	No comparator group	Mavacamten (n = 56)	Placebo (n = 56)
Disopyramide (monotherapy or in combination), n (%)	NA	NA	NA	-	14 (25)	8 (14.4)
None, medication intolerance, n (%)	NA	NA	NA	-	3 (5.4)	3 (5.4)
Pathogenic/likely pathogenic HCM gene variant, n/N tested (%)	28/90 (31)	22/100 (22)	NA	-	NA	NA
LVEF, %	74 (6)	74 (6)	74.0 (5.9)	-	67.9 (3.7)	68.3 (3.2)
Maximum left ventricular wall thickness, mm	20 (4)	20 (3)	NA	-	NA	NA
LVOT gradient, rest mmHg	52 (29)	51 (32)	48.3 (31.9)	-	51.2 (31.4)	51 (32)
LVOT gradient, Valsalva manoeuvre, mmHg	72 (32)	74 (32)	69.5 (33.3)	-	75.3 (30.8)	76.2 (29.9)
LVOT gradient, post-exercise, mmHg	86 (34)	84 (36)	NA	-	82.5 (34.7)	85.2 (37.0)
Left atrial volume index, mL/m^2	40 (12)	41 (14)	NA	-	41.3 (16.5)	40.9 (15.2)
Left atrial diameter, mm	42 (5)	42 (6)	NA	-	NA	NA

AF = atrial fibrillation; BB = beta-blocker; CCB = calcium channel blocker; NYHA = New York Heart Association; NA = not available; HCM = hypertrophic cardiomyopathy; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; NT-proBNP = N-terminal pro–B-type natriuretic peptide; pVO_2 = peak oxygen consumption; SD = standard deviation; SRT = septal reduction therapy. Note: Coefficient of variation % is defined as the ratio of the SD to the mean.

[a] NYHA class II with exertional syncope

[b] NYHA class III or higher

Sources: Rader et al. (2022)[91]; Desai et al. (2022)[94]; Olivotto et al. (2020)[53]

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

In Denmark, it has been estimated that the median age at diagnosis is 67.8 years,[48] and 42.2% of patients are treated with BBs and/or CCBs[49] (see Section 3.2.1[49]). Therefore, the 3 included studies were considered comparable to the Danish population, although no formal analysis was performed. The relevant population for this economic analysis was assumed to be the same as the ITT population of EXPLORER-HCM.[53] Section 6.1.1.2 presents key inclusion criteria.

The baseline characteristics of patients in EXPLORER-HCM (Table 15) are expected to reflect those of patients in Danish clinical practice. The proportion of males and females was used to generate the weighted average background mortality rates. The mean age of patients at baseline was considered to be the patient's starting age in the model. The proportion of patients in each NYHA class at study baseline was used to distribute patients across model health states at the first cycle/baseline. Finally, the proportion of patients taking background monotherapy of BB/CCB was used to estimate the drug cost for BB/CCB monotherapy.

Table 15. Patient characteristics in EXPLORER-HCM used in the model

Patient population: important baseline characteristics	Value	Reference
Age (years), mean	59	EXPLORER-HCM[53]
Male sex, (%)	59.4	
NYHA class (%)		
I	0.0	
II	72.9	
III	27.1	
IV	0.0	
Background therapy, %		
BB	81.8	
CCB	18.2	

BB = beta-blocker; CCB = calcium channel blocker; NYHA = New York Heart Association.
Source: Olivotto et al. (2020)[53]

6.1.4 Efficacy: results per EXPLORER-HCM

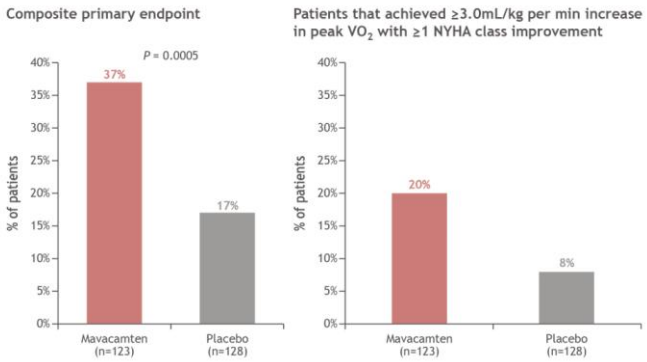
This section presents results from analyses of the primary efficacy endpoints and secondary/exploratory endpoints from the pivotal study EXPLORER-HCM and the LTE study EXPLORER-LTE. Currently, no comparable treatment exists; therefore, EXPLORER-HCM, which evaluated mavacamten versus placebo, is the relevant head-to-head study. For detailed efficacy results, see Appendix B.

6.1.4.1 EXPLORER-HCM: primary efficacy endpoint

A greater proportion of patients in the mavacamten group compared with the placebo group achieved the primary composite endpoint (37% vs. 17%; $P < 0.0005$) (Figure 5).

While only 8% of placebo patients had a ≥ 3.0 mL/kg/min increase in pVO_2 and ≥ 1 NYHA class improvement, 20% of mavacamten-treated patients had both.[53] Hence, treatment with mavacamten provided clinically relevant improvements in functional capacity concomitant with a reduction in symptom burden compared with placebo.

Figure 5. EXPLORER-HCM: proportion of patients achieving the primary composite endpoint and the patients achieving both 1 NYHA class improvement and ≥ 3 mL/kg



NYHA = New York Heart Association; pVO_2 = peak oxygen consumption.
Notes: ≥ 1.5 mL/kg/min increase in pVO_2 with ≥ 1 NYHA class improvement or ≥ 3.0 mL/kg/min increase in pVO_2 with no worsening of NYHA class.
P value is not alpha controlled.
Adapted from Olivotto et al. (2020)[53]

The between-group difference for patients who achieved the composite functional endpoint was statistically significant based on the primary analysis (Table 16).[53]

Table 16. EXPLORER-HCM: primary composite endpoint

	Mavacamten (n = 123)	Placebo (n = 128)	Mavacamten vs. placebo Difference (95% CI)
Met primary composite endpoint, n (%)	45 (36.6)	22 (17.2)	19.4 (8.67-30.13) *P* = 0.0005
Composite 1, n (%)	41 (33)	18 (14)	19.3 (9.0-29.6)
Composite 2, n (%)	29 (24)	14 (11)	12.6 (3.4-21.9)
≥ 3.0 mL/kg/min increase in pVO_2 AND ≥ 1 NYHA class improvement	25 (20.3)	10 (7.8)	12.5 (4.02-21.01)

CI = confidence interval; NYHA = New York Heart Association; pVO_2 = peak oxygen consumption.
Note: The primary composite endpoint was defined as achieving an improvement of ≥ 1.5 mL/kg/min pVO_2 and a reduction of ≥ 1 class in NYHA class (Composite 1) or an improvement of ≥ 3.0 mL/kg/min in pVO_2 with no worsening in NYHA class (Composite 2). Patients with a non-evaluable primary endpoint and NYHA secondary endpoint were considered to be non-responders. The response rates were calculated with the N value as the denominator.
Source: Olivotto et al. (2020)[53]

Prespecified subgroup analyses found that the effect of mavacamten on the primary composite endpoint was generally consistent across subgroups (Figure 6).[53] When looking at the subgroups of patients receiving or not receiving concomitant BBs, the analyses found that a larger effect on the primary composite endpoint was observed in patients not receiving BBs.[53] Olivotto et al. (2020)[53] argued that the use of BBs did not reduce the primary mechanism by which mavacamten works, but rather the effect on the primary endpoint could be due to heart rate limitations of BBs on CPET performance. Indeed, the mean peak heart rate with exercise at baseline was also decreased for the subgroup of mavacamten patients receiving BBs compared with patients without BBs (119 beats per minute [bpm] vs. 138 bpm, respectively). In line with this view, further

subgroup analysis by BB use in patients from EXPLORER-HCM and EXPLORER-LTE demonstrated that despite the use of BBs, mavacamten improved measures of functional capacity, LVOT, symptom burden as proportion of patients with reduction ≥ 1 NYHA class, KCCQ scores, and NT-proBNP. Beta-blockers were often associated with chronotropic incompetence, affecting pVO_2 and other heart rate–dependent measures, but BBs had minimal impact on heart rate–independent measures.[127]

CI = confidence interval; HCM = hypertrophic cardiomyopathy; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association.
Note: No treatment effect is at 0, with a positive mean percentage difference indicative of favoring mavacamten treatment, and a negative mean percentage difference indicative of favoring placebo.
Source: Olivotto et al. (2020)[53]

6.1.4.2 EXPLORER-HCM: secondary efficacy endpoint

Mavacamten-treated patients demonstrated statistically significant improvements compared with placebo for all secondary endpoints, including post-exercise LVOT peak gradient, pVO_2, 23-item KCCQ (KCCQ-23) CSS, and HCMSQ-SoB score.[53] Across multiple measures of symptoms and function evaluated in EXPLORER-HCM, the results demonstrate that myosin inhibition with mavacamten normalizes contractility, reduces dynamic LVOT obstruction, improves cardiac filling pressures, and reduces biomarkers of cardiac stress, improving symptoms and exercise capacity.[53]

All secondary endpoints showed consistent benefit for mavacamten across prespecified subgroups, irrespective of BB use.[53]

Physician-reported outcomes

Patients treated with mavacamten showed decreased LVOT gradient, increased pVO_2, and improved symptoms as evaluated by physicians (NYHA class; Table 17).[53]

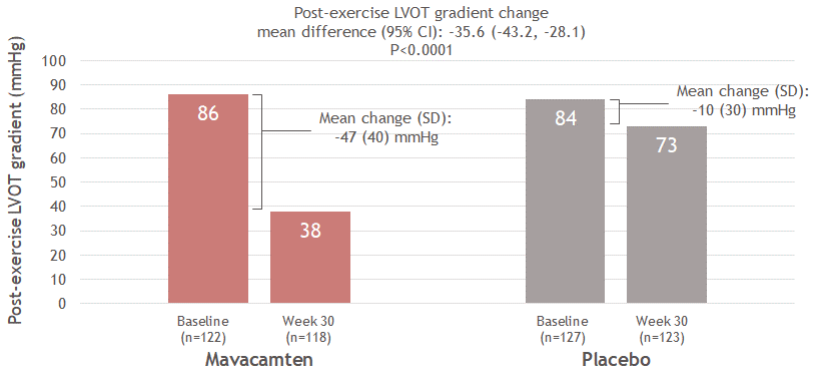
Table 17. Secondary endpoints: EXPLORER-HCM physician-reported outcomes

Change from baseline to Week 30 in:	Mavacamten (n = 123)	Placebo (n = 128)	Mavacamten vs. placebo difference (95% CI)
Post-exercise LVOT peak gradient,[a] mmHg, mean (SD)	−47 (40)	−10 (30)	−35.6 (−43.2 to −28.1) $P < 0.0001$
pVO_2,[b] mL/kg/min, mean (SD)	1.4 (3.1)	−0.1 (3.0)	1.4 (0.6-2.1) $P = 0.0006$
NYHA improved ≥ 1 class,[c] n (%)	80 (65)	40 (31)	34 (22-45) $P < 0.0001$

CI = confidence interval; HCM = hypertrophic cardiomyopathy; LVOT = left ventricular outflow tract; NYHA = New York Heart Association; pVO_2 = peak oxygen consumption; SD = standard deviation.
Note: n is the number analyzable for secondary endpoints based on availability of both baseline and week 30 values.
[a] Mavacamten (n = 117), placebo (n = 122).
[b] Mavacamten (n = 120), placebo (n = 125).
[c] Due to the smaller numbers evaluable for patient-reported outcome endpoints, additional post hoc analyses compared the reasons for missing data.
Source: Olivotto et al. (2020)[53]

There was a decrease in peak post-exercise LVOT gradient from 86 mmHg (95% CI, 79.5-91.8) to 38 mmHg (32.3-44.0) with mavacamten; for placebo, there was a change from 84 mmHg (78.4-91.0) to 73 mmHg (67.2-79.6), showing a greater mean reduction by 35.6 mmHg with mavacamten (Figure 7).[53]

Figure 7. EXPLORER-HCM: post-exercise LVOT gradient change



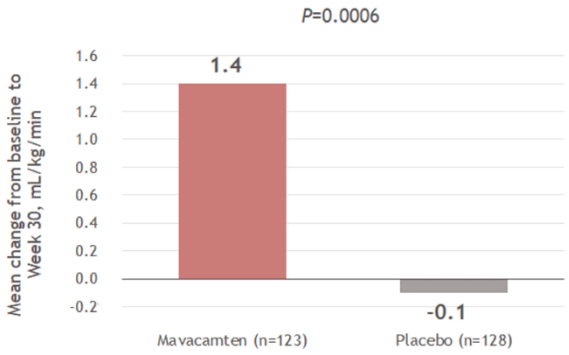
CI = confidence interval; LVOT = left ventricular outflow tract; SD = standard deviation.
Adapted from Olivotto et al. (2020)[53]

Prespecified subgroup analyses found that the benefit of mavacamten extended across subgroups when assessing post-exercise LVOT gradient (Figure 8).[53]

CI = confidence interval; HCM = hypertrophic cardiomyopathy; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association.
Note: No treatment effect is at 0, with a positive mean difference indicative of favoring placebo, and a negative mean difference indicative of favoring mavacamten treatment.
Source: Olivotto et al. (2020)[53]

Mavacamten patients demonstrated a statistically significant increase in exercise capacity, as measured by pVO_2. Mavacamten was associated with a mean difference in increase in pVO_2 by 1.4 mL/kg/min (95% CI, 0.6-2.1; *P* = 0.0006) versus placebo (Figure 9).[53]

Figure 9. Improvement in exercise capacity, measured by peak oxygen consumption (pVO_2)

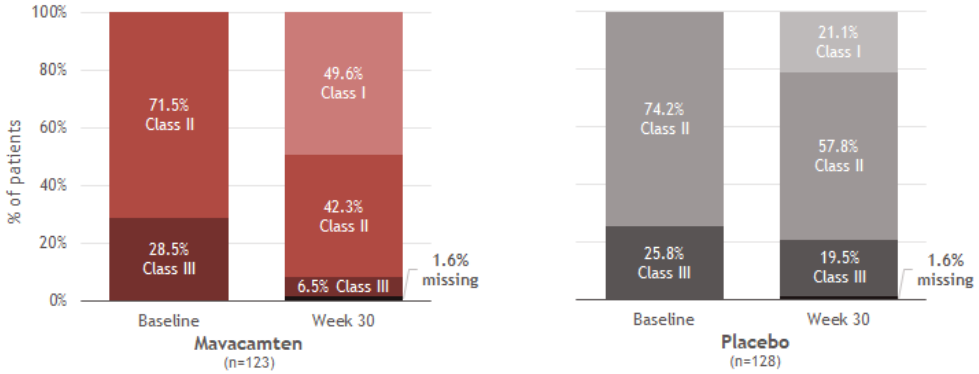


Adapted from Olivotto et al. (2020)[53]

In prespecified subgroup analyses comparing mavacamten patients taking BBs versus not taking BBs, the mean change from baseline in pVO_2 was lower in the BB subgroup (1.1 mL/kg/min vs. 2.2 mL/kg/min), likely due to the effect of BBs on heart rate; the heart rate–independent parameter (i.e., minute ventilatory/carbon dioxide production slope) improved similarly in both groups (−2.4 vs. −2.7).[125]

In the mavacamten group, 80 of 123 patients (65%) had at least 1 NYHA class improvement compared with 40 of 128 (31%) in the placebo group (difference, 33.8%; 95% CI, 22.2-45.4; *P* < 0.0001). In total, 50% of patients (61 of 123) reached NYHA class I status with mavacamten and 21% (27 of 128) reached NYHA class I status with placebo (Figure 10).[53] It should be noted that the percentages of patients who reached each NYHA class status between baseline and week 30 were not evaluated across treatment groups for statistical significance.

Figure 10. Change in NYHA class from baseline to week 30



NYHA = New York Heart Association.
Adapted from Olivotto et al. (2020)[53]

Prespecified subgroup analyses demonstrated that, regardless of BB use, patients treated with mavacamten showed similar rates of improvement in NYHA class (65% for patients with BBs vs. 66% without).[125]

Patient-reported outcomes

Improvements in symptoms as evaluated by PROs were also observed with mavacamten compared with placebo (Table 18).[63,88] In general, there was a significant treatment benefit with mavacamten across all patient-reported endpoints, and the effects rapidly diminished upon cessation of mavacamten treatment for all endpoints during the washout period from week 30-38. Some of the effects were evident as early as week 4 (HCMSQ-SoB); in general, effects found were clinically important from the perspectives of both patients and providers.

Prespecified subgroup analyses demonstrated that, patients treated with mavacamten had a similar mean KCCQ-CSS score at week 30 regardless of BB use (14.2 for those with BBs vs. 11.0 without).[125]

Table 18. EXPLORER-HCM: secondary endpoints, PROs

Change from baseline to Week 30 in:	Mavacamten (n = 92)[a]	Placebo (n = 88)[a]	Mavacamten vs. placebo, difference (95% CI)
KCCQ-CSS,[b] mean (SD)	13.6 (14.4)	4.2 (13.9)	9.1 (5.5-12.7); *P* < 0.0001
KCCQ-OS,[b] mean (SD)	14.9 (15.8)	5.4 (13.7)	9.1 (5.5-12.8); *P* < 0.0001
HCMSQ-SoB subscore,[a,c] mean (SD)	−2.8 (2.7)	−0.9 (2.4)	−1.8 (−2.4 to −1.2); *P* < 0.0001

CI = confidence interval; HCM = hypertrophic cardiomyopathy; HCMSQ-SoB = Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath; KCCQ-23 = 23-item Kansas City Cardiomyopathy Questionnaire; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire–Overall Summary; PRO = patient-reported outcome; SD = standard deviation.
Note: n was the number analyzable for secondary endpoints based on availability of both baseline and week 30 values. In EXPLORER-HCM, 21.9% of the baseline KCCQ-23 Clinical Summary Score baseline values were missing. The missing baseline data were primarily due to operational challenges with the use of the electronic device used to collect these data and thus unrelated to patient characteristics. After imputing missing data with unfavorable outcomes for mavacamten and favorable outcomes for the placebo arm, the estimated treatment effects on the PROs remained statistically significant.
[a] Due to the smaller numbers evaluable for PRO endpoints, additional post hoc analyses compared the reasons for missing data.
[b] A positive change in KCCQ-CSS or KCCQ-OS indicates improvement.
[c] Mavacamten (n = 85), placebo (n = 86). A negative change in HCMSQ-SoB subscore indicates improvement.
Sources: Spertus et al. (2021)[63]; Xie et al. (2021)[88]; Olivotto et al. (2020)[53]

Patient-reported outcome assessments using KCCQ-CSS, KCCQ-OS, and HCMSQ-SoB showed a favorable effect of mavacamten on a patient's QoL and well-being.

KCCQ-CSS and KCCQ-OS (Figure 11) showed that, during the 38-week study, there was a rapid separation in scores between mavacamten and placebo within the first 6 weeks of treatment, such that patients treated with mavacamten had significantly higher scores than placebo patients. This separation was maintained through the 30 weeks of treatment.[63] There was a rapid decrease of these differences from weeks 30 through 38, with cessation of the study drug at week 30. For both KCCQ-CSS and KCCQ-OS, when comparing week 38 assessments with baseline, there was little difference observed between treatment groups, revealing that any health status benefits achieved with mavacamten during the 30 weeks of treatment returned to baseline levels.[63]

Note: Mean change from baseline over time in KCCQ-OS score. Error bars are standard error.
Source: Spertus et al. (2021)[63]

Unlike KCCQ-CSS, which includes only the Physical Limitation and Total Symptom scores, the KCCQ-OS score is a more general overview of the patient's health status, combining the total Symptom, Physical and Social Limitation, and QoL scores.

The subdomains of KCCQ-OS also showed more significant treatment benefits with mavacamten than placebo (Table 19), with the largest benefit seen in the Physical Limitation domain, which measures limitations that patients experienced because of health failure symptoms while performing routine physical activities.[128]

Table 19. EXPLORER-HCM: secondary endpoints, KCCQ subdomain scores

Change from baseline to week 30 in:	Mavacamten (n = 92) [a]	Placebo (n = 88) [a]	Mavacamten vs. placebo, difference (95% CI)
Total symptom score,[b] mean (SD)	12.4 (15.0)	4.8 (15.9)	7.7 (3.7-11.5); *P* = 0.0002
Physical limitation score,[b] mean (SD)	14.7 (17.0)	3.6 (15.4)	10.6 (6.2-14.8); *P* < 0.0001
Social limitation score,[b] mean (SD)	13.5 (22.9)	5.1 (19.2)	9.3 (4.5-14.1); *P* = 0.0002
Quality-of-life score,[b] mean (SD)	18.8 (21.6)	8.3 (18.8)	9.6 (4.7-14.5); *P* = 0.0001

CI = confidence interval; KCCQ = Kansas City Cardiomyopathy Questionnaire; SD = standard deviation.
Note: n was the number analyzable for secondary endpoints based on availability of both baseline and week 30 values.
[a] Due to the smaller numbers evaluable for patient-reported outcome endpoints, additional post hoc analyses compared the reasons for missing data.
[b] A positive change in score indicates improvement.
Source: Spertus et al. (2021)[63]

The HCMSQ-SoB favored mavacamten over placebo at week 30. The mean improvement from baseline on the HCMSQ-SoB was greater in the mavacamten arm compared with placebo at week 30 (*P* < 0.0001), with effects observed as early as 4 weeks (Figure 12). A greater proportion of patients taking mavacamten compared with placebo (50% vs. 21%) achieved a clinically meaningful response, defined as a decrease of ≥ 2.5 points between baseline and week 30 in the HCMSQ-SoB.[129]

= least squares; SE = standard error.
Source: BMS data on file (2021)[129]

Consistent with KCCQ regression observed upon cessation of treatment at week 30, mean HCMSQ-SoB scores returned to baseline values at week 38 for the mavacamten group, while decreases from baseline were maintained for the placebo group.[129]

6.1.4.3 EXPLORER-HCM: exploratory efficacy endpoint

Physician-reported outcomes

Compared with placebo, mavacamten demonstrated quick improvements in resting and vLVOT gradients, which were maintained during the study.[53] Treatment with mavacamten relieved LVOT obstruction (post-exercise LVOT gradient < 30 mmHg) in 50% more patients and decreased the gradient to less than the standard threshold for SRT (post-exercise LVOT gradient < 50 mmHg) in 53.5% more patients than placebo (Table 20). A complete response (NYHA class I status and all LVOT gradients < 30 mmHg) was achieved by 26.6% more mavacamten-treated patients than placebo patients. The

mean reduction in LVEF was −3.9% with mavacamten and −0.01% with placebo (difference, −4.0%; 95% CI, −5.5 to −2.5).[53]

Table 20. EXPLORER-HCM: key exploratory endpoints

	Mavacamten, n/N (%)	Placebo, n/N (%)	Difference (95% CI)
Complete response [a]	32/117 (27)	1/126 (1)	26.6 (18.3-34.8)
Post-exercise LVOT peak gradient < 50 mmHg [b]	75/101 (74)	22/106 (21)	53.5 (42.0-65.0)
Post-exercise LVOT peak gradient < 30 mmHg [c]	64/113 (57)	8/114 (7)	49.6 (39.3-59.9)

CI = confidence interval; LVOT = left ventricular outflow tract; NYHA = New York Heart Association.
[a] Defined as NYHA class I and all LVOT peak gradients < 30 mmHg (post-exercise, resting, and Valsalva manoeuvre).
[b] Threshold for guideline-based invasive intervention. Only patients with baseline post-exercise LVOT peak gradient of < 50 mmHg were assessed.
[c] Threshold for guideline-based diagnosis of obstruction. Only patients with baseline post-exercise LVOT peak gradient < 30 mmHg were assessed.
Source: Olivotto et al. (2020)[53]

Patient-reported outcomes

Improvements in EQ-5D-5L and EQ VAS were also observed with mavacamten compared with placebo.[63,88,130] In Xie et al., the EQ-5D-5L index score was calculated based on the US value set. Patients taking mavacamten, compared with placebo, significantly improved their EQ-5D-5L index score and EQ VAS score from baseline to week 30 (Figure 13). More patients treated with mavacamten than placebo had at least a meaningful change threshold (1/2 SD of the baseline value) improvement in EQ-5D-5L index score (69% vs. 39%) and in EQ VAS score (44% vs. 29%).[88]

MCT = meaningful change threshold.
Source: Xie et al. (2021)[88]

Cardiac biomarkers

Consistent with hemodynamic changes, cardiac biomarkers also decreased quickly and were sustained to week 30. At week 30, compared with baseline, the reduction in cardiac biomarkers NT-proBNP (indicator for cardiac wall stress) and hs-cTnI (indicator for cardiac injury) after mavacamten were 80% and 41% greater than placebo, respectively (proportion of geometric mean between groups for NT-proBNP, 0.202; 95% CI, 0.169-0.241; for hs-cTnI, 0.589; 95% CI, 0.500-0.693).[53] These biomarkers are predictive of long-term outcome in patients with HCM.[53] Prespecified subgroup analyses

demonstrated that, regardless of BB use, patients treated with mavacamten had similar improvement in biomarkers (both NT-proBNP and hs-cTnI).[125]

Cardiac structure and function

Echocardiogram parameters of left ventricular structure and function from patients in the EXPLORER-HCM cohort were analyzed. The analysis found that, after 30 weeks, mavacamten led to consistent improvement in diastolic function, early diastolic mitral annular velocity [e'], early mitral inflow velocity and mitral annular early diastolic velocity [E/e'] ratios, while maintaining contractile function (LVEF) within the normal range.[89,90] The presence or absence of SAM of the mitral valve leaflets, indicative of reduced blood flow from the left ventricular to the aorta, was also assessed. Furthermore, the results demonstrated a favorable effect of mavacamten on cardiac remodelling (left ventricular wall thickness, fibrosis) (Figure 14).

ek 30

CI = confidence interval; LS = least squares; LV = left ventricular.
Notes: For mavacamten group: n = 117 at week 0, n = 113 at week 18, n = 112 at week 30.
For placebo group: n = 123 at week 0, n = 117 at week 18, n = 115 at week 30.
Source: Hegde et al. (2021)[90]

Patients with higher baseline vLVOT gradients demonstrated greater reductions in left atrial volumes (*P* for interaction = 0.03). No significant interaction was seen between baseline vLVOT gradients and left ventricular wall thickness, e' velocities, or E/e' ratios. The presence or absence of SAM and mitral regurgitation was also assessed via ECG; this found that significantly more patients treated with mavacamten than placebo had resolution of SAM at week 30 (80.9% vs. 34.0%, respectively; difference, 46.8%; $P < 0.0001$). Resolution of mitral regurgitation at week 30 was achieved by 9% of mavacamten-treated patients vs. no placebo patients (difference, 9.0%; $P < 0.001$).[90]

6.1.5 Efficacy: results per EXPLORER-LTE

Patients enrolled in the EXPLORER-LTE study demonstrated benefit consistent with that achieved in the parent study.[92] Of note, the interim findings presented below are for different timepoints because they come from different parent studies.

6.1.5.1 EXPLORER-LTE: interim findings

At week 180, 87.2% of patients were treated with mavacamten ≤ 10 mg.[92] Similar to EXPLORER-HCM, rapid and sustained improvements in both resting and vLVOT gradients were seen with mavacamten starting as early as week 4. At week 180, mean change from

baseline (SD) was −40.3 mmHg (32.7) for resting LVOT gradient and −55.3 mmHg (33.7) for vLVOT gradient.[92] At week 180, 64 of 95 patients (67.4%) improved NYHA class by one class from baseline and 10 of 95 patients (10.5%) improved by 2 classes from baseline.[92]

EXPLORER-LTE cohort: secondary efficacy endpoint, interim findings

A small decrease in resting LVEF over 60 weeks was observed (mean change from baseline [SD], −7.6% [6.9%]).[131] This was sustained at weeks 156 (mean change from baseline [SD], −9.6 [8.3%]) and 180 (mean change from baseline [SD], −11.0 [8.9%]).[92] Improvements in left ventricular filling pressure (lateral E/e' and left atrial volume index) were seen through week 180.[92] Decreases in NT-proBNP levels were seen at week 4 and sustained through week 180; the median change from baseline to week 180 was −562 ng/L.[92]

6.1.6 Efficacy: results per REMS program (RWE)

Patients enrolled in the REMS program from April 2022 through February 2024 who received at least 1 dose of mavacamten due to diagnosis of symptomatic oHCM showed favorable real-world experience with mavacamten.

6.1.6.1 REMS program: LVEF

Of the 5,573 patients on mavacamten with evaluable data (as of 27 February 2024)[87]:

- 256 (4.6%) experienced a decrease in LVEF to < 50%
- 71 (1.3%) experienced heart failure requiring hospitalization
- 17 (0.3%) experienced both a decrease in LVEF to < 50% and heart failure requiring hospitalization

For patients with ≥ 1 year of treatment with mavacamten (n = 1,929), 78 (4.0%) had an LVEF reduction to < 50%, 29 (1.5%) experienced heart failure requiring hospitalization, and 4 (0.2%) experienced LVEF < 50% and heart failure requiring hospitalization.[87]

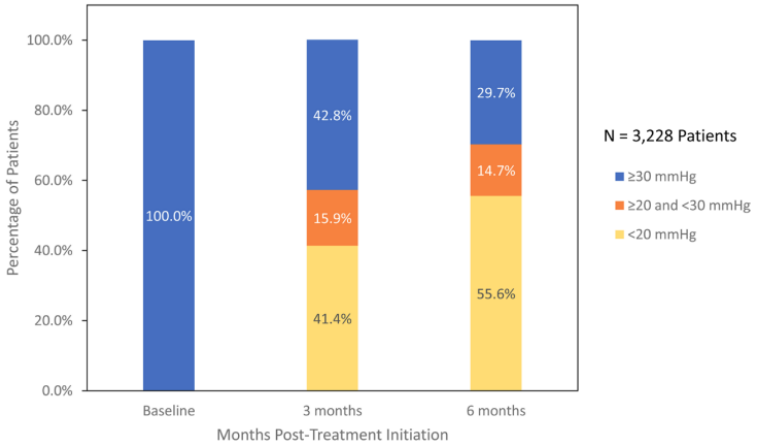
6.1.6.2 REMS program: dosage analysis

As of a data cutoff of 29 February 2024, 6,176 patients were started at the recommended dosage of 5 mg/day and 3,228 patients had been on treatment for at least 6 months; of these, 2,391 (74.1%) were on a dosage of 5 or 10 mg/day. Only 732 patients (22.7%) required a dose reduction at the second dispense.[87]

6.1.6.3 REMS program: post-vLVOT gradient

A total of 3,228 patients received mavacamten 5 mg/day for at least 6 months.[87] The percentage of patients with vLVOT gradients < 30 mmHg increased to 70.3% at 6 months. Figure 15 presents the percentage of patients with vLVOT gradients of ≥ 30 mmHg, ≥ 20 mmHg and < 30 mmHg, and < 20 mmHg.

Figure 15. Valsalva Manoeuvre LVOT gradients for patients who began treatment with mavacamten at 5 mg/day and were treated for at least 6 months



vLVOT = Valsalva manoeuvre left ventricular outflow tract.
Note: The percentage of patients with a vLVOT gradient ≥ 30 mmHg (assumed to be 100% at baseline), based on the clinical and diagnostic definition of obstructive HCM, which would qualify for commercial mavacamten therapy. The period of data collection was extended 2 days (from 28 April 2022 through 29 February 2024) for this analysis.
Source: Desai et al. (2025)[87]

6.1.7 Efficacy conclusion

Mavacamten is a first-in-class cardiac myosin inhibitor designed to treat the underlying pathophysiological changes in oHCM. The efficacy and safety of mavacamten were investigated in a large, placebo-controlled RCT (EXPLORER-HCM), designed specifically for patients with oHCM with NYHA class II-III symptoms. Most patients (73%) were NYHA class II at enrollment. The study showed significant effect of treatment with mavacamten on the primary endpoint and all secondary and exploratory endpoints compared with placebo.

A total of 37% of patients treated with mavacamten reached the primary endpoint, which was a composite endpoint including improvement in functional capacity (pVO_2) and change in NYHA class, compared with 17% of patients in the placebo group.[53] Patients treated with mavacamten had greater reductions than those on placebo in post-exercise LVOT gradient, and more patients treated with mavacamten improved ≥ 1 NYHA class (65% vs. 31%, respectively). Notably, 27% of patients had a complete response to treatment (i.e., all LVOT gradients < 30 mmHg and NYHA class I) with mavacamten compared with 1% of patients on placebo.[53] In addition, patients treated with mavacamten significantly improved their symptom and health status scores (KCCQ-CSS, HCMSQ-SoB, EQ-5D-5L, and EQ VAS) compared with patients on placebo, with clinically relevant improvements; some effects were seen as early as week 4 and maintained through week 30.[63,88] A favorable real-world experience with mavacamten was presented from the REMS program as supportive evidence to this submission. The need for temporary interruption for LVEF < 50% was low, with similar results for patients on mavacamten for ≥ 1 year. Most patients only required a dose of 5 mg or 10 mg to achieve efficacy. The vLVOT gradient decreased, with more than half of patients experiencing a reduction to < 20 mmHg.[87] In conclusion, mavacamten improved both functional status and symptom burden for patients with oHCM and provides a new, effective treatment modality of symptomatic (NYHA, class II-III) oHCM in adults.

7 Comparative analyses of efficacy

The intervention (mavacamten in combination with standard of care) and comparators (placebo in combination with individually optimized standard of care comprising BBs and/or CCBs) that are being considered have been evaluated within a single RCT; therefore, no comparative analyses were required.

8 Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

Table 21 presents the data sources of efficacy parameters used in the base-case model; a detailed description of each input (in both base-case and scenario analyses) is provided in subsequent sections.

Table 21. Summary of clinical input data used in the model and sources

Name of estimates[a]	Results from study or indirect treatment comparison	Input value used in the model	How is the input value obtained/estimated
Clinical inputs			
Short-term TPs	Based on EXPLORER-HCM (for both intervention and BB/CCB monotherapy arm)	Presented in Section 8.1.2	EXPLORER-HCM; Olivotto et al. (2020)[53]
Long-term TPs	Retain NYHA class (for both intervention and BB/CCB monotherapy arm)	Presented in Section 8.1.2	Assumption, supported by EXPLORER-LTE and BMS data on file (2021)[132]
Inputs related to discontinuation of mavacamten			
Due to AEs or other reasons	Trial period: discontinuation rate due to SAEs at week 30 (one-off)	Presented in Section 8.4.1	EXPLORER-HCM; Olivotto et al. (2020)[53]
	Post-trial period: annual rate of discontinuation due to any reasons after week 30	Presented in Section 8.4.1	Assumption based on EXPLORER-HCM and Olivotto et al. (2020)[53]
Due to lack of response	Discontinue if no NYHA class improvement from baseline at end-of-trial period	Presented in Section 8.4.2	EXPLORER-HCM; Olivotto et al. (2020)[53]
Treatment distribution of patients who discontinued mavacamten	All patients revert to pre-existing treatment with BB/CCB monotherapy	Presented in Section 0	Assumption
Inputs related to treatment escalation within standard of care pathway			
Escalation from BB/CCB monotherapy to SRT	Percentage of patients escalated (per year) by NYHA class	Presented in Table 29	SHaRe, subpopulation HCM-LVSD
	SRT + BB/CCB	Presented in Table 29	BMS data on file (2022)[49]

Name of estimates[a]	Results from study or indirect treatment comparison	Input value used in the model	How is the input value obtained/estimated
Efficacy of subsequent treatments	After SRT (BB/CCB monotherapy)	Presented in Section 8.3	Assumption
Other clinical inputs			
Natural disease progression	Disease progression rates by NYHA	Presented in Section 8.2	Maron et al. (2016)[133]; Maron (2018)[28]
AE incidence rates	Mavacamten + BB/CCB	Presented in Section 9.1.3	EXPLORER-HCM; Olivotto et al. (2020)[53]
	BB/CCB monotherapy	Presented in Section 9.1.3	EXPLORER-HCM; Olivotto et al. (2020)[53]
	SRT + BB/CCB	Presented in Section 9.1.3	Assumption, same as BB/CCB monotherapy arm in EXPLORER-HCM
Mortality inputs	All-cause mortality (age adjusted)	Presented in Section 8.2	Statistics Denmark (2021)[134]
	Mortality by NYHA, based on Wang et al	Presented in Section 8.2	Wang et al.
	Surgical mortality due to SRT (incident)	Presented in Section 8.2	Mentias et al. (2023)[110]; Hadaya et al. (2023)[120]

AE = adverse event; BB/CCB = beta-blocker/calcium channel blocker; HCM-LVSD = hypertrophic cardiomyopathy left ventricular systolic dysfunction; NYHA = New York Heart Association; SAE = serious adverse event; SRT = septal reduction therapy; TP = transition probability.
[a] Some of these estimates will be presented in other tables in the document.

8.1.1 Extrapolation of efficacy data

Not applicable because no extrapolation or parameterization has been performed.

8.1.1.1 Extrapolation of [effect measure 1]

Not applicable.

Table 22. Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
Data input	N/A
Model	N/A
Assumption of proportional hazards between intervention and comparator	N/A
Function with best AIC fit	N/A
Function with best BIC fit	N/A
Function with best visual fit	N/A
Function with best fit according to evaluation of smoothed hazard assumptions	N/A
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	N/A
Selected parametric function in base-case analysis	N/A
Adjustment of background mortality with data from Statistics Denmark	N/A
Adjustment for treatment switching/cross-over	N/A
Assumptions of waning effect	N/A
Assumptions of cure point	N/A

AIC = Akaike information criterion; BIC = Bayesian information criterion; N/A = not applicable.

8.1.1.2 Extrapolation of [effect measure 2]

Not applicable.

8.1.2 Calculation of transition probabilities

The model differentiates between 2 periods: short-term and long-term. The short-term period uses trial-based TPs. For both the mavacamten + BB/CCB arm and the BB/CCB monotherapy arm, short-term was defined as the first 30 weeks (i.e., EXPLORER-HCM trial period). Section 8.1.2.2 describes short-term TPs, and Section 8.1.2.3 describes the rationale behind the choice of short-term TPs in the base case of the model. The long-term period relies solely on modelling based on trial-based TPs. Long-term TPs are described in detail in Section 8.1.2.4.

8.1.2.1 Handling missing data

Patients in EXPLORER-HCM occasionally missed scheduled assessments, and their NYHA class was not observed at those assessment points. To compute TPs, a last-observation-carried-forward imputation was performed for any missed NYHA assessments before a patient's last observed assessment (which can be earlier than the end of study in case of discontinuation from the study). This imputation was necessary to ensure alignment between the model and the observed final NYHA distribution, such that all patients who had not discontinued the trial were included within each cycle transition.

Table 23 summarizes the number of patients at risk of HCM, with observed and imputed NYHA class at each assessment point. The slight reduction in the number of patients at risk during the first 30 weeks reflects discontinuations from EXPLORER-HCM.

Table 23. Patients at risk of HCM with observed and imputed NYHA class at each assessment timepoint by treatment arm

	Mavacamten + BB/CCB			BB/CCB monotherapy		
Timepoint	At risk	Observed	Imputed[a]	At risk	Observed	Imputed[a]
Week 0	123	123	0	128	128	0
Week 4	123	119	4	128	121	7
Week 6	123	116	7	128	115	13
Week 8	122	119	3	127	125	2
Week 12	122	116	6	127	120	7
Week 14	121	111	10	127	122	5
Week 18	121	119	2	127	126	1
Week 22	121	119	2	127	125	2
Week 26	121	120	1	126	125	1
Week 30	121	119	2	126	124	2

BB/CCB = beta-blocker/calcium channel blocker; HCM = hypertrophic cardiomyopathy; NYHA = New York Heart Association.
Note: The following discontinuations were observed. During the first 30 weeks of EXPLORER-HCM, in the mavacamten + BB/CCB arm, 1 patient was last observed at week 6, another at week 12. In the BB/CCB monotherapy arm, 1 patient was last observed at week 6, another at week 22, and another at week 30.
[a] Imputations done in the clinical study report.

8.1.2.2 Short-term TPs per treatment arm

Between weeks 30 and 38 of EXPLORER-HCM follow-up period, there was a washout period. Between week 38 of EXPLORER-HCM and the baseline assessment in EXPLORER-LTE, patients who were not taking part in the study were still blinded to the initial randomization. Thus, in the CEM, TPs for this group were computed only from the trial data for the period until week 30 (see Table 24). Section 8.1.2.3 provides further

information on the rationale for not including EXPLORER-LTE data in the short-term TP estimation. Section 8.1.2.4 describes the TPs used in the model for the mavacamten + BB/CCB arm after week 30.

Both the comparator arm of EXPLORER-HCM and data on these patients from the period between EXPLORER-HCM and EXPLORER-LTE were used to inform the short-term TPs for the BB/CCB monotherapy arm. The average number of days between the week 38 assessment of EXPLORER-HCM and the baseline assessment of EXPLORER-LTE was 59.7 (SD, 56.1; range, 3-262 days); as such, this timepoint is referred to as *week 46* (38-week end of study + 8-week average re-initiation = 46).[131] The data from the baseline assessment of EXPLORER-HCM to the baseline assessment of EXPLORER-LTE are the data held longest on file or obtained that inform disease progression for patients with oHCM on BB/CCB monotherapy.

Table 24 presents the TPs across various NYHA classes at each cycle/assessment point during EXPLORER-HCM and until the baseline assessment of EXPLORER-LTE (week 46) by treatment-arm allocation in EXPLORER-HCM, after carrying out the imputation procedure described above.

Table 24. TPs across various NYHA classes

		Mavacamten + BB/CCB, %				BB/CCB monotherapy, %			
Week	To From	NYHA I	NYHA II	NYHA III	NYHA IV	NYHA I	NYHA II	NYHA III	NYHA IV
Baseline to week 4	NYHA I[a]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	NYHA II	29.6	69.3	1.1	0.0	10.5	88.4	1.1	0.0
	NYHA III	11.4	40.0	48.6	0.0	0.0	42.4	57.6	0.0
	NYHA IV[a]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Weeks 4-6	NYHA I	70.0	30.0	0.0	0.0	20.0	80.0	0.0	0.0
	NYHA II	9.3	90.7	0.0	0.0	5.1	89.8	5.1	0.0
	NYHA III	0.0	44.4	50.0	5.6	5.0	20.0	75.0	0.0
	NYHA IV	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Weeks 6-8	NYHA I	78.6	21.4	0.0	0.0	87.5	12.5	0.0	0.0
	NYHA II	13.0	83.5	3.5	0.0	8.1	86.9	4.0	1.0
	NYHA III	0.0	12.5	87.5	0.0	0.0	15.0	85.0	0.0
	NYHA IV	0.0	100.0	0.0	0.0	N/A	N/A	N/A	N/A
Weeks 8-12	NYHA I	87.9	12.1	0.0	0.0	73.3	26.7	0.0	0.0
	NYHA II	21.5	76.0	2.5	0.0	7.8	88.9	3.3	0.0
	NYHA III	10.0	40.0	50.0	0.0	0.0	33.3	66.7	0.0
	NYHA IV	N/A	N/A	N/A	N/A	0.0	100.0	0.0	0.0
Weeks 12-14	NYHA I	78.7	21.3	0.0	0.0	66.7	33.3	0.0	0.0
	NYHA II	16.4	83.6	0.0	0.0	9.8	84.8	5.4	0.0
	NYHA III	0.0	42.9	57.1	0.0	0.0	17.6	82.4	0.0
	NYHA IV	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Weeks 14-18	NYHA I	83.3	14.6	2.1	0.0	71.4	28.6	0.0	0.0
	NYHA II	17.4	81.2	1.4	0.0	8.0	86.2	5.8	0.0
	NYHA III	0.0	0.0	100.0	0.0	0.0	10.5	89.5	0.0
	NYHA IV	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Weeks 18-22	NYHA I	86.6	11.5	1.9	0.0	95.5	4.5	0.0	0.0
	NYHA II	9.5	87.3	3.2	0.0	12.1	79.5	8.4	0.0
	NYHA III	0.0	33.3	50.0	16.7	0.0	40.9	59.1	0.0
	NYHA IV	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Weeks 22-26	NYHA I	94.1	5.9	0.0	0.0	80.6	12.9	6.5	0.0
	NYHA II	11.1	88.9	0.0	0.0	6.7	92.0	1.3	0.0
	NYHA III	0.0	16.7	83.3	0.0	0.0	20.0	80.0	0.0
	NYHA IV	0.0	0.0	100.0	0.0	N/A	N/A	N/A	N/A

Week	To / From	Mavacamten + BB/CCB, % NYHA I	NYHA II	NYHA III	NYHA IV	BB/CCB monotherapy, % NYHA I	NYHA II	NYHA III	NYHA IV
Weeks 26-30	NYHA I	87.3	12.7	0.0	0.0	76.7	23.3	0.0	0.0
	NYHA II	21.7	73.3	5.0	0.0	5.2	83.1	11.7	0.0
	NYHA III	0.0	16.7	83.3	0.0	0.0	15.8	84.2	0.0
	NYHA IV	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Weeks 30-38[b]	NYHA I					33.3	66.7	0.0	0.0
	NYHA II					4.1	86.3	9.6	0.0
	NYHA III					4.0	12.0	84.0	0.0
	NYHA IV					N/A	N/A	N/A	N/A
Weeks 38-46[b,c]	NYHA I					50.0	50.0	0.0	0.0
	NYHA II					5.1	86.1	8.8	0.0
	NYHA III					0.0	22.2	77.8	0.0
	NYHA IV					N/A	N/A	N/A	N/A

BB/CCB = beta-blocker/calcium channel blocker; N/A = not applicable; NYHA = New York Heart Association; TP = transition probability.

Notes: TPs used in the model for the mavacamten + BB/CCB arm could not be computed from the trial data for periods between weeks 30 and 38 and between weeks 38 and 46 due to patients being off treatment (i.e., a washout period took place between weeks 30 and 38 of EXPLORER-HCM and there was an additional period of time until the baseline assessment of EXPLORER-LTE in which patients were not taking part in the study). N/A represents a timepoint within the trial in which no patients were assessed to be within the defined NYHA class. Grey shaded cells represent the intervention group.

[a] No TP data for NYHA I and IV were available from EXPLORER-HCM for week 0 (i.e., baseline) to week 4 because the trial included only patients in NYHA class II-III.

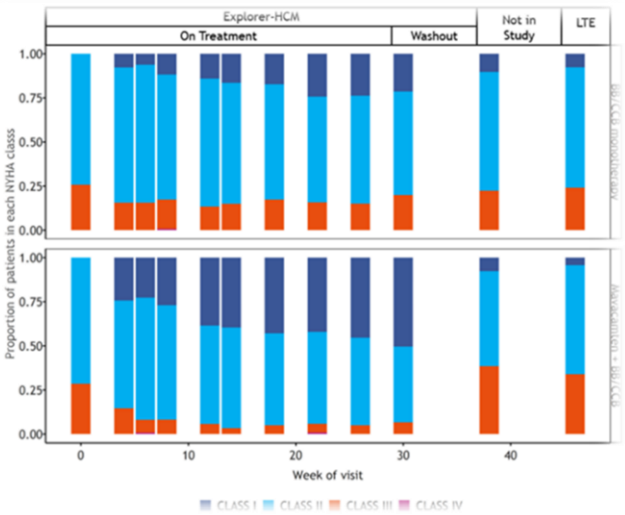
[b] TPs for weeks 30-38 and weeks 38-46 were reported for 8 weeks. These estimates were converted to 4 weeks to be used in the model (i.e., to adjust as per the cycle length).

[c] Week 46 refers to day 0 of the EXPLORER-LTE cohort of the MAVA-LTE trial NYHA distribution.

8.1.2.3 Rationale for the choice of short-term TPs in the base case

To explain the rationale for the short-term TPs used for the base case of the model, Figure 16 shows the evolution of the NYHA class distribution throughout EXPLORER-HCM and the baseline assessment of EXPLORER-LTE, separated by treatment arm.

Figure 16. Evolution of NYHA class distribution in EXPLORER-HCM and baseline assessment of EXPLORER-LTE by treatment-arm allocation in EXPLORER-HCM



BB/CCB = beta-blocker/calcium channel blocker; LTE = long-term extension; NYHA = New York Heart Association.

Note: This figure was built using the total number of observations at a given assessment timepoint, which is lower in later timepoints because some patients were censored. The last bar corresponds to the baseline assessment of MAVA-LTE. For this study, the assessment at day 0 was defined as week 46, although the actual collection was on average 59.7 days after the end of study.

8.1.2.4 Long-term TPs

Patients in both treatment arms were modelled to retain the NYHA class attained at the end of week 30 as the main response measure and only changed NYHA class based on natural disease progression thereafter.

Although there are longer-term efficacy data (i.e., up to 108 weeks) for patients on mavacamten that were collected as part of EXPLORER-LTE, these data were not used to compute TPs for the mavacamten + BB/CCB arm because of the open-label nature of this study and because approximately half of the patients were restarting mavacamten (i.e., they had received mavacamten + BB/CCB in EXPLORER-HCM), whereas the other half were starting mavacamten for the first time (i.e., they had been on BB/CCB monotherapy in EXPLORER-HCM). Therefore, these long-term data were used as a validation measure within the long-term TPs.

The choice of long-term TPs in the base case of the model is primarily supported by the stabilization of the NYHA class distribution observed toward the later periods of EXPLORER-HCM for mavacamten patients (see Figure 16). A similar pattern was observed in the EXPLORER-LTE cohort of MAVA-LTE (see bottom panel of Figure 19).

8.1.2.5 Natural disease progression

The model considered long-term impact of natural disease progression, accounting for the natural increase in NYHA class associated with disease duration and increasing age.

Based on suggestions from clinical experts and because natural disease progression in oHCM is documented in the literature, the economic model allows a patient's NYHA class to worsen over time due to the natural progression of the disease.[133,135]

There is a relative paucity of evidence to quantify the rate of disease progression for patients with oHCM. Maron et al. (2016)[133] quantified this effect, with 3.2% and 7.4% of patients progressing from NYHA class I or II to class III or IV per year for the provocable and rest obstruction subgroups, respectively.[133] Within the model, a weighted average of 4.55% per year was used and applied universally across each single interstate transition, with a proportion of patients per cycle moving from each NYHA class to the class above. The mechanism of action of mavacamten may have a positive impact on underlying natural disease progression. Thus, patients treated with mavacamten would have a slower disease progression relative to patients receiving standard of care.

To quantify the relative impact of mavacamten, EXPLORER-HCM was used to inform the relative reduction in disease progression.[53] After the first 30 weeks in EXPLORER-HCM, 7.03% of patients on placebo and 0.81% of those on mavacamten saw NYHA class worsening; there was a relative difference of 11.56% (mavacamten vs. placebo arm) resulting in an annual disease progression rate (i.e., proportion of patients who worsen by 1 NYHA class) for patients on mavacamten + BB/CCB of 0.53%. Because a relative difference derived from the proportion of patients who worsen by 1 NYHA class is deemed more appropriate to use in natural disease progression and was used in the Zorginstituut Nederland (ZIN) submission in the Netherlands, it is used in the base case.

NICE submission TA913 for mavacamten cited a relative difference of 50.85%, which was derived using a proportion of patients in both arms who saw no NYHA class improvement. Table 25 provides inputs used to model natural disease progression in the base case.

Table 25. Annual disease progression rates

NYHA class	Mavacamten + BB/CCB	BB/CCB monotherapy	SRT + BB/CCB
I to II	0.53%	4.55%	4.55%
II to III	0.53%	4.55%	4.55%
III to IV	0.53%	4.55%	4.55%
Reference	Applied as relative difference for patients who worsen by 1 NYHA class for mavacamten vs. placebo (11.56%), based on EXPLORER-HCM[53]	Maron et al. (2016) [133]	Maron et al. (2016) [133]

BB/CCB beta-blocker/calcium channel blocker; SRT = septal reduction therapy.

8.1.2.6 Summary of TPs and health-state occupancy

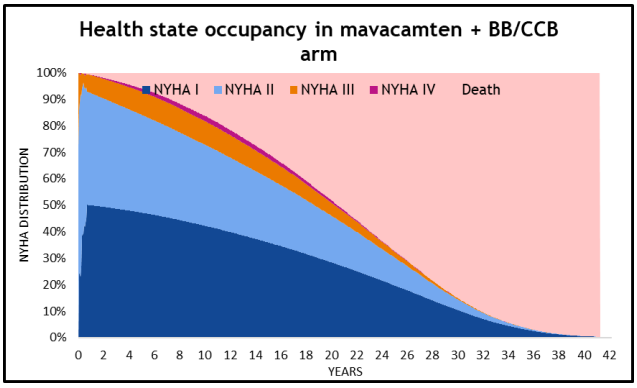
Table 26. Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Short-term TPs		Based on EXPLORER-HCM (for both intervention and BB/CCB monotherapy arm)	EXPLORER-HCM; Olivotto et al. (2020)[53]
Long-term TPs		Retain NYHA class (for both intervention and BB/CCB monotherapy arm)	Assumption, supported by EXPLORER-LTE and BMS data on file (2021)[132]
Natural disease progression		Disease progression rates by NYHA	Maron et al. (2016)[133]; Maron (2018)[28]

BB/CCB beta-blocker/calcium channel blocker; NYHA = New York Heart Association; TP = transition probability.

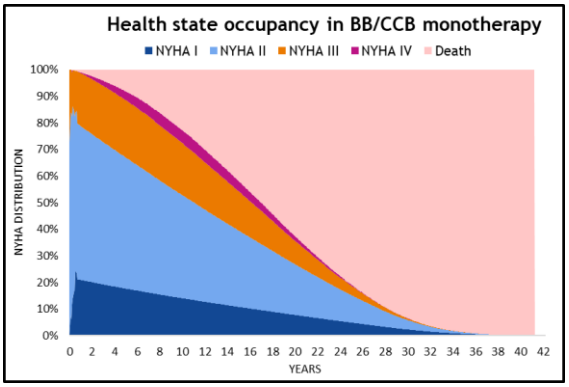
Figure 17 and Figure 18 show the proportion of patients in each health state per cycle for the mavacamten + BB/CCB and BB/CCB monotherapy arms, respectively.

Figure 17. Proportion of patients in each health state per cycle for mavacamten + BB/CCB



BB/CCB beta-blocker/calcium channel blocker; NYHA = New York Heart Association.

Figure 18. Proportion of patients in each health state per cycle for BB/CCB monotherapy



BB/CCB beta-blocker/calcium channel blocker; NYHA = New York Heart Association.

8.2 Presentation of efficacy data from the literature

General population and all-cause mortality rates were obtained from the latest (i.e., 2023) national life tables from Statistics Denmark (2021)[134]. These rates reflect the average mortality rates of the Danish population, adjusted for age and gender distribution provided by the clinical trial.

Within the model, patients in NYHA class I are assumed to have the same mortality risk as the Danish background population. Hazard ratios or relative risks were used to reflect the excess mortality associated with NYHA classes II, III, and IV.

Inputs on excess mortality for each NYHA class (II, III, IV vs. I) were obtained from 2 different studies:

- Wang et al. (2023)[34] conducted an analysis of oHCM mortality data using a cardiac cohort of the Optum Market Clarity database with linked claims and electronic health records in a US setting. The study included 4,631 adults with oHCM (NYHA class I: 23.9%; II: 38.8%; III: 32.4%; IV: 5.0%) who had a NYHA class ≥ I after first observed oHCM diagnosis. This study provided HR estimates for all-cause mortality adjusted by age, gender, and race. Mean age was 59 years at first observed diagnosis, 47% of the population was female, and 77% of the population was white.[34]
- [redacted]

In the base case, HRs from Wang were used due to the study's more granular data, providing data for all NYHA classes. Scenario analyses included use of HRs from the study using SHaRe. Only a composite HR for NYHA class III-IV was available; thus, the same was applied to both class III and IV patients. Table 27 provides the HRs by NYHA class.

Table 27. HRs for each NYHA class compared with NYHA I

NYHA class	HR (95% CI) from Wang (base case)	HR (95% CI) from SHaRe analysis[6] (scenario)
I	Reference class; as per all-cause mortality; HR, 1.00	
II vs. I	1.80 (1.40-2.32)	[redacted]
III vs. I	4.12 (3.24-5.25)	[redacted]
IV vs. I	10.90 (8.28-14.4)	

CI = confidence interval; HR = hazard ratio; NYHA = New York Heart Association.
[a] Composite NYHA class III-IV HR applied to both class III and IV separately.

The effect on mortality of mavacamten in oHCM patients is also shown by Patel et al. (2026)[7], demonstrating a reduction on all-cause mortality of mavacamten in patients with oHCM, thus supporting the assumption of a mortality benefit of mavacamten.[7] The study was a U.S. multi-center TriNetX cohort of 12,784 oHCM patients which compared mavacamten (n=550) to standard medical therapy. The results demonstrated a reduction in mortality risk for mavacamten compared to standard medical therapy:

Relative risk for mortality (median follow up 19 months)

- All-cause mortality in the mavacamten group after 19 months: 5/550 =0.9%
- All-cause mortality in the comparator group: 393/12 234 =3.2%
- Absolute risk reduction, all-cause mortality: 3.2-0.9 =2.3%
- Relative risk reduction, all-cause mortality, 72% (2.3/3.2).

To further support the mortality benefit of mavacamten, evidence for an increased mortality risk for oHCM patients is provided, demonstrating that NYHA class III/IV was the most important risk factor for cardiovascular death (HR = 2.53, 95% CI (2.10, 3.07).[5]

In addition to the NYHA-based mortality rates, the model captured the effect of SRT on mortality, considering that a proportion of patients receiving SRT experience surgical mortality (one-off). A list of published sources was collected by a targeted literature review to obtain a weighted mortality associated with SRT procedure for alcohol ablation therapy and myectomy. Mentias et al. (2023)[110] reported a short-term mortality risk of 1.70% in patients receiving alcohol ablation therapy. Hadaya et al. (2023)[120] reported a short-term mortality risk of 3.36% in patients receiving myectomy. A weighted average of 1.78% was used as a one-off surgical mortality in the model within the SRT state.

One sudden death occurred in the placebo + BB/CCB monotherapy arm during EXPLORER-HCM. This did not allow computing TPs from each NYHA class to Death for inclusion in the CEM.

8.3 Modelling effects of subsequent treatments

In the model, patients receiving BB/CCB monotherapy could escalate to treatment with SRT, which was modelled based on the ESC guidelines.[12]

In the first 30 weeks, all patients on BB/CCB monotherapy continued their initial treatment, similar to the intervention arm. After 30 weeks, a constant proportion of patients (by NYHA class as shown in Table 28) was permitted to escalate from BB/CCB monotherapy to SRT + BB/CCB at each cycle.

The proportion of NYHA I and II patients undergoing SRT procedures (i.e., myectomy, alcohol ablation therapy) over a lifetime (I: 0.0%, II: 2.0%) was collected via an expert elicitation study[49]. The NYHA III proportion was collected from SHaRe (27%).[56] The NYHA

IV proportion (0%) is according to ESC guidelines, stating NYHA class IV is not eligible for SRT. As noted in Section 3.3, in SHaRe, 18% of patients with HCM underwent SRT at any time (27% of patients with HCM-LVSD, 17.5% without LVSD). In the base case, the subgroup with HCM-LVSD (27%) was used as a conservative assumption since HCM-LVSD is a more severe population. A scenario analysis explored the total population (18%).

These lifetime SRT rates were converted to annual rates by using NYHA class–specific life expectancy from the model (I: 23.49 years; II: 19.01 years; III: 13.13 years; IV: 7.45 years).

Table 28. Proportion of patients escalated from BB/CCB monotherapy

Treatment	NYHA I	NYHA II	NYHA III	NYHA IV	Reference
Proportion of patients who escalated from BB/CCBs monotherapy (annual),[a] %	0.0	0.11	2.06[b]	0.0	Expert elicitation study[49]; SHaRe registry [56], ESC guidelines

BB/CCB = beta-blocker/calcium channel blocker; HCM-LVSD = hypertrophic cardiomyopathy left ventricular systolic dysfunction; NYHA = New York Heart Association.
[a] Escalation rates from BB/CCB monotherapy were adjusted dynamically based on mean survival by each NYHA class. Mean survival was estimated in the model based on all-cause mortality and NYHA class–specific mortality informed by expert elicitation results.
[b] Calculated using 27% of escalation rates reported from SHaRe of patient subgroup with HCM-LVSD; this is a conservative assumption because HCM-LVSD is a more severe population.

Efficacy estimates of SRT + BB/CCB used in the base-case analysis were collected via the expert elicitation study.[49] In addition, a scenario with efficacy estimates reported by a Ukraine-based study—Knyshov et al. (2013)[136]—was explored. In this study, 42 patients received either myectomy or ASA therapy with a mean baseline age of 29 and 34 years, respectively. Because of limited data, the difference in mean age, and the questionable applicability of the Ukraine setting, evidence collected via the expert elicitation study was used as the source of SRT efficacy data in the base-case analysis. [49]

Treatment with SRT was modelled as an event. Patients treated with SRT had incident TPs applied (Table 29) and were moved to a post-SRT state after 1 cycle.

Table 29. TPs for patients receiving SRT + BB/CCB

Option	To / From	TPs, % NYHA I	NYHA II	NYHA III	NYHA IV
Expert elicitation study[49]	NYHA I	90.0	10.0	0.0	0.0
	NYHA II	53.4	44.1	2.5	0.0
	NYHA III	39.4	44.2	14.4	2.0
	NYHA IV	6.3	45.0	33.8	15.0
Scenario					
Knyshov et al[136]	NYHA I	100.0	0.0	0.0	0.0
	NYHA II	33.3	66.7	0.0	0.0
	NYHA III	0.0	85.7	14.3	0.0
	NYHA IV	0.0	0.0	33.3	66.7

BB/CCB = beta-blocker/calcium channel blocker; NYHA = New York Heart Association; SRT = septal reduction therapy; TP = transition probability.

In the base case, we considered a conservative assumption in the post-SRT state that patients would maintain the NYHA class gained due to the incident SRT event, and no interstate transitions (i.e., among various NYHA states) were modelled using the previous assumption for consistency purposes. However, a re-intervention rate (i.e., repeat intervention) ranging from 4.4% to 20% has been reported among patients receiving

SRT.[137,138] Also, the evidence collected as part of the expert elicitation study confirmed that up to 20% of patients who received SRT may require a re-intervention (both planned and unplanned).[49]

8.4 Other assumptions regarding efficacy in the model

In the model, patients in the intervention arm were allowed to discontinue mavacamten for various reasons (described below), whereas patients in the BB/CCB monotherapy arm could escalate treatment by adding other subsequent treatments (e.g., SRT) to BB/CCB monotherapy. Like patients in the BB/CCB monotherapy arm, those in the intervention arm who discontinued mavacamten and continued receiving BB/CCB monotherapy could also escalate treatment by adding other subsequent treatments (e.g., SRT).

The DMC has requested the option to assume patients who discontinue mavacamten treatment revert to the NYHA class they had at baseline before initiating treatment. To address this, a "back-to-baseline" approach was implemented as an option in the model. Under this approach, once treatment is discontinued, the patient returns to their baseline NYHA functional class rather than remaining in the improved health state achieved during treatment. A scenario with the implementation of this model update has been added, see Table 59. Please see a more detailed summary of the model update in Appendix M.

8.4.1 Discontinuation of mavacamten due to AEs

It was assumed that no patients in the intervention arm discontinued mavacamten during the first 30 weeks, but a proportion of patients discontinued mavacamten at the end of the trial period (i.e., at week 30) due to the incidence of SAEs. EXPLORER-HCM reported a discontinuation rate of 1.4% due to SAEs within 30 weeks (see Table 33). This rate was used in the model at the end of the trial period as a one-off proportion (i.e., applied evenly across all NYHA health states).[53]

For the post–EXPLORER-HCM trial period/beyond week 30, in the base case, we assumed that the discontinuation rate of mavacamten would be similar to the rate observed in EXPLORER-HCM. The model used an annual discontinuation rate of 2.42% based on the long-term efficacy study for mavacamten in oHCM conducted by Garcia-Pavia et al.[92] In that study, 8.658% of patients (20 of 231) discontinued and had a median follow-up of 166 weeks. The annual discontinuation rate was applied evenly regardless of NYHA class because implementation at the conclusion of the trial period was explored. [53]

8.4.2 Discontinuation of mavacamten due to lack of response

At the end of the short-term period (week 30) of the model, the treatment discontinuation rules were applied so that patients who did not experience any improvement in NYHA class relative to baseline discontinued mavacamten (base case). The share of patients who experienced no NYHA improvement from baseline to week 30 was assessed as the secondary efficacy outcome (and a component of the primary efficacy outcome) of EXPLORER-HCM. Simply, if patients had no NYHA benefit while receiving treatment, they were assumed to discontinue due to lack of response. This approach aligns with the SmPC that states consideration should be given to discontinuing treatment in patients who have shown no response after 4 to 6 months.[64] Distribution of treatments after mavacamten discontinuation

It was assumed in the base case that all patients who discontinued mavacamten would revert to the underlying treatment (i.e., BB/CCB monotherapy) with the possibility to escalate to subsequent treatments later.

8.5 Overview of modelled average treatment length and time in model health state

Estimates for the modelled average and modelled median of the effect measures predicted by the extrapolation model is not applicable as no extrapolation has been done for the current model.

Table 30. Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
Mavacamten + BB/CCB	[X months/years]	[X months/years]	NA
BB/CCB monotherapy	[X months/years]	[X months/years]	NA

NA = not available.

Table 31 provides the average treatment length and time in the model health state.

Table 31. Modelled average treatment length and time in model health state, undiscounted and not adjusted for half-cycle correction

Treatment	Treatment length (years)	NYHA I (years)	NYHA II (years)	NYHA III (years)	NYHA IV (years)
Mavacamten + BB/CCB	19.78	10.44	7.25	1.78	0.31
BB/CCB monotherapy	16.78	3.36	8.85	3.86	0.71

BB/CCB = beta-blocker/calcium channel blocker; NYHA = New York Heart Association.

9 Safety

9.1 Safety data from the clinical documentation

In EXPLORER-HCM, 251 patients were included in the safety analysis for the safety population (all patients who received at least 1 dose of mavacamten), which consisted of 123 patients in the mavacamten arm and 128 patients in the placebo arm.

In EXPLORER-LTE, 231 patients were included in the analysis for the safety population (all patients who received at least 1 dose of mavacamten).[92]

In VALOR-HCM, patients treated in the double-blind period (day 1 to week 16) received either mavacamten (n = 56) or placebo (n = 55), and the long-term follow-up period included the all-mavacamten exposure group (n = 108) with timepoints reaching up to week 128.[94,95] Overall, mavacamten displayed an acceptable safety profile in VALOR-HCM (Appendix L).

Table 32. Overview of safety events

	EXPLORER-HCM		EXPLORER-LTE	VALOR-HCM		
	Double-blind period		Long-term follow-up	Double-blind period		Long-term follow-up
	Mavacamten (n = 123)	Placebo (n = 128)	Overall mavacamten (n = 231)	Mavacamten (n = 56)	Placebo (n = 55)	Overall mavacamten (n = 108)
Number of AEs, n	536	495	1,870	123	95	347
Number and proportion of patients with ≥ 1 AE, n (%)	108 (87.8)	104 (81.3)	228 (98.7)	41 (73.2)	34 (61.8)	81 (75.0)
Number of SAEs,[a] n	24	23	117	4	1	NR
Number and proportion of patients with ≥ 1 SAE,[a] n (%)	14 (11.4)	12 (9.4)	63 (27.3)	3 (5.4)	1 (1.8)	21 (19.4)
Number of CTCAE grade ≥ 3 events,[b] n	22	24	81	3	2	42
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events,[c] n (%)	12 (9.8)	14 (10.9)	43 (18.6)	3 (5.4)	1 (1.8)	20(18.5)
Number of adverse reactions, n	NR	NR	128	123	93	NR
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	19 (15.4)	18 (14.1)	54 (23.4)	9 (16.1)	9 (16.4)	17 (15.7)
Number and proportion of patients who had a dose reduction, n (%)	17 (13.8)	NR	142 (61.5)	24 (42.9)	NA	8 (7.4)
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	4 (3.3)	3 (2.3)	45 (19.5)	4 (7.1)	10 (18.2)	15 (13.9)
Number and proportion of patients who discontinue treatment due to AEs, n (%)	2 (1.6)	0	11 (4.8)	0	0	0

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; NR = not reported; SAE = serious adverse event.

[a] An SAE is an event or reaction that, at any dose, results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the International Council for Harmonisation's complete definition).

[b] The rate of CTCAE grade ≥ 3 AEs were reported from the following data cut-offs: July 2020 (EXPLORER-HCM), August 2023 (EXPLORER LTE), February 2022 (VALOR Double-blind period) and July 2024 (VALOR Long-term follow-up period).

[c] CTCAE v. 5.0 must be used if available.

Sources: Desai et al. (2022)[94]; Desai et al. (2025)[95]; BMS data on file (2022)[139]; Garcia-Pavia et al. (2024)[92]; Olivotto et al. (2020)[53]

9.1.1 Effect of mavacamten on LVEF

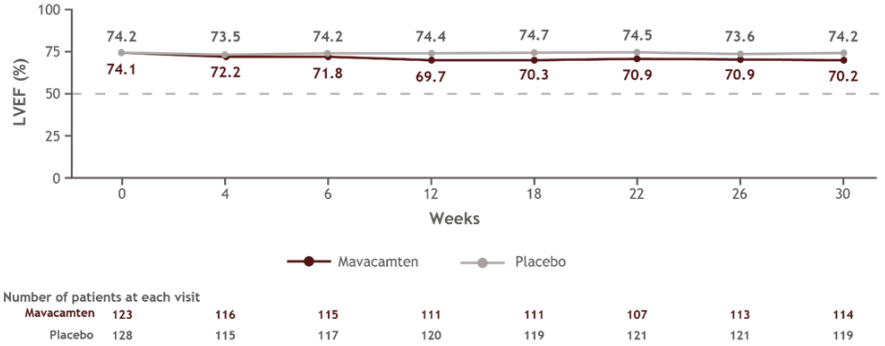
An LVEF ≤ 30% was a prespecified AE of special interest in EXPLORER-HCM; therefore, safety in terms of LVEF is presented here.

At baseline, the **mean LVEF** in the mavacamten group (n = 123) and placebo group (n = 128) was 74.1% and 74.2%, respectively. At week 30, the **mean reduction in LVEF** was −3.9% with mavacamten compared with −0.01% with placebo (difference −4.0%; 95% CI, −5.5 to −2.5) (Figure 19).[53] Nine patients (mavacamten, n = 7; placebo, n = 2) experienced a **transient LVEF < 50%.** Five patients (mavacamten, n = 3; placebo, n = 2) had **protocol-driven temporary treatment discontinuation** for LVEF < 50% during the treatment period (median LVEF, 48%). LVEF normalized in all patients, and all patients resumed treatment and completed the study. Additionally, 4 patients in the mavacamten group had LVEF < 50% (range, 48%-49%) at week 30 (end-of-treatment visit), which returned to baseline levels in 3 patients after the 8-week washout period. The fourth patient had an LVEF drop after AF ablation during the washout period, which recovered partially to LVEF of 50%.[53]

More patients taking mavacamten met the primary composite endpoint than placebo irrespective of baseline LVEF < 75% or ≥ 75%[53]:

- LVEF < 75%: 36% of mavacamten patients versus 16% of placebo patients.
- LVEF ≥ 75%: 37% of mavacamten patients versus 19% of placebo patients.
- The **EXPLORER-CMR substudy** examined the effect of mavacamten versus placebo on cardiac structure and function in 35 patients (mavacamten, n = 17; placebo, n = 18). **LVEF reduction** with mavacamten was assessed to be −6.6% compared with −0.3% with placebo.[89,140]
- There was no LVEF reduction < 50% by cardiac magnetic resonance. Of the 9 patients in EXPLORER-HCM (mavacamten, n = 7; placebo; n = 2) with a transient decrease in LVEF of < 50% by ECG, 2 were in the cardiac magnetic resonance sub-study (1 patient for each arm) and both were asymptomatic at time of measure.

Figure 19. EXPLORER-HCM: LVEF over time



LVEF = left ventricular ejection fraction.
Note: Dashed line represents the protocol threshold for temporary discontinuation (LVEF < 50%).
Adapted from Olivotto et al. (2020)[53]

At week 84 of EXPLORER-LTE, 85% of patients were receiving **mavacamten ≤ 10 mg. A decrease in** resting LVEF was noted over 84 weeks; the mean (SD) change from baseline was −9.0% (8.1%), as assessed by the central laboratory. In total, 12 patients (5.2%) with **LVEF < 50% experienced a temporary treatment discontinuation per protocol.** The LVEF

of all 12 patients recovered without further sequelae. Of these patients, 2 experienced events of LVEF < 50% that were considered to be a treatment-emergent AE (TEAE), and 5 patients permanently discontinued the study, although 1 patient was later re-enrolled. The exposure-adjusted incidence of decreased LVEF was 2.53 per 100 patient-years; a rate similar to that reported in prior analyses.[91]

At week 180 of EXPLORER-LTE, 87.2% of patients were receiving **mavacamten ≤ 10 mg.**[92] **No patients had experienced LVEF < 30%** during treatment in the study. In total, 20 patients (8.7%) with **LVEF < 50% experienced a temporary treatment discontinuation per protocol.** Of these patients, 14 resumed treatment, and 6 permanently discontinued the study, although 1 patient was later re-enrolled.[92]

At baseline, the **mean LVEF** in the mavacamten group (n = 56) and placebo group (n = 56) was 67.9% and 68.3%, respectively. At week 16, the **mean (SD) change in LVEF** from baseline was −3.4 (6.2) in the mavacamten group and 0.3 (4.2) in the placebo group (treatment difference [95% CI]: −4.0 [−5.5 to −2.5]). In total, 2 patients (3.6%) receiving mavacamten had an **LVEF < 50%,** leading to temporary drug discontinuation compared with no patients on placebo. These 2 patients later resumed treatment without further AEs and remain in the LTE study. No patient experienced a reduction of LVEF ≤ 30% necessitating permanent drug discontinuation.[94]

9.1.2 Safety: integrated summary of safety

9.1.2.1 Summary of safety data

The data from 5 phase 2 and 3 clinical studies (EXPLORER-HCM, PIONEER-HCM, MAVERICK-HCM, EXPLORER-LTE, PIONEER-OLE) were analyzed in integrated populations and by indications for the integrated summary of safety for submission to the EMA. Table 33 presents data for the integrated pool of all patients with oHCM who received at least 1 dose of mavacamten in any of the integrated clinical studies (i.e., the all-mavacamten combined column) alongside data from EXPLORER-HCM. The studies included in the integrated safety summary ranged from 30 weeks (EXPLORER-HCM) to 104 weeks (EXPLORER-LTE) in duration.

Table 33. Integrated summary of safety (day 1 to week 38)

	Number of patients (%)		
	All-mavacamten combined (n = 314)	Patients with oHCM from EXPLORER-HCM	
		Mavacamten (n = 123)	Placebo (n = 128)
[redacted]			

	Number of patients (%)		
	All-mavacamten combined (n = 314)	Patients with oHCM from EXPLORER-HCM	
		Mavacamten (n = 123)	Placebo (n = 128)
[redacted]			

9.1.2.2 Summary of SAE safety data

Across indications, 18.5% of mavacamten-treated patients in the integrated summary of safety analyses experienced at least 1 SAE (Table 34).

In the EXPLORER-HCM treatment group, SAEs were most frequently reported in the system organ class of cardiac disorders (5 patients [4.1%] in the mavacamten arm vs. 5 patients [3.9%] in the placebo arm); nervous system disorders (4 patients [3.3%] vs. 2 patients [1.6%]); infections and infestations (3 patients [2.4%] vs. 2 patients [1.6%]); and injury, poisoning, and procedural complications (2 patients [1.6%] vs. 0). There were no other system organ classes for which more than 1 patient in the mavacamten group experienced an SAE (Table 34). Appendix E presents all SAEs observed in the study.

Table 34. Integrated analysis: patient incidence of SAEs reported by ≥ 2 patients (day 1 to week 38)

	Number of patients (%)		
	All-mavacamten combined (n = 314)	Patients with oHCM from EXPLORER-HCM	
		Mavacamten (n = 123)	Placebo (n = 128)
[redacted]			

9.1.3 AEs used in the health economic model

Based on results from EXPLORER-HCM, various TEAEs were included in the model to capture the impact on costs and utilities. The comparator arm over the 30-week period

was used to inform the standard-of-care treatments (BB/CCB monotherapy, SRT + BB/CCB), whereas the intervention arm over the 30-week period was used to inform mavacamten + BB/CCB. In all cases, the 30-week probability was converted to a 4-week incidence rate. Adverse events defined as not related to treatment per the clinical study report (e.g., stress cardiomyopathy, diverticulitis) were not included. In addition, sudden death was not included due to the potential of double counting relative to the mortality inputs.

Table 35 presents the treatment-related AEs and their corresponding incidence rates for the intervention and each of the standard-of-care treatments used in the model. Sections 10 and 11.5 present Inputs related to disutilities and costs associated with AEs.

Table 35. Treatment-related AEs and incidence rates used in the economic model

AE	Intervention arm: mavacamten + BB/CCB (%)		Comparator arm: BB/CCB monotherapy (%)		After SRT: BB/CCB monotherapy (%)
	n	4-week rate	n	4-week rate	
Syncope	2 (1.6)	0.22	1 (0.8)	0.10	0.10
Transient ischemic attack	0 (0.0)	0.00	1 (0.8)	0.10	0.10
Cardiac failure congestive	0 (0.0)	0.00	1 (0.8)	0.10	0.10
Viral gastroenteritis	0 (0.0)	0.00	1 (0.8)	0.10	0.10
Urinary tract infection	0 (0.0)	0.00	2 (1.6)	0.21	0.21
Reference	EXPLORER-HCM[53]		EXPLORER-HCM[53]		Assumption, same as BB/CCB monotherapy

AE = adverse event; BB/CCB = beta-blocker/calcium channel blocker; SRT = septal reduction therapy.
Note: Intervention arm: n = 123; comparator arm: n = 128.

9.1.4 Safety conclusion

The intervention (mavacamten in combination with standard of care) and comparators (placebo in combination with individually optimized standard of care comprising BBs and/or CCBs) that are being considered have been evaluated within a single RCT; therefore, no comparative analyses were required. In conclusion, mavacamten displayed an acceptable safety profile across 6 clinical studies (EXPLORER-HCM, PIONEER-HCM, MAVERICK-HCM, EXPLORER-LTE, and PIONEER-OLE, VALOR-HCM). A reduction in LVEF is consistent with the known mechanism of action of mavacamten as an inhibitor selective for cardiac myosin. Across trials, there was a mean reduction in LVEF after treatment with mavacamten (EXPLORER-HCM: mean change in LVEF, −3.9%; EXPLORER-LTE: mean change in LVEF over 84 weeks, −9.0% ± 8.1%; VALOR-HCM: mean change in LVEF, −3.4%).[53,91] In total, 21 patients treated with mavacamten across trials had an LVEF < 50% leading to temporary drug discontinuation. No patients experienced a reduction of LVEF ≤ 30% necessitating permanent drug discontinuation. No SAEs of heart failure occurred. Of note, the side effect profile of mavacamten remained consistent even with a longer treatment time and did not differ from that established in the main pivotal trial. Regardless of treatment group or indication, TEAEs were generally mild.[53]

A favorable real-world experience with mavacamten was presented from the REMS program as supportive evidence to this submission (see Section 6.1.6). The need for temporary interruption for LVEF < 50% was low, with similar results for patients on

mavacamten for ≥ 1 year. The vLVOT gradient decreased, with more than half of patients experiencing a reduction to < 20 mmHg. A low proportion of patients experienced heart failure requiring hospitalization (1.3%), including similar results for patients with ≥ 1 year of treatment with mavacamten (1.5%).[87]

9.2 Safety data from external literature applied in the health economic model

Not applicable.

10 Documentation of health-related quality of life (HRQoL)

Table 36. Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	EXPLORER-HCM	Clinical effectiveness, utility estimates

HRQoL = health-related quality of life.

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

EXPLORER-HCM is a phase 3, randomized, double-blind, placebo-controlled trial assessing the efficacy of mavacamten in patients with symptomatic oHCM with an LVOT gradient of ≥ 50 mmHg and NYHA class II-III. Section 6.1 presents the study design.

The base case in the CEM will rely on the utilities estimated based on the EQ-5D-5L index score collected as part of EXPLORER-HCM.

10.1.2 Data collection

The utility analysis was performed on the safety population from EXPLORER-HCM, which included all randomly assigned participants who received at least 1 dose of the study drug, with analyses conducted according to the actual study drug received. Among the safety population, patients were excluded from the utility analysis if they did not have any response assessment or they did not have at least one complete measurement at a given assessment timepoint.

A comprehensive analysis was conducted on the reasons for and impact of these missing data. There were missing baseline data primarily due to operational challenges with the use of the electronic device used to collect these data and thus were unrelated to patient characteristics. After imputing missing data with unfavorable outcomes for mavacamten and favorable outcomes for placebo, the estimated treatment effects on PROs remained statistically significant. Additionally, Table 37 and Table 38 show that response rates for the EQ-5D at each assessment point were similar across treatment arms. Table 39 shows that there were no statistically significant differences in baseline characteristics (i.e., age, gender, and body mass index) between patients with and without missing observations for the EQ-5D by treatment arm. Finally, Table 40 shows that there were no statistically significant differences in the mean EQ-5D scores reported throughout the trial for patients who completed all EQ-5D assessments and those who

did not complete at least one assessment for each treatment arm. Overall, these results indicate that patients with missing EQ-5D assessments are similar to those with complete assessments.

Table 37. Pattern of missing data and completion for mavacamten arm (EXPLORER-HCM)

	HRQoL population, N	Missing, N (%)	Expected to complete, N	Completion, N (%)
Timepoint	No. of patients at randomization	No. of patients for whom data are missing (% at randomization)	No. of patients "at risk" at timepoint X	No. of patients who completed (%expected to complete)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HRQoL = health-related quality of life.

Table 38. Pattern of missing data and completion for placebo arm (EXPLORER-HCM)

	HRQoL population, N	Missing, N (%)	Expected to complete, N	Completion, N (%)
Timepoint	No. of patients at randomization	No. of patients for whom data are missing (%at randomization)	No. of patients "at risk" at timepoint X	No. of patients who completed (%expected to complete)
[redacted]	[redacted]	30 (23.4%)	[redacted]	[redacted]
[redacted]	[redacted]	24 (18.8%)	[redacted]	[redacted]
[redacted]	[redacted]	18 (14.1%)	[redacted]	[redacted]
[redacted]	[redacted]	9 (7.0%)	[redacted]	[redacted]
[redacted]	[redacted]	15 (11.7%)	[redacted]	[redacted]
[redacted]	[redacted]	47 (36.7%)	[redacted]	[redacted]

HRQoL = health-related quality of life.

Table 39. Baseline characteristics of responders and non-responders to the EQ-5D by treatment arm

Treatment arm	Variable	Responder	Mean	SD	95% CI
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]

Treatment arm	Variable	Responder	Mean	SD	95% CI
[redacted]					

Table 40. **Mean EQ-5D scores throughout EXPLORER-HCM for patients who completed all EQ-5D assessments and those who did not complete at least one assessment by treatment arm**

Treatment arm	Responder	N	Mean	SD	95% CI
[redacted]					

10.1.3 HRQoL results

- Figure 20 and Table 41 present results of the HRQoL analysis for EQ-5D-5L and the Danish value set.

Figure 20. **HRQoL EQ-5D-5L change from baseline through data collection timepoints for**

[redacted]

Table 41. **HRQoL EQ-5D-5L summary statistics**

	Intervention		Comparator		Intervention vs. comparator	
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI)	*P* value
Baseline	[redacted]					

	Intervention		Comparator		Intervention vs. comparator	
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI)	*P* value
Week 6	[redacted]					
Week 12	[redacted]					
Week 18	[redacted]					
Week 30	[redacted]					
Week 38	[redacted]					

CI = confidence interval; HRQoL = health-related quality of life; SE = standard error.

10.2 Health state utility values (HSUVs) used in the health economic model

In the model, QALYs were incorporated using utilities by NYHA class. Hence, AE-related utility decrements were not applied to avoid potential double counting of the impact of AEs within the underlying utilities observed in the trial because the impact of AEs on utility already is included in the health-state utility where related to the NYHA class level.

An SLR was undertaken to identify HRQoL studies relevant to this submission from the published literature. The SLR identified 12 studies that investigated HRQoL and utilities in patients with oHCM. However, no publications reporting study utilities by NYHA class that were needed for the health economic model were identified (except 1 reporting EXPLORER-HCM utilities using US value set[88]) (see Appendix I). Thus, trial-based (i.e., EXPLORER-HCM) utilities that reflect the actual experiences of patients with oHCM in different NYHA classes who were treated with mavacamten and/or BB/CCB monotherapy were used in the model.

10.2.1 HSUV calculation

The EQ-5D-5L data collected within EXPLORER-HCM were analyzed to estimate health-state utility values. EQ-5D-5L responses were provided by each patient at multiple assessment points during the trial. Hence, linear mixed-effects models were used to derive health-state utility values ranging from 0 to 1. Several model structures were considered, including random intercepts, random slopes, and random intercepts and slopes. Several potential covariates were included in the models, such as age, gender, treatment arm, assessment points, and current NYHA class. The preferred model structure included a random intercept at the patient level. In addition, only binary indicators for current NYHA class were statistically significant in the model. Of note, the treatment arm was not found to be a statistically significant variable and was dropped by the backward and forward stepwise covariate selection procedure, indicating that 1 health-state (NYHA)–specific utility value across both treatment arms should be used in the CEM. The EQ-5D-5L Danish value set proposed by Jensen et al. (2021)[142] was applied to the EQ-5D-5L data collected in EXPLORER-HCM to derive utility values.[141]

Table 42 presents Danish utility values obtained from the EQ-5D-5L assessments conducted in EXPLORER-HCM (regardless of treatment arm). Data from EXPLORER-LTE

were not used for obtaining utility values due to the lack of granularity of the data and lack of BB/CCB monotherapy arm, for which utility estimates are also needed in the CEM.

Due to the small number of observations in NYHA class IV in EXPLORER-HCM, it was not possible to estimate a utility value for those patients. Of the 3 NYHA class IV observations, 2 were measured at timepoints when the EQ-5D was not assessed, so these data cannot be used in the linear mixed models. As for the remaining observation in NYHA IV, it had missing values for some of the potential covariates considered in the utility analysis, so it could not be considered in the covariate selection procedure. Therefore, it is assumed that the same utilities estimated for NYHA III patients are used for NYHA IV patients in this model. In a previous health economic model, it was assumed that health utilities decrease with increasing NYHA class severity, so this assumption is likely to underrepresent of the real utility values for NYHA IV patients, which will potentially favor the BB/CCB monotherapy arm because of the lower NYHA class profile of that cohort.[143] However, the proportion of patients in NYHA IV is likely to be small, so this assumption is expected to have a limited impact on model outcomes.

Of note, NYHA class I mean utility is higher than the population norm (0.95 vs. 0.90, respectively).[144] Based on internal clinical input, it is assumed that this higher utility may come from the high unmet need in this disease area, wherein patients with NYHA II/III (i.e., the population eligible for mavacamten) have made significant lifestyle modifications in the absence of appropriate therapies to treat their condition. Subsequent initiation of a new therapy may result in changes to the patient's lifestyle, resulting in "feeling" better (i.e., a halo effect) than the norm.

10.2.1.1 Mapping

Not applicable because no mapping of HRQoL data has been performed.

10.2.2 Disutility calculation

Disutility associated with AEs was not included in the model due to the potential double counting of the impact of AEs within the underlying utilities observed in the trial. Also, the impact of age-related utility decrements was included in the model to consider the natural decline in QoL associated with increasing age. This was implemented in the model using the method provided by the Danish Medicines Council (DMC).[145]

10.2.3 HSUV results

Table 42. Overview of health-state utility values used in the model

Health state	Results (95% CI)	Instrument	Tariff (value set) used	Comments
NYHA I	[redacted]	EQ-5D-5L	DK	EXPLORER-HCM analysis[146] (Denmark specific)
NYHA II	[redacted]	EQ-5D-5L	DK	
NYHA III	[redacted]	EQ-5D-5L	DK	
NYHA IV	[redacted]	EQ-5D-5L	DK	Assumed to be the same as NYHA class III

CI = confidence interval; NYHA = New York Heart Association.

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Not applicable.

10.3.1 Study design

Not applicable.

10.3.2 Data collection

Not applicable.

10.3.3 HRQoL results

Not applicable.

10.3.4 HSUV and disutility results

Not applicable.

Table 43. Overview of health-state utility values

Not applicable.

11 Resource use and associated costs

Modelled cost categories were chosen to reflect the expected key cost components related to the treatment, management, and monitoring of patients with oHCM. These included:

- Treatment acquisition costs, including test costs
- Treatment monitoring costs
- Healthcare resource utilization (HCRU)
- AE management costs
- Patient time-related costs
- Transportation costs

For each cost category, unit costs were multiplied by the frequency of a certain type of resource used within each cycle. The cost per cycle was then multiplied by the distribution of patients in each health state per cycle to calculate the total costs. All costs in this report are expressed in 2025 Danish krone (DKK).

11.1 Medicine - intervention and comparator

Treatment acquisition costs were estimated using data on treatment prices, dosing at presentation, and the dosing schedule for each regimen. Information on the dosing schedule was obtained from drug labels (Table 44), whereas costs and presentation of metoprolol and verapamil were extracted from the Lægemiddelstyrelsen medicinpriser (www.medicinpriser.dk; accessed January 2026)[147] (Table 45).

Table 44. Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Mavacamten	2.5 mg	100%	Once daily	N/A
Metoprolol	50 mg	100%	Twice daily	N/A
Verapamil	120 mg	100%	Thrice daily	N/A

N/A = not applicable.

Table 45. Drug acquisition costs used in the model

Medicine	Citations	Dose per unit	Pack Size	Cost per package (DKK)	Cost per unit (DKK)
Mavacamten	BMS	2.5/5/10/15 mg	28	11,614.89 (price: 151,512 per patient per year)	414.82
Metoprolol	Lægemiddelstyrelsen Medicinpriser [147]	50 mg	100	138	1.38
Verapamil	Lægemiddelstyrelsen Medicinpriser [147]	120 mg	100	78	0.78

Mavacamten will be marketed as a pack of 28 capsules with an expected pharmacy purchase price of 11,614.89 DKK per pack (151,512 DKK per patient per year). Mavacamten will be launched with the same price for all packages; hence, any dose escalation will not impact the cost of treatment of mavacamten. The impact of missing doses or protocol-driven temporary discontinuation of mavacamten was included within the drug cost. EXPLORER-HCM reported that [redacted] of patients adhered to the treatment protocol, which was used in the model to derive the acquisition cost of mavacamten.

Cost per dose was multiplied by the number of doses per cycle to estimate the cost per cycle.

Patent expiry is expected in 2034, which is approximately 8 years after the assessment at the DMC. Generic drug uptake in Denmark is, in general, fast and results in significantly lower prices,[148] often a reduction of 80-90%.

In the base case, the patent expiration is not considered. The impact of patent expiration is explored in a scenario where the price of mavacamten is reduced by 80% after 8 years.

11.2 Medicines– co-administration

The impact of genotype testing (i.e., cytochrome P450 [CYP] test) costs was included as a one-off cost (985 DKK, sourced from Gentest-Filadelfia[149]) in the model; it was assumed that all patients treated with mavacamten were tested for genotype.

11.3 Administration costs

No administration costs were incurred because all treatment options (except surgical SRT procedures) within this indication are oral formulations that can be self-administered by the patient.

11.4 Disease management costs

11.4.1 Health resource utilization cost

Data on HCRU were collected from an expert elicitation study.[49] To align with the economic model and to provide credible estimates of HCRU that would accurately reflect varying HCRU by disease status, all estimates were based on the patient's NYHA classification. Per the expert elicitation study, ECGs and 12-lead ECGs are done at every CV-related outpatient visit. However, costs associated with ECGs/12-lead ECGs were not explicitly included in the model because these costs were already considered in diagnosis-related group (DRG) tariffs of CV-related visits. Table 46 presents the HCRU

used in the model along with unit costs. Unit cost associated with each resource was collected from Sundhedsdatastyrelsen, DRG-takster 2025.[150]

Table 46. Frequencies of resources used and their unit costs

Resources	Resources by NYHA class per year				Unit cost (DKK)	DRG code/DRG tariff	Reference
	I	II	III	IV			
Secondary care							
Day case admissions	0.39	0.59	2.06	3.50	1,268	05MA98 (MDC05 1-dagsgruppe, pat. mindst 7 år)	Sundhedsdatastyrelsen (2025)[150]
Outpatient (CV-related) visits	0.69	0.88	2.13	3.25	2,111	05PR04 (Kardiologisk undersøgelse, udvidet)	
Outpatient (non–CV-related) visits	0.31	0.63	0.00	0.00	1,268	05MA98 (MDC05 1-dagsgruppe, pat. mindst 7 år)	
Inpatient (elective) ≤ 1 days	0.00	0.04	0.60	1.01	2,240	05MA08 (Andre hjertesygdomm)	
Inpatient (elective) > 1 day	0.00	0.00	0.60	4.04	2,404	lang-ligger-takst 2,240 DKK per dag efter dag 1	
Inpatient (emergency) ≤ 1 day	0.00	0.14	1.73	2.24	2,240	05MA08 (Andre hjertesygdomme)	
Inpatient (emergency) > 1 day	0.00	0.00	6.92	15.68	2,404	lang-ligger-takst 2,240 DKK per dag efter dag 1	
Tests/procedures							
Cardiac MRI procedures	0.10	0.13	0.34	0.29	2,212	30PR03 (MRI scan, uncomplicated)	Sundhedsdatastyrelsen (2025)[150]

CV = cardiovascular; DRG = diagnosis resource group; MRI = magnetic resonance imaging; NYHA = New York Heart Association.

11.4.2 Treatment monitoring costs

Because of the significant overlap between treatment monitoring and HCRU, treatment monitoring includes monitoring of mavacamten over and above traditional standard of care. Based on the SmPC,[64] it was assumed that monitoring of mavacamten would, on average, require 6 CV-related outpatient visits in total, with an ECG performed at each visit within the first year after initiation, irrespective of NYHA class. It was assumed no monitoring would be required in addition to that required for standard of care beyond year 2. If the underlying HCRU for CV-related outpatient visits and ECGs was greater than the anticipated monitoring requirements for mavacamten within the scenario or sensitivity analyses, the uplift was capped in the model to ensure that the monitoring requirements for mavacamten were not lower than that of standard of care. In the current model, frequency and costs of ECGs were not implemented separately because the DRG tariffs for CV visits included ECG-related costs.

Table 47 presents the additional monitoring requirements needed while receiving mavacamten, by NYHA class, based on the underlying base-case assumption of HCRU as discussed in Section 11.4.1. Although no explicit scenario analyses were conducted to

test the absolute monitoring required by mavacamten (because of the uplift relative to HCRU), scenario analyses undertaken within those analyses will dynamically modify the uplift so that, in all cases, patients receiving mavacamten will have an equivalent absolute monitoring profile.

Table 47. Inputs for monitoring costs for patients receiving mavacamten in year 1

Resource per annum	NYHA I	NYHA II	NYHA III	NYHA IV	Unit costs (DKK)	Reference
CV-related office visits[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Camzyos SmPC (2021)[64]; Sundhedsdatastyrelsen (2025)[150] (05PR04 (Kardiologisk undersøgelse, udvidet)

CV = cardiovascular; DRG = diagnosis resource group; ECG = electrocardiogram; NYHA = New York Heart Association. Note: ECGs are done at every CV-related outpatient visit. However, costs associated with ECGs/12-lead ECGs were not explicitly included in model because these costs were already considered in DRG tariffs of CV-related visits.

[a] Values in parentheses represent the frequency of resource use for standard of care. The sum of the 2 values equals 5 for all NYHA classes, as described above (e.g., the total number of CV visits for NYHA I class is a sum of 4.31 and 0.69, which equals 5).

11.5 Costs associated with management of adverse events

To ascertain AE management costs, resources used to manage AEs were identified with associated costs based on Sundhedsdatastyrelsen, DRG-takster 2025.[150] In the model, AE management costs were estimated as the sum product of the AE incidence (see Table 35) and the associated costs of each AE. Table 48 presents the management costs associated with each AE.

Table 48. Cost associated with management of AEs

AE	Unit cost (DKK)	DRG code/DRG tariff	Reference
Syncope	21,047	05MA07 (cardiac arrhythmia and syncope)	Sundhedsdatastyrelsen (2025)[150]
Transient ischemic attack	25,301	01MA13 (transient insufficient blood supply to brain and occlusion of precerebral arteries)	
Cardiac failure congestive	40,702	05MA04 (heart failure and shock)	
Viral gastroenteritis	4,977	06MA11 (malabsorption and inflammation of the oesophagus, stomach, and intestines, patients 18 years +)	
Urinary tract infection	32,416	11MA07 (infection in the kidneys and urinary tract, patients 16 years +)	

AE = adverse event.

11.6 Subsequent treatment costs

As outlined in Section 8.3, in the model, patients receiving BB/CCB monotherapy could escalate to treatment with SRT, which was modelled based on the ESC guidelines.[12] The proportion of patients undergoing various SRT procedures (i.e., myectomy, alcohol ablation therapy) over a lifetime (by NYHA class, I: 0.0%, II: 2.0%, III: 27%, IV: 0.0%) was collected via an expert elicitation study[49] except for NYHA III collected from SHaRe registry.[56] The NYHA IV proportion reflects the ESC guidelines. For the model these lifetime risks were incorporated as annual probability of SRT. In addition to SRT procedure costs, costs for cardiac rehabilitation were included that reflect the additional burden of SRT not captured in the SRT costings themselves. The model also captured the

additional cost of complications related to SRT procedures, considering the proportion of patients with complication of SRT procedure (ASA and myectomy) and their respective costs.

11.6.1 SRT procedures costs

The market share of ASA therapy and myectomy were used based on DMC mavacamten assessment 2023 (Table 49). Costs associated with SRT were collected from Sundhedsdatastyrelsen, DRG-takster 2025[150] (Table 50).

Table 49. Market share of various SRT

Treatment	Proportion of patients (%)	Reference
ASA therapy	95.0	DMC mavacamten assessment 2023
Myectomy	5.0	

ASA = alcohol septal ablation; SRT = septal reduction therapy.

Table 50. SRT procedure costs

Treatment	Form/administration route	Dose per unit	Pack size	Price (per pack or per procedure) (DKK)	Reference
ASA therapy	Surgical procedure	One-time procedure in model	N/A	80,278	Sundhedsdatastyrelsen (2025)[150]; 05MP52
Myectomy			N/A	83,180	Sundhedsdatastyrelsen (2025)[150]; 05MP13

ASA = alcohol septal ablation; N/A = not applicable; SRT = septal reduction therapy.

11.6.2 Cardiac rehabilitation cost

Additional costs were included that reflect the additional burden of SRT not captured in the SRT costings. Patients who require additional help with recovery after SRT are assumed to undergo cardiac rehabilitation; thus, cost of cardiac rehabilitation is included in the analysis that is irrespective of SRT procedure.

The percentage of patients who completed phase 2 sessions of cardiac rehabilitation, number of sessions, and cost per session are used to estimate the one-off cost of cardiac rehabilitation (Table 51).

Table 51. Input related to cardiac rehabilitation cost

Input	Value	Reference
Percentage of patients completed phase 2 cardiac rehabilitation	63.24%	Tower-Rader et al. (2023)[124]
Number of phase 2 sessions	1.0	Assumption
Cost per phase 2 session (DKK)	25,335	Sundhedsdatastyrelsen (2025)[150]; 05MA14 (Rehabilitering efter hjertetilfælde)

11.6.3 Complication of SRT procedure cost

The model also captured the additional cost of complications related to SRT procedures, considering the proportion of patients with complication of SRT procedure (alcohol ablation therapy and myectomy) and their respective costs.

A list of published sources was collected by a targeted literature review to obtain a percentage of patients with complications for alcohol ablation therapy and myectomy. Table 52 presents the proportion of patients with complications for SRT procedures used in the model.

Table 52. Proportion of patients experiencing SRT complications

Treatment	Complications	Proportion of patients (%)	Reference
ASA therapy	Acute kidney injury/acute renal failure (dialysis)	0.85%	Altibi et al. (2023)[109]
	Acute kidney injury/acute renal failure (overall)	5.32%	Weighted average of Altibi et al. (2023)[109]; Kim et al. (2016)[111]; and Maksabedian Hernandez et al. (2023)[112]
	Permanent Pacemaker	11.30%	Weighted average of Altibi et al. (2023)[109]; Kim et al. (2016)[111]; Mutlak et al. (2002)[113]; Pedernera (2015)[114]; Rigopoulos et al. (2020)[115]; Maksabedian Hernandez et al. (2023)[112]; and Ullah et al. (2023)[116]
	Stroke	0.47%	Weighted average of Altibi et al. (2023)[109]; Kim et al. (2016)[111]; Maksabedian Hernandez et al. (2023)[112]; Pedernera (2015)[114]; and Ullah et al. (2023)[116]
Myectomy	Acute kidney injury/acute renal failure (dialysis)	2.26%	Weighted average of Altibi et al. (2023)[109] and Mentias et al. (2023)[110]
	Acute kidney injury/acute renal failure (overall)	12.79%	Weighted average of Altibi et al. (2023)[109]; Kim et al. (2016)[111]; Mazine et al. (2016)[117]; and Maksabedian Hernandez et al. (2023)[112]
	Permanent pacemaker	9.79%	Weighted average of Altibi et al. (2023)[109]; Kim et al. (2016)[111]; Bogachev-Prokophiev et al. (2018)[118]; Guclu et al. (2017)[119]; Maksabedian Hernandez et al. (2023)[112]; Hadaya et al. (2023)[120]; Ullah et al. (2023)[116]; Holst et al. (2022)[121]; and Holst et al. (2019)[122]
	Stroke	2.19%	Weighted average of Altibi et al. (2023)[109]; Kim et al. (2016)[111]; Maksabedian Hernandez et al. (2023)[112]; Mentias et al. (2023)[110]; Ullah et al. (2023)[116]; and Panaich et al. (2014)[123]

SRT = septal reduction therapy.

Table 53 depicts the cost of complications, and Table 52 presents the percentage of patients with complications related to SRT procedures to obtain weighted complication costs of both SRT procedures.

Table 53. Unit cost of complications of SRT procedures

Adverse event	Unit cost (DKK)	DRG code/DRG tariff	Reference
Acute kidney injury/acute renal failure (dialysis)	138,760.00	11MP27 (Akutte medicinske nyresygdomme med dialyse el. plasmaferese)	Sundhedsdatastyrelsen (2025)[150]
Acute kidney injury/acute renal failure (overall)	51,134.00	11MA01 (Akutte medicinske nyresygdomme uden dialyse og uden plasmaferese)	
Permanent pacemaker	46,536.61[a]	N/A	Pilgaard et al. (2020)[151]; Converted from US dollars to DKK in 2020 and inflated to 2023

Adverse event	Unit cost (DKK)	DRG code/DRG tariff	Reference
Stroke	25,301.00	01MA13 (Forbigående utilstrækkelig blodforsyning til hjerne og okklusion af prækerebrale arterier)	Sundhedsdatastyrelsen (2025)[150]

N/A = not applicable; SRT = septal reduction therapy; US = United States.

11.7 Patient costs

Along with the before-mentioned cost components, transportation and time spent by patient because of the treatment were also included in current analysis (Table 54). Transportation costs were estimated as a product of the number of CV visits and transportation costs per visit. Costs related to patient time were estimated as a product of time spent (number of hours) for each resource with hourly cost.

Table 54. Inputs related to patient time and transportation

Resource	Time spent (hours)	Reference
Inpatient/admissions	24.00	Assumption
Day admissions	3.00	
Other contacts	1.00	
	Cost inputs	
Cost of patient time (per hour)	203.00	Medicinrådet (2024)[152]
Transportation cost per hospital visit	140.00	

11.8 Other costs (e.g., costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable.

12 Results

12.1 Base case overview

Table 55. Base case overview

Feature	Description
Comparator	BB/CCB
Type of model	Markov model
Time horizon	40 years (lifetime)
Treatment line	First line. Subsequent treatment lines not included.
Measurement and valuation of health effects	HRQoL measured with EQ-5D-5L in EXPLORER-HCM. Danish population weights were used to estimate health-state utility values.
Costs included	▪ Treatment acquisition costs ▪ Drug monitoring cost ▪ One-off CYP test cost ▪ HCRU cost ▪ AE cost ▪ Patient time costs ▪ Transportation costs
Dosage of medicine	Fixed
Average time on treatment (Years)	▪ Mavacamten + BB/CCB: 19.78 ▪ BB/CCB monotherapy: 16.78

Feature	Description
Average time in model health state (Years)	
NYHA I	▪ Mavacamten + BB/CCB: 10.44 ▪ BB/CCB monotherapy: 3.36
NYHA II	▪ Mavacamten + BB/CCB: 7.25 ▪ BB/CCB monotherapy: 8.85
NYHA III	▪ Mavacamten + BB/CCB: 1.78 ▪ BB/CCB monotherapy: 3.86
NYHA IV	▪ Mavacamten + BB/CCB: 0.31 ▪ BB/CCB monotherapy: 0.71

AE = adverse event; BB/CCB = beta-blocker/calcium channel blocker; CYP = cytochrome P450; HCRU = healthcare resource utilization; HRQoL = health-related quality of life.

12.1.1 Base case results

Table 56. Base case results for the comparison of mavacamten + BB/CCB versus BB/CCB monotherapy, discounted estimates

	Mavacamten + BB/CCB	BB/CCB monotherapy	Difference
Medicine costs	1,169,470	11,471	1,157,999
Medicine costs: co-administration	985	0	985
Administration	N/A	N/A	N/A
Disease management costs	99,857	153,592	−53,735
Costs associated with management of AEs	17,510	26,124	−8,614
Subsequent treatment costs	8,791	6,814	−1,977
Patient costs	105,140	218,016	−112,876
Palliative care costs	0	0	0
Total costs	**1,401,753**	**416,016**	**985,737**
LYs gained (NYHA I)	[redacted]	[redacted]	[redacted]
LYs gained (NYHA II)	[redacted]	[redacted]	[redacted]
LYs gained (NYHA III)	[redacted]	[redacted]	[redacted]
LYs gained (NYHA IV)	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
QALYs (NYHA I)	[redacted]	[redacted]	[redacted]
QALYs (NYHA II)	[redacted]	[redacted]	[redacted]
QALYs (NYHA III)	[redacted]	[redacted]	[redacted]
QALYs (NYHA IV)	[redacted]	[redacted]	[redacted]
QALYs (adverse reactions)	[redacted]	[redacted]	[redacted]
QALYs (SRT)	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs per LY gained		[redacted]	
Incremental cost per QALY gained (ICER)		[redacted]	

AE = adverse event; BB/CCB = beta-blocker/calcium channel blocker; ICER = incremental cost-effectiveness ratio; LY = life-year; N/A = not applicable; QALY = quality-adjusted life-year; SRT = septal reduction therapy.

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

Table 57 presents the upper and lower bound values for each parameter tested in the one-way sensitivity analysis and the incremental cost-effectiveness ratios (ICERs).

Table 57. One-way sensitivity analyses results

	Value	Change (lower; upper bound)	Incremental cost (DKK) (lower; upper bound)	Incremental benefit (QALYs) (lower; upper bound)	ICER (DKK/QALY) (lower; upper bound)
Base case					[redacted]
Mortality in NYHA III	4.12	(3.37; 4.98)	(974,546; 996,699)	[redacted]	[redacted]
Mortality in NYHA II	1.8	(1.47; 2.18)	(994,405; 977,134)	[redacted]	[redacted]
Annual discontinuation rate beyond week 30	2.42%	(2.2%; 3.3%)	(1,028,191; 942,277)	[redacted]	[redacted]
Health-state utility in NYHA I	0.95	(0.94; 0.96)	(985,737; 985,737)	[redacted]	[redacted]
% of patients in each NYHA class who achieved NYHA improvement (week 30 vs. baseline): NYHA II	36.50%	(29.50%; 43.79%)	(945,878; 1,027,280)	[redacted]	[redacted]
Health-state utility in NYHA III	0.82	(0.79; 0.84)	(985,737; 985,737)	[redacted]	[redacted]
Resource per year in NYHA III inpatient (emergency) > 1 day	6.92	(5.63; 8.34)	(1,000,699; 969,254)	[redacted]	[redacted]
NYHA III patients escalated from BB/CCB monotherapy (annual)	2.06%	(1.67%; 2.48%)	(984,191; 987,379)	[redacted]	[redacted]
Mortality in NYHA IV	10.90	(8.92; 13.19)	(978,598; 992,028)	[redacted]	[redacted]
Health-state utility in NYHA II	0.90	(0.89; 0.91)	(985,737; 985,737)	[redacted]	[redacted]

BB/CCB = beta-blocker/calcium channel blocker; ICER = incremental cost-effectiveness ratio; NYHA = New York Heart Association; QALY = quality-adjusted life-year.

12.2.2 Probabilistic sensitivity analyses

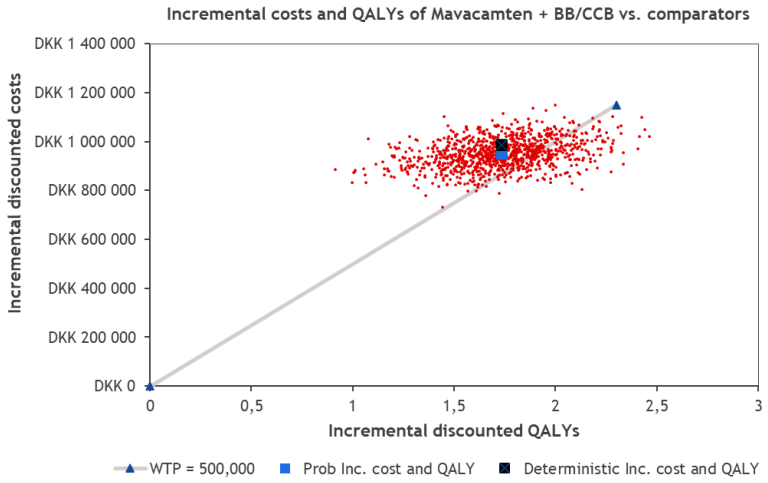
Probabilistic results were consistent with the deterministic results, suggesting model stability (Table 58). Figure 21 compares the incremental costs and QALYs of mavacamten + BB/CCB versus BB/CCB. Figure 22 shows the cost-effectiveness acceptability curves of mavacamten + BB/CCB and BB/CCB. Below a threshold of 550,000 DKK, BB/CCB had the highest probability of being cost-effective; thereafter, mavacamten + BB/CCB had the highest probability of being cost-effective.

Table 58. Probabilistic results

Comparator	Incremental costs	Incremental QALYs	ICER	Deterministic ICER
BB/CCB monotherapy	950,941 DKK	1.73	548,857 DKK	568,103 DKK

BB/CCB = beta-blocker/calcium channel blocker; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Figure 21. Cost-effectiveness plane comparison of incremental costs and QALYs for mavacamten + BB/CCB versus BB/CCB



BB/CCB = beta-blocker/calcium channel blocker; QALY = quality-adjusted life-year; WTP = willingness to pay.

Figure 22. Cost-effectiveness acceptability curves

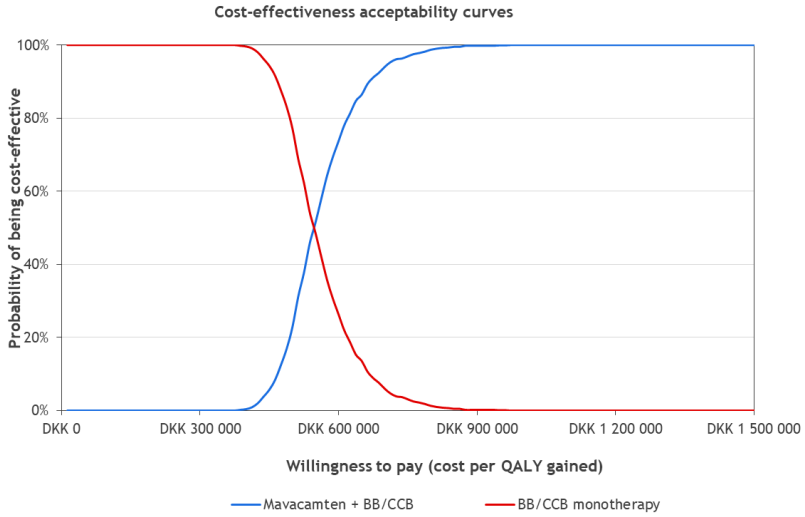


Table 59 presents the results of the scenario analysis that was conducted. Notably, when using percentage of patients with HCM (including both HCM with and without LVSD) instead of percentage of patients with only HCM-LVSD to estimate the proportion of NYHA III patients escalating from BB/CCB monotherapy annually, the ICER decreased, suggesting that the base case analysis is conservative. Applying a conservative, but realistic price decrease, due to patent expiry after year 8 caused a significant decrease in

the ICER. Overall, the scenario analyses confirm the robustness of mavacamten + BB/CCB as a cost-effective option.

Table 59. Summary of results of the scenario analysis

Comparator	Incremental costs (DKK)	Incremental QALYs	ICER (DKK)
Base case	985,737	1.74	568,103
Excess mortality by NYHA class from SHaRe	924,814	1.36	681,005
Patients revert to baseline NYHA class after discontinuation of mavacamten	1,015,463	1,31	774,928
Using % of patients with HCM (including both HCM with and without LVSD, 18%) from SHaRe	982,934	1.76	557,575
80% price decrease due to patent expiry after year 8	563,610	1.74	324,822

13 Budget impact analysis

The impact of introducing mavacamten in the treatment landscape of oHCM was estimated using the CEM. According to the DMC's methodological guidance, the budget-impact results reflect the healthcare payer perspective; therefore, results do not include patient and transport costs, and the discount rate for costs is to set to 0 in the analysis. The mortality from the CEM is included in the estimates. Section 3.2 describes the estimation of eligible patients within the 5-year period.

Number of patients (including assumptions of market share)

BMS has estimated the uptake for mavacamten over a 5-year period if mavacamten is introduced. Table 60 shows the uptake figures used in the budget impact analysis.

Table 60. Market shares

	Year 1	Year 2	Year 3	Year 4	Year 5
Recommendation					
Mavacamten + BB/CCB	20%	23%	26%	29%	34%
BB/CCB monotherapy	80%	77%	74%	71%	66%
Non-recommendation					
Mavacamten + BB/CCB	0%	0%	0%	0%	0%
BB/CCB monotherapy	100%	100%	100%	100%	100%

Table 61 shows the resulting number of patients based on the uptake shown above and the patient numbers presented in Section 3.2.

Table 61. Number of new patients expected to be treated over the next 5-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
Recommendation					
Mavacamten + BB/CCB	50	100	150	200	250
BB/CCB monotherapy	194	170	146	122	98
Non-recommendation					
Mavacamten + BB/CCB	0	0	0	0	0

	Year 1	Year 2	Year 3	Year 4	Year 5
BB/CCB monotherapy	244	270	296	322	348

Note: Totals may not sum due to rounding.

Budget impact

Table 62 presents the expected budget impact of recommending mavacamten + BB/CCB for the indication over the 5-year time horizon.

Table 62. Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended (DKK)	9,179,955	14,235,517	18,911,506	23,402,543	27,720,072
The medicine under consideration is NOT recommended (DKK)	2,793,031	3,532,905	4,046,055	4,560,570	5,074,161
Budget impact of the recommendation (DKK)	**6,386,925**	**10,702,611**	**14,865,451**	**18,841,973**	**22,645,911**

14 List of experts

Not applicable.

15 References

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Appendix A. Main characteristics of studies included

Table 63. Main characteristics of studies included: EXPLORER-HCM

Trial name: EXPLORER-HCM (MYK-461-005)	NCT number: NCT03470545
Objective	To evaluate the efficacy and safety of mavacamten compared with placebo in adult patients with symptomatic oHCM (NYHA II-III)
Publications – title, author, journal, year	▪ Olivotto et al. (2020)[53] ▪ Spertus et al. (2021)[63] ▪ Xie et al. (2021)[88]
Study type and design	▪ Double-blind, multi-center (68 sites, including 31 sites in Europe, of which 3 sites were in Denmark), randomized, placebo-controlled, phase 3 trial. ▪ Randomization was done on a 1:1 ratio and patients were stratified by – NYHA class (II or III) – Current BB use (yes or no) – Ergometer type (treadmill or bicycle) ▪ Consent for cardiovascular magnetic resonance imaging substudy (yes or no)
Sample size (n)	251
Main inclusion criteria	▪ ≥ 18 years of age, body weight > 45 kg ▪ Has adequate acoustic windows to enable accurate transthoracic echocardiogram ▪ Diagnosed oHCM consistent with ACCF/AHA/ESC guidelines and with – LVEF ≥ 55% – NYHA II-III ▪ Documented oxygen saturation at rest of ≥ 90% at screening ▪ Able to safely perform the CPET and has a respiratory exchange ratio ≥ 1.0 at screening per central reading
Main exclusion criteria	▪ Known infiltrative or storage disorder causing cardiac hypertrophy that mimics oHCM ▪ History of syncope or sustained ventricular tachyarrhythmia with exercise within 6 months prior to screening ▪ History of resuscitated sudden cardiac arrest (at any time) or appropriate ICD discharge for life-threatening ventricular arrhythmia within 6 months prior to screening ▪ Paroxysmal or intermittent AF present at screening ▪ Persistent or permanent AF and not receiving anti-coagulation treatment for ≥ 4 weeks prior to screening and/or not adequately rate controlled within 6 months prior to screening ▪ Treatment (within 14 days prior to screening) or planned treatment with disopyramide, ranolazine, or a combination of BBs and CCBs LVOT gradient with Valsalva manoeuvre < 30 mmHg at screening ▪ Successfully treated with invasive septal reduction (surgical myectomy or percutaneous ASA) within 6 months prior to Screening or plans to have either of these treatments during the study ▪ ICD placement within 2 months before screening or planned ICD placement during the study

Trial name: EXPLORER-HCM (MYK-461-005)	NCT number: NCT03470545
	▪ Has a history or evidence of any other clinically significant disorder, condition, or disease that, in the opinion of the investigator, would pose a risk to participant safety or interfere with the study evaluation, procedures, or completion ▪ Prior treatment with cardiotoxic agents such as doxorubicin or similar
Intervention	Mavacamten (2.5 mg/5 mg/10 mg) per day + BB/CCB monotherapy (n = 123) Starting dose was 5 mg, and dose adjustments occurred at weeks 8 and 14 until a target reduction in LVOT gradient < 30 mmHg and a mavacamten plasma concentration between 350 ng/mL and 700 ng/mL was achieved.
Comparator(s)	**Placebo + BB/CCB monotherapy (n = 128)**
Follow-up time	▪ Study duration: 30 weeks ▪ Follow-up: 38 weeks
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	Composite primary endpoints ▪ Composite 1: change from baseline to week 30, increase in pVO_2 of ≥ 1.5 mL/kg/min and improvement of ≥ 1 NYHA class ▪ Composite 2: change from baseline to week 30, increase in pVO_2 of ≥ 3.0 mL/kg/min and no worsening in NYHA class Secondary endpoints ▪ Post-exercise LVOT gradient, from baseline to week 30 ▪ pVO_2, from baseline to week 30 ▪ Proportion of patients with ≥ 1 NYHA class improvement, from baseline to week 30 ▪ HRQoL, which was assessed by several patient-reported outcome questionnaires: – KCCQ-CSS and KCCQ-OS, from baseline to week 30 – HCMSQ-SoB subscore, specifically designed to evaluate symptomatic burden in patients with HCM, from baseline to week 30 Exploratory endpoints ▪ EQ-5D-5L index score and EQ VAS score, from baseline to week 30 ▪ Proportion of patients with a complete response (all LVOT gradients < 30 mmHg and NYHA I status), from baseline to week 30 ▪ Proportion of patients with improvement in LVOT gradients, from baseline to week 30 ▪ Serum concentrations of cardiac biomarkers (NT-proBNP, hs-cTnI), from baseline to week 30 ▪ Echocardiogram parameters of left ventricular structure and function, including systolic and diastolic function (left ventricular mass index, left atrial volume index, lateral early diastolic mitral annular velocity [e'], septal e', lateral ratio between early mitral inflow velocity and mitral annular early diastolic velocity [E/e'], and septal E/e'), from baseline to week 30
Method of analysis	All efficacy and safety analyses were ITT analyses. The primary efficacy endpoint and improvement in NYHA class were analyzed with the Cochran-Mantel-Haenszel test for stratified categorical data. Continuous variables in secondary efficacy endpoints were compared between treatment groups

Trial name: EXPLORER-HCM (MYK-461-005)	NCT number: NCT03470545
	by analysis of covariance or by mixed-effect model repeated measures. Safety data were analyzed as descriptive statistics. Additionally, efficacy was also assessed in prespecified subgroups based on observed baseline demographic and disease characteristics.
Subgroup analyses	None
Other relevant information	None

ACCF = American College of Cardiology Foundation; AF = atrial fibrillation; AHA = American Heart Association; BB = beta-blocker; CCB = calcium channel blocker; CPET = cardiopulmonary exercise test; ESC = European Society of Cardiology; hs-cTnI = high-sensitivity cardiac troponin I; HCMSQ-SoB = Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath; HRQoL = health-related quality of life; ICD = implantable cardioverter-defibrillator; ITT = intention to treat; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire–Overall Summary; LVOT = left ventricular outflow tract; NCT = National Clinical Trial; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; oHCM = obstructive hypertrophic cardiomyopathy; pVO_2 = peak oxygen consumption.
Sources: Olivotto et al. (2020)[53]; ClinicalTrials.gov NCT03470545 (2021)[153]

Table 64. Main characteristic of studies included: EXPLORER-LTE

Trial name: MAVA-LTE (contains EXPLORER-LTE cohort)[91]	NCT number: NCT03723655[154]
Objective	To assess the long-term safety and tolerability of mavacamten in patients with oHCM who were previously enrolled in EXPLORER-HCM
Publications – title, author, journal, year	▪ Rader et al. (2021)[131] ▪ Rader et al. (2022)[91] ▪ Garcia-Pavia et al. (2024)[92]
Study type and design	This multi-center study enrolled participants who completed the EXPLORER-HCM trial through week 38 (n = 244), following the same randomization, assessment, and visit schedule as in EXPLORER-HCM (see Table 63).
Sample size (n)	231 participants from the EXPLORER-HCM (116 placebo arm and 115 from the mavacamten arm) were enrolled and received mavacamten once daily for a duration of 104 weeks
Main inclusion and exclusion criteria	Because patients in EXPLORER-LTE were previously enrolled in EXPLORER-HCM, the inclusion and exclusion criteria were the same for both trials (see Table 63)
Intervention	Mavacamten once daily + BB/CCB monotherapy (n = 231) Starting dose was 5 mg, and dose adjustments occurred at weeks 8 and 14, until a target reduction in LVOT gradient < 30 mmHg and a mavacamten plasma concentration between 350 ng/mL and 700 ng/mL was achieved.
Comparator(s)	No comparator
Follow-up time	Study duration was 104 weeks
Is the study used in the health economic model?	Yes, TPs.
Primary, secondary and exploratory endpoints	Efficacy and pharmacodynamic endpoints ▪ Change from baseline in echocardiographic parameters of systolic function (e.g., LVEF) and diastolic function (e.g., peak velocity of early diastolic septal and lateral mitral annular motion [e'], ratio of peak

Trial name: MAVA-LTE (contains EXPLORER-LTE cohort)[91]	NCT number: NCT03723655[154]
	velocity of early diastolic transmitral flow [E] to e' [E/e'], ratio of E to peak velocity of late transmitral flow [A] [E/A], pulmonary artery systolic pressure, left atrium size) over time ▪ Change from baseline in resting and vLVOT gradient ▪ Change from baseline in NYHA class over time ▪ Change from baseline in NT-proBNP over time ▪ Frequency of cardiac transplant Exploratory endpoints ▪ Change from baseline over time in participant-reported severity of HCM symptoms as assessed by the HCMSQ score ▪ Change from baseline in health status as assessed by the EQ-5D scores
Method of analysis	▪ ITT population: all participants ▪ Safety analysis population: all participants who received at least 1 dose of study drug, with analyses conducted by actual treatment received. ▪ Pharmacokinetic analysis population: all participants who received at least 1 dose of study drug and had at least 1 evaluable mavacamten plasma drug concentration. ▪ Continuous variables were summarized by number of patients, mean, standard deviation, median, minimum, and maximum. ▪ Categorical variables were summarized by counts and percentages. Unless otherwise stated, denominators for percentages were the number of patients in the analysis population with non-missing variables of interest for the column of interest. ▪ Body surface area was derived using the Du Bois method. ▪ Statistical tests were conducted at a 2-sided significance level of 0.05 unless otherwise noted. ▪ All CIs were constructed based on the normal approximation unless otherwise noted.
Subgroup analyses	None
Other relevant information	None

BB = beta-blocker; CI = confidence interval; EQ-5D = HCM = hypertrophic cardiomyopathy; HCMSQ = Hypertrophic Cardiomyopathy Symptom Questionnaire; ITT = intention to treat; NCT = National Clinical Trial; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; oHCM = obstructive hypertrophic cardiomyopathy; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; TP = transition probability; vLVOT = Valsalva manoeuvre left ventricular outflow tract.
Sources: Rader et al. (2022)[91]; ClinicalTrials.gov NCT03723655 (2021)[154]

Table 65. Main characteristic of studies included: VALOR-HCM

Trial name: VALOR-HCM	NCT number: NCT04349072
Objective	To determine if mavacamten reduces the need for SRT[93]
Publications – title, author, journal, year	▪ Desai et al. (2021)[93] ▪ Desai et al. (2022)[94] ▪ Desai et al. (2025)[95]
Study type and design	A multi-center, randomized, double-blind, placebo-controlled, phase 3 trial conducted at 19 sites in the United States.[94] Randomization was stratified by the type of SRT recommended (surgical myectomy or alcohol ablation) and NYHA class.

Trial name: VALOR-HCM	NCT number: NCT04349072
Sample size (n)	112
Main inclusion criteria	▪ At least 18 years old at screening and body weight > 45 kg at screening ▪ Diagnosed with oHCM consistent with current ACCF/AHA 2011 and/or ESC 2014 guidelines and meet their recommendations for invasive therapies ▪ Referred or under active consideration within the past 12 months for SRT procedure and willing to have SRT procedure ▪ Has documented LVEF ≥ 60% at screening ▪ Has documented oxygen saturation at rest ≥ 90% at screening
Main exclusion criteria	▪ Persistent or permanent AF and subject not on anti-coagulation for ≥ 4 weeks prior to screening and/or not adequately rate controlled ≤ 6 months prior to screening ▪ Previously treated with invasive septal reduction (surgical myectomy or percutaneous ASA) ▪ For individuals on BBs, CCBs, or disopyramide, any dose adjustment of these medications < 14 days prior to screening or an anticipated change in regimen during the first 16 weeks of the study ▪ Any medical condition that precludes upright exercise stress testing ▪ Paroxysmal, intermittent AF with AF present at screening ▪ Prior treatment with cardiotoxic agents, such as doxorubicin or similar ▪ Has a history or evidence of any other clinically significant disorder, condition, or disease that would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion
Intervention	Patients initially treated with mavacamten (n = 56): Oral mavacamten 5 mg/day from week 1 to week 32 (32 weeks of mavacamten exposure). Dose titrations were based on investigator-blinded echocardiographic assessment of LVOT gradient and LVEF.[94]
Comparator(s)	Patients who crossed over to mavacamten (n = 52) Placebo from week 1 to 15, then dose-blinded mavacamten from week 16 to 32 (16 weeks of mavacamten exposure).
Follow-up time	Study was 136 weeks in duration
Is the study used in the health economic model?	Yes, as part of scenario analysis
Primary, secondary and exploratory endpoints	Primary endpoint ▪ Composite of a patient decision to proceed with SRT or eligibility for SRT according to the 2011 AHA/ACC guidelines. Patients who discontinued the study or whose response status could not be assessed after 32 weeks were classified as SRT-eligible (treatment failure). Other endpoints ▪ Changes from baseline in: – Post-exercise LVOT gradient – NYHA functional class – Kansas City Cardiomyopathy Questionnaire 23-item Clinical Summary Score – N-terminal pro brain natriuretic peptide – Cardiac troponin I

Trial name: VALOR-HCM	NCT number: NCT04349072
	– Left ventricular mass index – Left ventricular systolic and diastolic volume index – Left atrial volume index and septal E/e' ▪ Incidence of LVEF < 50% ▪ Hospitalization for heart failure ▪ AF or ventricular tachyarrhythmia
Method of analysis	The analysis includes all patients originally randomly assigned to mavacamten and initial placebo patients who crossed over to mavacamten at 16 weeks. Categorical variables are reported as number and percent. Changes from baseline for continuous variables are summarized using mean and 95% confidence intervals. Continuous variables are presented as mean (SD) and compared via a T-test while biomarkers were presented as median (interquartile range) and compared using a non-parametric Wilcoxon rank sum test.
Subgroup analyses	None
Other relevant information	None

ACC = American College of Cardiology; ACCF = American College of Cardiology Foundation; AF = atrial fibrillation; AHA = American Heart Association; BB = beta-blocker; CCB = calcium channel blocker; ESC = European Society of Cardiology; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; NCT = National Clinical Trial; NYHA = New York Heart Association; oHCM = obstructive hypertrophic cardiomyopathy; SD = standard deviation; SRT = septal reduction therapy.
Source: Desai et al. (2022)[94]

Table 66. Main characteristic of studies: REMS program

Study name: REMS Program	
Objective	To report the cumulative results of the first 22 months of real-world, post-approval use of mavacamten in the United States under the REMS program
Publications – title, author, journal, year	Desai et al. (2025)[87]
Study type and design	A real-world experience with mavacamten. The REMS program for mavacamten includes education and monitoring strategies, including the requirement for healthcare professionals to complete a training program and regular echocardiograms.
Sample size (n)	6,299
Main inclusion criteria	▪ Patients with symptomatic oHCM who received at least 1 dose of mavacamten. ▪ Per the stipulations of the REMS program, while on mavacamten treatment, all new patients were required to have a clinical and echocardiographic assessment at baseline and at 4, 8, and 12 weeks after treatment initiation and every 12 weeks thereafter (unless there was a dose change or initiation of a weak CYP2C19 inhibitor or moderate CYP3A4 inhibitor) to determine the appropriateness of continuing treatment documented using the Patient Status Form. ▪ The Patient Status Form provided the following documentation: – The echocardiogram was performed and reviewed; – Post-vLVOT gradient on echocardiogram (< 20 mmHg, ≥ 20 mmHg and < 30 mmHg, or ≥ 30 mmHg)

Study name: REMS Program	
	— Whether or not the patient experienced a decrease in LVEF to < 50% — What action was taken with the patient's dose of mavacamten (no change, dose decrease, dose increase, or dose interruption) — Whether or not the patient experienced clinical heart failure requiring hospitalization — Whether or not the patient required a dose adjustment due to a potential drug-drug interaction — Whether or not the patient was authorized to continue treatment
Main exclusion criteria	NR
Intervention	Patients who received at least 1 dose of mavacamten during the reporting period (n = 6,299)
Comparator(s)	N/A
Follow-up time	The current data were collected from patients enrolled from 28 April 2022 through 27 February 2024. For the dosage and vLVOT analyses, as well as patients with ≥ 1 year of data, the period of data collection was extended by 2 days (from 28 April 2022 through 29 February 2024).
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	▪ Incidence of LVEF < 50% ▪ Incidence of clinical heart failure requiring hospitalization ▪ Dosage analysis ▪ Post-vLVOT gradient ▪ Drug interaction and counselling checklists
Method of analysis	Analysis was limited to providing summary statistics.
Subgroup analyses	None
Other relevant information	None

LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; N/A = not applicable; NR = not reported; oHCM = obstructive hypertrophic cardiomyopathy; vLVOT = Valsalva manoeuvre left ventricular outflow tract. Source: Desai et al. (2025)[87]

Appendix B. Efficacy results per study

B.1 Results per study

Table 67. Results of EXPLORER-HCM (NCT03470545)

Outcomes	Study arm	N	Result at week 30	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference (AD or RD [%])	95% CI	*P* value (2-tailed test)	Difference (risk ratio)	95% CI	*P* value (2-tailed test)		
Met primary composite endpoint	Mavacamten	123	n (%): 45 (36.59)	19.40%	8.67-30.13	0.0005	2.13	1.36-3.32	0.0009	Risk difference and risk ratio calculated using proportion of responders (n) in mavacamten and placebo arms	Olivotto et al. (2020)[53]
	Placebo	128	n (%): 22 (17.19)								
Composite 1 to ≥ 1.5 mL/kg per min increase in pVO_2 with ≥ 1 NYHA class improvement	Mavacamten	123	n (%): 41 (33.33)	19.27%	8.99-29.55	0.0003	2.37	1.44-3.89	0.0006	Risk difference and risk ratio calculated using proportion of responders (n) in mavacamten and placebo arms	Olivotto et al. (2020)[53]
	Placebo	128	n (%): 18 (14.06)								
Composite 2 to ≥ 3.0 mL/kg per min increase in pVO_2 with no worsening of NYHA class	Mavacamten	123	n (%): 29 (23.58)	12.64%	3.39-21.89	0.0079	2.16	1.20-3.88	0.0104	Risk difference and risk ratio calculated using proportion of responders (n) in mavacamten and placebo arms	Olivotto et al. (2020)[53]
	Placebo	128	n (%): 14 (10.94)								

Outcomes	Study arm	N	Result at week 30	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference (AD or RD [%])	95% CI	*P* value (2-tailed test)	Difference (risk ratio)	95% CI	*P* value (2-tailed test)		
≥ 3.0 mL/kg/min increase in pVO_2 and ≥ 1 NYHA class improvement	Mavacamten	123	n (%): 25 (20.33)	12.51%	4.02-21.01	0.0042	2.60	1.30-5.19	0.0066	Risk difference and risk ratio calculated using proportion of responders (n) in mavacamten and placebo arms	Olivotto et al. (2020)[53]
	Placebo	128	n (%): 10 (7.81)								
Post-exercise LVOT peak gradient, mmHg, change from baseline	Mavacamten	117	Mean (SD): −47 (40.0)	−35.6	−43.2 to −28.1	< 0.0001	NA	NA	NA	LS mean difference and *P* value calculated using ANCOVA	Olivotto et al. (2020)[53]
	Placebo	122	Mean (SD): −10 (30.0)								
pVO_2, mL/kg/min, change from baseline	Mavacamten	120	Mean (SD): 1.4 (3.1)	1.4	0.6-2.1	0.0006	NA	NA	NA	LS mean difference and *P* value calculated using ANCOVA	Olivotto et al. (2020)[53]
	Placebo	125	Mean (SD): −0.1 (3.0)								
≥ 1 NYHA class improvement	Mavacamten	123	n (%): 80 (65.04)	33.79%	22.15-45.43	< 0.0001	2.08	1.56-2.78	< 0.0001	Risk difference and risk ratio calculated using proportion of responders (n) in mavacamten and placebo arms	Olivotto et al. (2020)[53]
	Placebo	128	n (%): 40 (31.25)								
KCCQ-CSS, change from baseline	Mavacamten	92	Mean (SD): 13.6 (14.4)	9.1	5.5-12.7	< 0.0001	NA	NA	NA	LS mean difference and *P* value calculated using mixed-effect model	Spertus et al. (2021)[63]
	Placebo	88	Mean (SD): 4.2 (13.9)								

Outcomes	Study arm	N	Result at week 30	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference (AD or RD [%])	95% CI	*P* value (2-tailed test)	Difference (risk ratio)	95% CI	*P* value (2-tailed test)		
										for repeated measures	
KCCQ-OS score, change from baseline	Mavacamten	92	Mean (SD): 14.9 (15.8)	9.1	5.5-12.8	< 0.0001	NA	NA	NA	LS mean difference and *P* value calculated using mixed-effect model for repeated measures	Spertus et al. (2021)[63]
	Placebo	88	Mean (SD): 5.4 (13.7)								
≥ 20 KCCQ-OS score improvement	Mavacamten	92	n (%): 33 (35.87)	21.10%	8.81-33.39	.0012	2.43	1.37-4.30	0.0023	Risk difference and risk ratio calculated using proportion of responders (n) in mavacamten and placebo arms	Spertus et al. (2021)[63]
	Placebo	88	n (%): 13 (14.77)								
KCCQ-Total symptom score, change from baseline	Mavacamten	92	Mean (SD): 12.4 (15.0)	7.7	3.7-11.5	0.0002	NA	NA	NA	LS mean difference and *P* value calculated using mixed-effect model for repeated measures	Spertus et al. (2021)[63]
	Placebo	88	Mean (SD): 4.8 (15.9)								
KCCQ-Physical limitation score, change from baseline	Mavacamten	92	Mean (SD): 14.7 (17.0)	10.6	6.2-14.8	< 0.0001	NA	NA	NA	LS mean difference and *P* value calculated using mixed-effect model for repeated measures	Spertus et al. (2021)[63]
	Placebo	88	Mean (SD): 3.6 (15.4)								

Outcomes	Study arm	N	Result at week 30	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference (AD or RD [%])	95% CI	*P* value (2-tailed test)	Difference (risk ratio)	95% CI	*P* value (2-tailed test)		
KCCQ-Social limitation score, change from baseline	Mavacamten	92	Mean (SD): 13.5 (22.9)	9.3	4.5-14.1	0.0002	NA	NA	NA	LS mean difference and *P* value calculated using mixed-effect model for repeated measures	Spertus et al. (2021)[63]
	Placebo	88	Mean (SD): 5.1 (19.2)								
KCCQ- Quality of life score, change from baseline	Mavacamten	92	Mean (SD): 18.8 (21.6)	9.6	4.7-14.5	0.0001	NA	NA	NA	LS mean difference and *P* value calculated using mixed-effect model for repeated measures	Spertus et al. (2021)[63]
	Placebo	88	Mean (SD): 8.3 (18.8)								
HCMSQ-SoB score, change from baseline	Mavacamten	85	Mean (SD): −2.8 (2.68)	−1.8	−2.40 to −1.20	< 0.0001	NA	NA	NA	LS mean difference and *P* value calculated using mixed-effect model for repeated measures	BMS data on file (2021)[129]
	Placebo	86	Mean (SD): −0.9 (2.41)								
≥ 2.5-point decrease in HCMSQ- SoB score	Mavacamten	90	n (%): 45 (50.00)	28.67%	14.79-42.55	0.0001	2.34	1.45-3.79	0.0005	Risk difference and risk ratio calculated using proportion of responders (n) in mavacamten and placebo arms	BMS data on file (2021)[129]
	Placebo	75	n (%): 16 (21.33)								
NYHA class I status and all	Mavacamten	117	n (%): 32 (27.35)	26.56%	18.33-34.78	< 0.0001	34.46	4.78-248.21	0.0004	Risk difference and risk ratio calculated	Olivotto et al. (2020)[53]

Outcomes	Study arm	N	Result at week 30	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference (AD or RD [%])	95% CI	*P* value (2-tailed test)	Difference (risk ratio)	95% CI	*P* value (2-tailed test)		
LVOT gradients < 30 mmHg	Placebo	126	n (%): 1 (0.79)							using proportion of responders (n) in mavacamten and placebo arms	
Post-exercise LVOT peak gradient < 50 mmHg	Mavacamten	101	n (%): 75 (74.26)	53.50%	42.00-65.01	< 0.0001	3.58	2.42-5.28	< 0.0001	Risk difference and risk ratio calculated using proportion of responders (n) in mavacamten and placebo arms	Olivotto et al. (2020)[53]
	Placebo	106	n (%): 22 (20.75)								
Post-exercise LVOT peak gradient < 30 mmHg	Mavacamten	113	n (%): 64 (56.64)	49.62%	39.35-59.89	< 0.0001	8.07	4.06-16.05	< 0.0001	Risk difference and risk ratio calculated using proportion of responders (n) in mavacamten and placebo arms	Olivotto et al. (2020)[53]
	Placebo	114	n (%): 8 (7.02)								
EQ-5D-5L score, change from baseline	Mavacamten	96	Mean (SD): 0.084 (0.163)	0.075	0.028-0.122	0.002	NA	NA	NA	Post hoc linear regression fitting unadjusted and adjusted models with unadjusted results presented; results were consistent between models	Xie et al. (2021)[155]
	Placebo	89	Mean (SD): 0.009 (0.163)								

Outcomes	Study arm	N	Result at week 30	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference (AD or RD [%])	95% CI	*P* value (2-tailed test)	Difference (risk ratio)	95% CI	*P* value (2-tailed test)		
EQ VAS score, change from baseline	Mavacamten	96	Mean (SD): 8.5 (20.3)	7.8	2.0-13.6	0.009	NA	NA	NA	Post hoc linear regression fitting unadjusted and adjusted models with unadjusted results presented; results were consistent between models	Xie et al. (2021)[155]
	Placebo	89	Mean (SD): 0.7 (20.1)								
Improvement of at least the MCT in EQ-5D-5L score (distribution-based approach)	Mavacamten	58	n (%): 40 (68.97)	29.68%	12.20-47.16	0.0015	1.76	1.21-2.54	0.0028	Risk difference and risk ratio calculated using proportion of responders (n) in mavacamten and placebo arms; MCTs were calculated using half of the SD of the baseline value	Xie et al. (2021)[155]
	Placebo	56	n (%): 22 (39.29)								
Improvement of at least the MCT in EQ VAS score (distribution-based approach)	Mavacamten	86	n (%): 38 (44.19)	14.92%	0.53-29.31	0.0452	1.51	1.00-2.28	0.0500	Risk difference and risk ratio calculated using proportion of responders (n) in mavacamten and placebo arms; MCTs were calculated using half of the SD of the baseline value	Xie et al. (2021)[155]
	Placebo	82	n (%): 24 (29.27)								

Outcomes	Study arm	N	Result at week 30	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference (AD or RD [%])	95% CI	*P* value (2-tailed test)	Difference (risk ratio)	95% CI	*P* value (2-tailed test)		
NT-proBNP ng/L, change from baseline	Mavacamten	116	Geometric mean ratio: 0.20	NA	NA	NA	0.202a	0.169-0.241a	< 0.0001	Proportion of geometric mean ratios and *P* value calculated using mixed-effect model for repeated measures	Olivotto et al. (2020)[53]; BMS data on file (2021)[129]
	Placebo	121	Geometric mean ratio: 1.02								
Hs-cTnI ng/L, change from baseline	Mavacamten	114	Geometric mean ratio: 0.58	NA	NA	NA	0.589 a	0.500-0.693 a	< 0.0001	Proportion of geometric mean ratios and *P* value calculated using mixed-effect model for repeated measures	Olivotto et al. (2020)[53]; BMS data on file (2021)[129]
	Placebo	111	Geometric mean ratio: 0.99								
Left atrial volume index, mL/m^2, change from baseline	Mavacamten	115	Mean (95% CI): −7.5 (−9.0 to −6.1)	−7.5	−9.4 to −5.5	< 0.0001	NA	NA	NA	LS mean difference and *P* value calculated using mixed-effect model for repeated measures	Hegde et al. (2021)[90]
	Placebo	123	Mean (95% CI): −0.09 (−1.6 to 1.5)								
Lateral e', cm/s, change from baseline	Mavacamten	107	Mean (95% CI): 1.6 (1.2-1.9)	1.3	0.9-1.8	< 0.0001	NA	NA	NA	LS mean difference and *P* value calculated using	Hegde et al. (2021)[90]

Outcomes	Study arm	N	Result at week 30	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference (AD or RD [%])	95% CI	*P* value (2-tailed test)	Difference (risk ratio)	95% CI	*P* value (2-tailed test)		
	Placebo	116	Mean (95% CI): 0.2 (−0.2 to 0.5)							mixed-effect model for repeated measures	
Septal e', cm/s, change from baseline	Mavacamten	113	Mean (95% CI): 0.7 (0.4-1.0)	0.7	0.4-1.0	< 0.0001	NA	NA	NA	LS mean difference and *P* value calculated using mixed-effect model for repeated measures	Hegde et al. (2021)[90]
	Placebo	119	Mean (95% CI): −0.02 (−0.2 to 0.2)								
E/e' lateral ratio, change from baseline	Mavacamten	104	Mean (95% CI): −3.8 (−4.7 to −2.8)	--3.8	-4.9 to −2.6	< 0.0001	NA	NA	NA	LS mean difference and *P* value calculated using mixed-effect model for repeated measures	Hegde et al. (2021)[90]
	Placebo	112	Mean (95% CI): 0.04 (−0.9 to 1.0)								
E/e' septal ratio, change from baseline	Mavacamten	111	Mean (95% CI): −3.5 (−4.7 to −2.4)	−3.4	−4.7 to −2.1	< 0.0001	NA	NA	NA	LS mean difference and *P* value calculated using mixed-effect model for repeated measures	Hegde et al. (2021)[90]
	Placebo	117	Mean (95% CI):								

Outcomes	Study arm	N	Result at week 30	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference (AD or RD [%])	95% CI	*P* value (2-tailed test)	Difference (risk ratio)	95% CI	*P* value (2-tailed test)		
			−0.3 (−1.1 to 0.6)								
LVEF, %, change from baseline	Mavacamten	114	Mean (95% CI): −3.9 (−5.3 to −2.5)	−4.0	−5.5 to −2.5	< 0.0001	NA	NA	NA	LS mean difference and *P* value calculated using mixed-effect model for repeated measures	Hegde et al. (2021)[90]
	Placebo	119	Mean (95% CI): −0.01 (−1.2 to 1.2)								
Left ventricular mass index, g/m^2, change from baseline	Mavacamten	108	Mean (95% CI): −7.4 (−10.8 to −3.9)	−15.5	−19.0 to −11.9	< 0.0001	NA	NA	NA	LS mean difference and *P* value calculated using mixed-effect model for repeated measures	Hegde et al. (2021)[90]
	Placebo	110	Mean (95% CI): 8.9 (6.0-11.7)								
Complete resolution of SAM	Mavacamten	94	n (%): 76 (80.85)	46.83%	34.49-59.17	< 0.0001	2.38	1.77-3.19	< 0.0001	Risk difference and risk ratio calculated using proportion of responders (n) in mavacamten and placebo arms	Hegde et al. (2021)[90]
	Placebo	97	n (%): 33 (34.02)								
	Mavacamten	111	10 (9.01)	9.01%	3.68-14.34	0.0008		Not estimable			Hegde et al. (2021)[90]

Outcomes	Study arm	N	Result at week 30	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference (AD or RD [%])	95% CI	*P* value (2-tailed test)	Difference (risk ratio)	95% CI	*P* value (2-tailed test)		
Complete resolution of mitral regurgitation	Placebo	120	0 (0)							Risk difference and risk ratio calculated using proportion of responders (n) in mavacamten and placebo arms	

AD = absolute difference; ANCOVA = analysis of covariance; CI = confidence interval; HCMSQ-SoB = Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath; hs-cTnI = high-sensitivity cardiac troponin I; KCCQ = Kansas City Cardiomyopathy Questionnaire; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire–Overall Summary; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; LS = least squares; MCT = meaningful change threshold; NA = not available; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; pVO_2 = peak oxygen consumption; RD = risk difference; SAM = systolic anterior motion; SD = standard deviation.

[a] Proportion of geometric mean ratio between treatment arms and associated 95% CI.

Appendix C. Comparative analysis of efficacy

Not applicable.

Appendix D. Extrapolation

Not applicable because no extrapolation or parameterization has been performed.

D.1 Extrapolation of [effect measure 1]

D.1.1 Data input

D.1.2 Model

D.1.3 Proportional hazards

[If the extrapolation model relies on proportional hazards, provide a plot with Schoenfeld residuals and a log-cumulative hazard plot.]

D.1.4 Evaluation of statistical fit (AIC and BIC)

[Provide a table with the Akaike information criterion and **Bayesian information criterion** and discuss the statistical fit.]

D.1.5 Evaluation of visual fit

D.1.6 Evaluation of hazard functions

[Provide a plot of the hazard function of the effect measure. The plots must be presented in separate figures for the intervention and comparator, respectively, and must include the estimated hazard for the observed data (if applicable). The plot must be discussed in the context of chosen the distribution for extrapolating the data of the effect measure.]

D.1.7 Validation and discussion of extrapolated curves

D.1.8 Adjustment of background mortality

D.1.9 Adjustment for treatment switching/cross-over

D.1.10 Waning effect

D.1.11 Cure-point

D.2 Extrapolation of [effect measure 2]

[For each effect measure please, fill in this section using the same template as stated in section 8.1.1]

Appendix E. Serious adverse events

Table 68. EXPLORER-HCM: SAEs

	Number of patients (%)	
	Patients with oHCM from EXPLORER-HCM	
	Mavacamten (n = 123)	Placebo (n = 128)
[redacted]		

	Number of patients (%)	
	Patients with oHCM from EXPLORER-HCM	
	Mavacamten (n = 123)	Placebo (n = 128)
[redacted]		

Appendix F. Health-related quality of life

All content is in the main dossier.

Appendix G. Probabilistic sensitivity analyses

Table 69 lists the distribution for each set of model inputs varied in the probabilistic sensitivity analysis and provides a brief description of each. Distributions selected follow the logical bounds allowed for each parameter. For example, probabilities must be between 0 and 1, so the beta distribution is used, which holds the same bounds. Similarly, costs incurred cannot be negative. Thus, gamma distribution with bounds between 0 and positive infinity is used in the probabilistic sampling.

Table 69. Overview of parameters in the probabilistic sensitivity analysis

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Patient population				
Male Proportion	0.594	0.48	0.71	Beta
Age at start (years)	59.00	58.00	60.00	Normal
Initial health-state distribution				
Proportion of patients in NYHA I	0.00	0.00	0.00	Dirichlet
Proportion of patients in NYHA II	0.73	0.73	0.73	Dirichlet
Proportion of patients in NYHA III	0.27	0.27	0.27	Dirichlet
Proportion of patients in NYHA IV	0.00	0.00	0.00	Dirichlet
Short-term Markov model				
Discontinuation rate (one-off), at wk 30	0.02	0.01	0.02	Beta
% of patients in each NYHA class who achieved NYHA or pVO2 improvement (wk-30 vs. baseline) -NYHA I	1.00	1.00	1.00	Beta
% of patients in each NYHA class who achieved NYHA or pVO2 improvement (wk-30 vs. baseline) -NYHA II	0.44	0.36	0.53	Beta
% of patients in each NYHA class who achieved NYHA or pVO2 improvement (wk-30 vs. baseline) -NYHA III	0.00	0.00	0.00	Beta
% of patients in each NYHA class who achieved NYHA or pVO2 improvement (wk-30 vs. baseline) -NYHA IV	0.00	0.00	0.00	Beta
% of patients in each NYHA class who achieved NYHA	1.00	1.00	1.00	Beta

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
improvement (wk-30 vs. baseline) -NYHA I				
% of patients in each NYHA class who achieved NYHA improvement (wk-30 vs. baseline) -NYHA II	0.37	0.30	0.44	Beta
% of patients in each NYHA class who achieved NYHA improvement (wk-30 vs. baseline) -NYHA III	0.00	0.00	0.00	Beta
% of patients in each NYHA class who achieved NYHA improvement (wk-30 vs. baseline) -NYHA IV	0.00	0.00	0.00	Beta
- Of those who retain NYHA class, % of patients who will discontinue (at wk-30)-NYHA I	0.50	0.40	0.60	Beta
- Of those who retain NYHA class, % of patients who will discontinue (at wk-30)-NYHA II	0.50	0.40	0.60	Beta
- Of those who retain NYHA class, % of patients who will discontinue (at wk-30)-NYHA III	0.50	0.40	0.60	Beta
- Of those who retain NYHA class, % of patients who will discontinue (at wk-30)-NYHA IV	0.50	0.40	0.60	Beta
% of patients in each NYHA class whose NYHA class worsened (wk-30 vs. baseline) NYHA I	0.00	0.00	0.00	Beta
% of patients in each NYHA class whose NYHA class worsened (wk-30 vs. baseline) NYHA II	0.00	0.00	0.00	Beta
% of patients in each NYHA class whose NYHA class worsened (wk-30 vs. baseline) NYHA III	0.13	0.10	0.15	Beta
% of patients in each NYHA class whose NYHA class worsened (wk-30 vs. baseline) NYHA IV	1.00	1.00	1.00	Beta
Long-term Markov model				
Annual discontinuation rate, beyond wk 30	2.7%	2.2%	3.3%	Gamma
Market share of subsequent treatments after mavacamten discontinuation (applicable only to Mavacamten + BB/CCBs arm)				

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Market share of BB/CCB monotherapy in pts discontinued mavacamten from NYHA I	1.00	1.00	1.00	Dirichlet
Market share of SRT + BB/CCB in pts discontinued mavacamten from NYHA I	0.00	0.00	0.00	Dirichlet
Market share of BB/CCB monotherapy in pts discontinued mavacamten from NYHA II	1.00	1.00	1.00	Dirichlet
Market share of SRT + BB/CCB in pts discontinued mavacamten from NYHA II	0.00	0.00	0.00	Dirichlet
Market share of BB/CCB monotherapy in pts discontinued mavacamten from NYHA III	1.00	1.00	1.00	Dirichlet
Market share of SRT + BB/CCB in pts discontinued mavacamten from NYHA III	0.00	0.00	0.00	Dirichlet
Market share of BB/CCB monotherapy in pts discontinued mavacamten from NYHA IV	1.00	1.00	1.00	Dirichlet
Market share of SRT + BB/CCB in pts discontinued mavacamten from NYHA IV	0.00	0.00	0.00	Dirichlet
Subsequent treatment options among patients receiving BB/CCBs monotherapy (irrespective of model treatment arm)				
% NYHA I pts escalated from BB/CCBs monotherapy (Annual)	0.00	0.00	0.00	Gamma
% NYHA II pts escalated from BB/CCBs monotherapy (Annual)	0.00	0.00	0.00	Gamma
% NYHA III pts escalated from BB/CCBs monotherapy (Annual)	1.81%	1.47%	2.18%	Gamma
% NYHA IV pts escalated from BB/CCBs monotherapy (Annual)	0.00	0.00	0.00	Gamma
Market share of SRT + BB/CCB in pts escalated from BB/CCBs monotherapy in NYHA I	1.00	1.00	1.00	Dirichlet
Market share of SRT + BB/CCB in pts escalated from BB/CCBs monotherapy in NYHA II	1.00	1.00	1.00	Dirichlet
Market share of SRT + BB/CCB in pts escalated from BB/CCBs monotherapy in NYHA III	1.00	1.00	1.00	Dirichlet

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Market share of SRT + BB/CCB in pts escalated from BB/CCBs monotherapy in NYHA IV	1.00	1.00	1.00	Dirichlet
Mortality rates				
Mortality in NYHA II	1.48	1.21	1.79	Lognormal
Mortality in NYHA III	3.17	2.59	3.84	Lognormal
Mortality in NYHA IV	3.17	2.59	3.84	Lognormal
% Surgical mortality (one-off) in patients receiving Alcohol ablation therapy	0.01700	0.01	0.02	Beta
% Surgical mortality (one-off) in patients receiving Myectomy	0.03360	0.03	0.04	Beta
Excess mortality (HR) in post-Alcohol ablation therapy (Post-SRT)	1.00	0.82	1.21	Lognormal
Excess mortality (HR) in post-Myectomy (Post-SRT)	1.00	0.82	1.21	Lognormal
Health state utility				
Health state utility in NYHA I	0.95	0.943	0.962	Beta
Health state utility in NYHA II	0.90	0.891	0.911	Beta
Health state utility in NYHA III	0.82	0.790	0.841	Beta
Health state utility in NYHA IV	0.82	0.790	0.841	Beta
AE Incidence				
Incidence rate (%), per cycle of Syncope in pts taking Mavacamten + BB/CCB	0.00	0.00	0.00	Beta
Incidence rate (%), per cycle of Transient ischemic attack (TIA) in pts taking Mavacamten + BB/CCB	0.00	0.00	0.00	Beta
Incidence rate (%), per cycle of Cardiac failure congestive in pts taking Mavacamten + BB/CCB	0.00	0.00	0.00	Beta
Incidence rate (%), per cycle of Viral å in pts taking Mavacamten + BB/CCB	0.00	0.00	0.00	Beta
Incidence rate (%), per cycle of Urinary tract infection (UTI) in pts taking Mavacamten + BB/CCB	0.00	0.00	0.00	Beta
Incidence rate (%), per cycle of Syncope in pts taking BB/CCB monotherapy	0.00	0.00	0.00	Beta

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Incidence rate (%), per cycle of Transient ischemic attack (TIA) in pts taking BB/CCB monotherapy	0.00	0.00	0.00	Beta
Incidence rate (%), per cycle of Cardiac failure congestive in pts taking BB/CCB monotherapy	0.00	0.00	0.00	Beta
Incidence rate (%), per cycle of Viral gastroenteritis in pts taking BB/CCB monotherapy	0.00	0.00	0.00	Beta
Incidence rate (%), per cycle of Urinary tract infection (UTI) in pts taking BB/CCB monotherapy	0.00	0.00	0.00	Beta
Incidence rate (%), per cycle of Syncope in pts taking Post-SRT	0.00	0.00	0.00	Beta
Incidence rate (%), per cycle of Transient ischemic attack (TIA) in pts taking Post-SRT	0.00	0.00	0.00	Beta
Incidence rate (%), per cycle of Cardiac failure congestive in pts taking Post-SRT	0.00	0.00	0.00	Beta
Incidence rate (%), per cycle of Viral gastroenteritis in pts taking Post-SRT	0.00	0.00	0.00	Beta
Incidence rate (%), per cycle of Urinary tract infection (UTI) in pts taking Post-SRT	0.00	0.00	0.00	Beta
Cost				
One-off CYP test cost (DKK)	985.00	801.44	1,187.21	Gamma
Alcohol ablation therapy, cost/procedure (DKK)	80,278.00	65,317.38	96,758.23	Gamma
Myectomy, cost/procedure (DKK)	83,180.00	67,678.57	100,255.98	Gamma
Market share of Beta-Blocker	0.82	0.82	0.82	Dirichlet
Market share of Calcium Channel Blocker	0.18	0.18	0.18	Dirichlet
Market share of SRT procedures - alcohol ablation	95.00%	0.95	0.95	Dirichlet
Market share of SRT procedures - myectomy	5.00%	0.05	0.05	Dirichlet
Percentage of patients completed phase II cardiac rehab (Cardiac Rehabilitation)	63.24%	0.50	0.75	Beta

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
% experiencing complication of alcohol ablation - dialysis	0.85%	0.69%	1.02%	Beta
% experiencing complication of alcohol ablation - renal complications overall	5.32%	4.33%	6.41%	Beta
% experiencing complication of alcohol ablation - permanent pacemaker	11.30%	9.18%	13.60%	Beta
% experiencing complication of alcohol ablation - stroke	0.47%	0.38%	0.56%	Beta
% experiencing complication of myectomy - dialysis	2.26%	1.84%	2.72%	Beta
% experiencing complication of myectomy - renal complications overall	12.79%	10.39%	15.40%	Beta
% experiencing complication of myectomy - permanent pacemaker	9.79%	7.96%	11.79%	Beta
% experiencing complication of myectomy - stroke	2.19%	1.78%	2.64%	Beta
Cost of complications: Acute kidney injury/acute renal failure (Dialysis)	138,760.00	112,900.67	167,245.97	Gamma
Cost of complications: Acute kidney injury/acute renal failure (Overall)	51,134.00	41,604.66	61,631.27	Gamma
Cost of complications: Permanent Pacemaker	46,536.61	37,864.04	56,090.09	Gamma
Cost of complications: Stroke	25,301.00	20,585.90	30,495.03	Gamma
Resource use				
Outpatient (CV related) visits in Year-1_monitoring of NYHA I pts taking Mavacamten + BB/CCB	5.31	4.32	6.40	Gamma
Outpatient (CV related) visits in Year-1_monitoring of NYHA II pts taking Mavacamten + BB/CCB	5.13	4.17	6.18	Gamma
Outpatient (CV related) visits in Year-1_monitoring of NYHA III pts taking Mavacamten + BB/CCB	3.88	3.15	4.67	Gamma
Outpatient (CV related) visits in Year-1_monitoring of NYHA IV pts taking Mavacamten + BB/CCB	2.75	2.24	3.31	Gamma

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
NYHA I_Health care resource utilization (HCRU), Lump-sum cost, per year (DKK)	4,430.30	3,604.67	5,339.79	Gamma
NYHA II_Health care resource utilization (HCRU), Lump-sum cost, per year (DKK)	5,536.70	4,504.88	6,673.33	Gamma
NYHA III_Health care resource utilization (HCRU), Lump-sum cost, per year (DKK)	10,066.60	8,190.59	12,133.17	Gamma
NYHA IV_Health care resource utilization (HCRU), Lump-sum cost, per year (DKK)	24,556.80	19,980.39	29,598.05	Gamma
Unit Cost_Day case admissions	1,268.00	1,031.70	1,528.31	Gamma
Unit Cost_Outpatient (CV related) visits	2,111.00	1,717.59	2,544.37	Gamma
Unit Cost_Outpatient (Non-CV related) visits	1,268.00	1,031.70	1,528.31	Gamma
Unit Cost_Inpatient (elective) day <=1	2,240.00	1,822.55	2,699.85	Gamma
Unit Cost_Inpatient (elective) > 1 day	2,404.00	1,955.99	2,897.52	Gamma
Unit Cost_Inpatient (emergency) day <=1	2,240.00	1,822.55	2,699.85	Gamma
Unit Cost_Inpatient (emergency) > 1 day	2,404.00	1,955.99	2,897.52	Gamma
Unit Cost_Cardiac MRI procedures	2,212.00	1,799.77	2,666.10	Gamma
Resource per year in NYHA I_Day case admissions	0.39	0.32	0.47	Gamma
Resource per year in NYHA I_Outpatient (CV related) visits	0.69	0.56	0.83	Gamma
Resource per year in NYHA I_Outpatient (Non-CV related) visits	0.31	0.25	0.38	Gamma
Resource per year in NYHA I_Inpatient (elective) day <=1	0.00	0.00	0.00	Gamma
Resource per year in NYHA I_Inpatient (elective) > 1 day	0.00	0.00	0.00	Gamma
Resource per year in NYHA I_Inpatient (emergency) day <=1	0.00	0.00	0.00	Gamma
Resource per year in NYHA I_Inpatient (emergency) > 1 day	0.00	0.00	0.00	Gamma

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Resource per year in NYHA I_Cardiac MRI procedures	0.10	0.08	0.12	Gamma
Resource per year in NYHA II_Day case admissions	0.59	0.48	0.71	Gamma
Resource per year in NYHA II_Outpatient (CV related) visits	0.88	0.71	1.05	Gamma
Resource per year in NYHA II_Outpatient (Non-CV related) visits	0.63	0.51	0.75	Gamma
Resource per year in NYHA II_Inpatient (elective) day <=1	0.04	0.03	0.05	Gamma
Resource per year in NYHA II_Inpatient (elective) > 1 day	0.00	0.00	0.00	Gamma
Resource per year in NYHA II_Inpatient (emergency) day <=1	0.14	0.11	0.17	Gamma
Resource per year in NYHA II_Inpatient (emergency) > 1 day	0.00	0.00	0.00	Gamma
Resource per year in NYHA II_Cardiac MRI procedures	0.13	0.11	0.16	Gamma
Resource per year in NYHA III_Day case admissions	2.06	1.68	2.48	Gamma
Resource per year in NYHA III_Outpatient (CV related) visits	2.13	1.73	2.56	Gamma
Resource per year in NYHA III_Outpatient (Non-CV related) visits	0.00	0.00	0.00	Gamma
Resource per year in NYHA III_Inpatient (elective) day <=1	0.60	0.49	0.72	Gamma
Resource per year in NYHA III_Inpatient (elective) > 1 day	0.60	0.49	0.72	Gamma
Resource per year in NYHA III_Inpatient (emergency) day <=1	1.73	1.41	2.09	Gamma
Resource per year in NYHA III_Inpatient (emergency) > 1 day	6.92	5.63	8.34	Gamma
Resource per year in NYHA III_Cardiac MRI procedures	0.34	0.28	0.41	Gamma
Resource per year in NYHA IV Day case admissions	3.50	2.85	4.22	Gamma
Resource per year in NYHA IV _Outpatient (CV related) visits	3.25	2.64	3.92	Gamma

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Resource per year in NYHA IV _Outpatient (Non-CV related) visits	0.00	0.00	0.00	Gamma
Resource per year in NYHA IV _Inpatient (elective) day <=1	1.01	0.82	1.22	Gamma
Resource per year in NYHA IV _Inpatient (elective) > 1 day	4.04	3.29	4.87	Gamma
Resource per year in NYHA IV _Inpatient (emergency) day <=1	2.24	1.82	2.70	Gamma
Resource per year in NYHA IV _Inpatient (emergency) > 1 day	15.68	12.76	18.90	Gamma
Resource per year in NYHA IV _Cardiac MRI procedures	0.29	0.24	0.35	Gamma
Terminal care cost (DKK), one-off	0.00	0.00	0.00	Gamma
Adverse event cost (DKK)_Syncope	21,047.00	17,124.68	25,367.73	Gamma
Adverse event cost (DKK)_Transient ischemic attack (TIA)	25,301.00	20,585.90	30,495.03	Gamma
Adverse event cost (DKK)_Cardiac failure congestive	40,702.00	33,116.77	49,057.69	Gamma
Adverse event cost (DKK)_Viral gastroenteritis	4,977.00	4,049.49	5,998.73	Gamma
Adverse event cost (DKK)_Urinary tract infection (UTI)	32,416.00	26,374.95	39,070.66	Gamma

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

The intervention (mavacamten in combination with standard care) and comparators (placebo in combination with individually optimized standard care comprising BBs, CCBs) considered have been evaluated within a single RCT. Therefore, an SLR has not been conducted and this dossier is based on the available head-to-head trials.

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

This literature search was, as described in Section 8.5.1, only used to look for health-state utilities. As seen in Section I.1.5.1.4, no values were identified in the literature.

The literature search was done as part of a greater economic SLR. However, it has not been possible to separate it out; therefore, Appendix I is lengthy.

I.1.1 Methods

Objective of literature search: The global economic SLR aimed to identify cost-effectiveness studies, studies on HCRU, and health-state utilities for people with oHCM. The methodology is aligned with the Centre for Reviews and Dissemination (CRD),[156] and the Cochrane Handbook for Systematic Reviews[157] guidance.

I.1.2 Protocol and eligibility criteria

The scope of the global SLR was defined using population, intervention, comparators, outcomes, and study design (PICOS) criteria. These eligibility criteria are presented in Table 70. The eligibility criteria were used as a guide for developing search strategies. For a study to be included it had to match the criteria from each of the PICOS components and study that did not match the criteria in at least one of the PICOS components was excluded. In addition, this report covers the studies published in English language only.

Table 70. Eligibility criteria as per PICOS

Parameter	Inclusion criteria			Exclusion criteria
	Healthcare resource use and costs	Utilities and health-related quality of life	Cost-effectiveness studies	
Population	Adults (≥ 18 years) diagnosed with oHCM			▪ Patients without a diagnosis of oHCM ▪ Individuals with concomitant malignancies ▪ Patients with genetic syndromes or other diagnoses that mimic oHCM (e.g., Noonan syndrome, Fabry syndrome, amyloidosis) ▪ Non-human subjects ▪ In-vitro studies
Interventions/ comparators	Not restricted by intervention or comparator		▪ Mavacamten ▪ Non-vasodilating BB – Atenolol – Bisoprolol – Metoprolol – Nadolol – Pindolol – Propranolol – Sotalol ▪ Non-dihydropyridine CCBs – Verapamil – Diltiazem ▪ Class IA anti-arrhythmic – Disopyramide – Cibenzoline ▪ Angiotensin receptor neprilysin inhibitor – Sacubitril valsartan (Entresto) ▪ Cardiac myosin inhibitor – CK-274 ▪ SRT	▪ Other interventions not specified under the inclusion criteria (applies to cost-effectiveness studies only)

Parameter	Inclusion criteria			Exclusion criteria
	Healthcare resource use and costs	Utilities and health-related quality of life	Cost-effectiveness studies	
			– Ventricular septal myectomy – Alcohol ablation ▪ Placebo ▪ Standard of care ▪ No comparator	
Outcomes	▪ Direct and indirect resource use ▪ Direct and indirect costs	▪ Utility and disutility data derived by: – EQ-5D – SF-36 Health Survey (SF-36) – Visual analog scale (VAS) – Kansas City Cardiomyopathy Questionnaire (KCCQ) – HCM Symptom Questionnaire Shortness-of-Breath (HCMSQ-SoB) – Time tradeoff – Standard gamble	▪ Incremental cost-effectiveness ratio ▪ Incremental cost-utility ratio ▪ Incremental costs ▪ Quality-adjusted life-years ▪ Life-years gained	▪ Other outcomes not specified under the inclusion criteria
Study design	▪ Randomized trials ▪ Non-randomized trials ▪ Systematic reviews[a]	▪ Randomized trials[b] ▪ Non-randomized trials[b] ▪ Patient interviews ▪ Systematic reviews[a] ▪ Patient surveys ▪ Economic evaluations and HTAs	▪ Cost-effectiveness evaluations ▪ Cost-utility evaluations ▪ Cost-benefit evaluations ▪ Cost-minimization analyses ▪ Systematic reviews[a]	▪ Editorials ▪ Commentaries ▪ Letters ▪ Case series
Geographic scope	Not restricted			
Language	No language restrictions[c]			

HCM = hypertrophic obstructive myocardiopathy; BB = beta-blocker; CCB = calcium channel blocker; SRT = septal reduction therapy; HTA = health technology assessment; SF-36 = SF-36 Health Survey; VAS = visual analog scale; KCCQ = Kansas City Cardiomyopathy Questionnaire; HCMSQ-SoB = HCM Symptom Questionnaire Shortness-of-Breath.

[a] Data from systematic reviews will not be extracted into the data extraction form. The references from 3 of the most recent reviews will be checked to ensure no relevant record was missed by the search strategy.

[b] Clinical Trials will be screened for humanistic burden outcomes.

[c] This report covers the studies reported in English language only.

Source: BMS data on file (2023)[158]

I.1.3 Data sources and searches

I.1.3.1 Electronic databases

The databases and search engines used to identify economic evidence are presented in Table 71. The Embase, MEDLINE, EconLit, PsychINFO databases were searched by means of the ProQuest engine. This search engine allows for the databases to be searched simultaneously and removes duplicates between databases. The search terms for oHCM consisted of words searched in title/abstract and as indexed terms (i.e., Emtree and MeSH).

Records from the National Health Service Economic Evaluation Database (NHS EED), the Database of Abstracts of Reviews of Effects (DARE) and the health technology assessment (HTA) database were searched via the CRD search engine. As this search engine has a limited search functionality, "cardiomyopathy" was used in the search field.

Table 71. Databases included in the literature search

Search Engine	Database	Date of search completion
ProQuest	MEDLINE	Original search: 2 August 2021
	Embase	Update search: 3 December 2021
	EconLit	Update search: 23 May 2022
	PsychINFO	
CRD	NHS EED	Original search: 2 August 2021
	DARE	Update search: 3 December 2021
	HTA database	Update search: 23 May 2022

CRD = Centre for Reviews and Dissemination; HTA = health technology assessment; DARE = Database of Abstracts of Reviews of Effects; NHS EED = National Health Service Economic Evaluation Database.
Source: BMS data on file (2023)[158]

I.1.3.2 Conference proceedings

A search of the following proceedings from the previous 3 years (2019-2021) was conducted in the original review and updated to ensure that recent economic data for oHCM were identified:

- American Heart Association (AHA)
- European Society of Cardiology (ESC)
- European Heart Disease and Heart Failure Congress
- American College for Cardiology (ACC)
- British Heart Foundation (BHF)
- British Cardiovascular Society (BCS)
- ISPOR
- Heart Failure Society of America (HFSA)
- Heart Failure Association of ESC (HFA)
- Quality of Care and Outcomes Research Conference (QCOR)

Conference proceedings that are indexed in Embase were searched electronically, using the same search strategy as for the studies. Conferences that are not indexed in Embase were "hand-searched" using cardiomyopathy derived search terms, namely hypertrophic cardiomyopathy, hypertrophic obstructive cardiomyopathy, in whichever format is provided by the conference (e.g., PDF booklet, online search portal).

I.1.3.3 HTA and other grey literature websites

Additional searches were performed on the websites of HTA authorities to retrieve critical appraisals from previous assessments. To identify relevant economic evidence in health technology appraisals, search terms for oHCM, namely hypertrophic cardiomyopathy, hypertrophic obstructive cardiomyopathy, were used in the website's search engines. HTA authorities were considered for inclusion in the SLR searches were:

- Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)/Agencia de Evaluación de Tecnologías Sanitarias (AETS)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Gemeinsamer Bundesausschuss (G-BA)
- Haute Autorité de santé (HAS)
- Institute for Clinical and Economic Review (ICER)
- National Centre for Pharmacoeconomics Ireland (NCPE)
- National Institute for Health and Care excellence (NICE)
- Pharmaceutical Benefits Advisory Committee (PBAC)
- Scottish Medicines Consortium (SMC)
- Tandvårds- och läkemedelsförmånsverket (TLV)

I.1.4 Study selection and data extraction

I.1.4.1 Selection of studies

Once the electronic searches were run, all retrieved references were downloaded and imported into an EndNote database and duplicates were removed. Subsequently, the references were exported into a reference screening software (DistillerSR) that was used for title and abstract screening.

All articles identified from the search were screened in 2 steps:

- Title/abstract screening
- Full-text screening

Inclusion or exclusion of studies was based on the PICOS eligibility criteria specified in Table 70. Abstract/title review of all references was performed independently by 2 reviewers. Any discrepancies were resolved by a third reviewer. The same process was applied for articles that were selected for full-text review. During both title/abstract and full-text screening phase, articles that were excluded were documented along with reasons for their exclusion.

The results of the selection phase were a final list of articles to be included for data extraction and reporting. A flow diagram from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was completed after the screening and selection step to provide an overview of the review process.

I.1.4.1.1 Conference proceedings and HTA websites

Hand searches of conference proceedings and HTA websites were performed by a single reviewer and checked by a second reviewer. Conference abstracts and HTA website results which met the eligibility criteria (Table 70) were collated in an Excel database and linked to included studies where possible to determine if any additional information was provided. If duplicate data was presented in multiple conference abstracts, only the most recent abstract was included.

I.1.4.2 Data extraction

After all relevant studies were identified and received, the relevant data were extracted from the articles. One researcher extracted the data, and the second researcher independently reviewed all data extracted for each endpoint. The second reviewer checked the data extraction file for accuracy and completeness, by checking if all data presented in the Excel file corresponds directly with what was presented in the selected articles. Thus, the second reviewer did not only check a data sample but checked all articles. Any discrepancies were resolved by a third reviewer.

For binary outcome data, the numerator and denominator (sample size) were extracted. For continuous scales and scores, the mean/median score was extracted as well as the standard error, standard deviation, or confidence interval, as reported by the study authors. Baseline, endpoint, and change-from-baseline values were extracted as well as mean differences (and their respective standard error, standard deviation, or confidence interval) between cohorts if reported.

I.1.5 Results

This section presents aggregated results from the original and update searches of the global economic SLR. It provides the details of the selection process and the number of identified studies (Section I.1.5.1). Details of the identified studies of HRQoL and health-state utilities of relevance to this submission are reported in Section I.2.

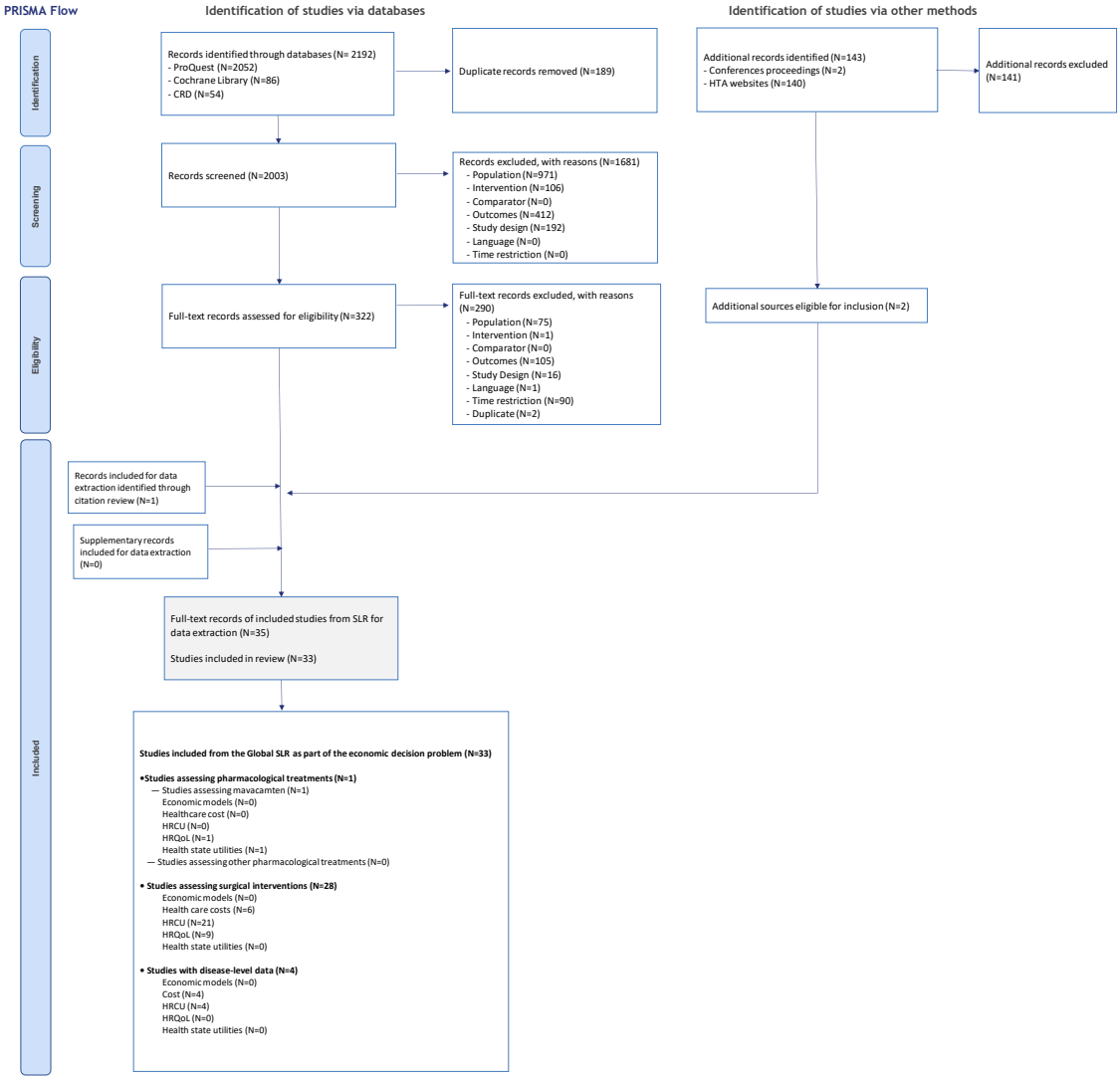
I.1.5.1 Search and study selection results

I.1.5.1.1 2 August 2021 searches

A total of 2,192 records were identified. After deduplication, the title, and abstracts of 2,003 records were screened. During the title and abstract review phase, 1,681 records were excluded. The eligibility of the remaining 322 records was assessed based on full-text review. After the exclusion of 290 full-text records and the inclusion of 3 additional records (2 from conference searches and 1 through citation review), 33 studies from 35

records met the inclusion criteria and were deemed eligible for inclusion, as described in Figure 23.

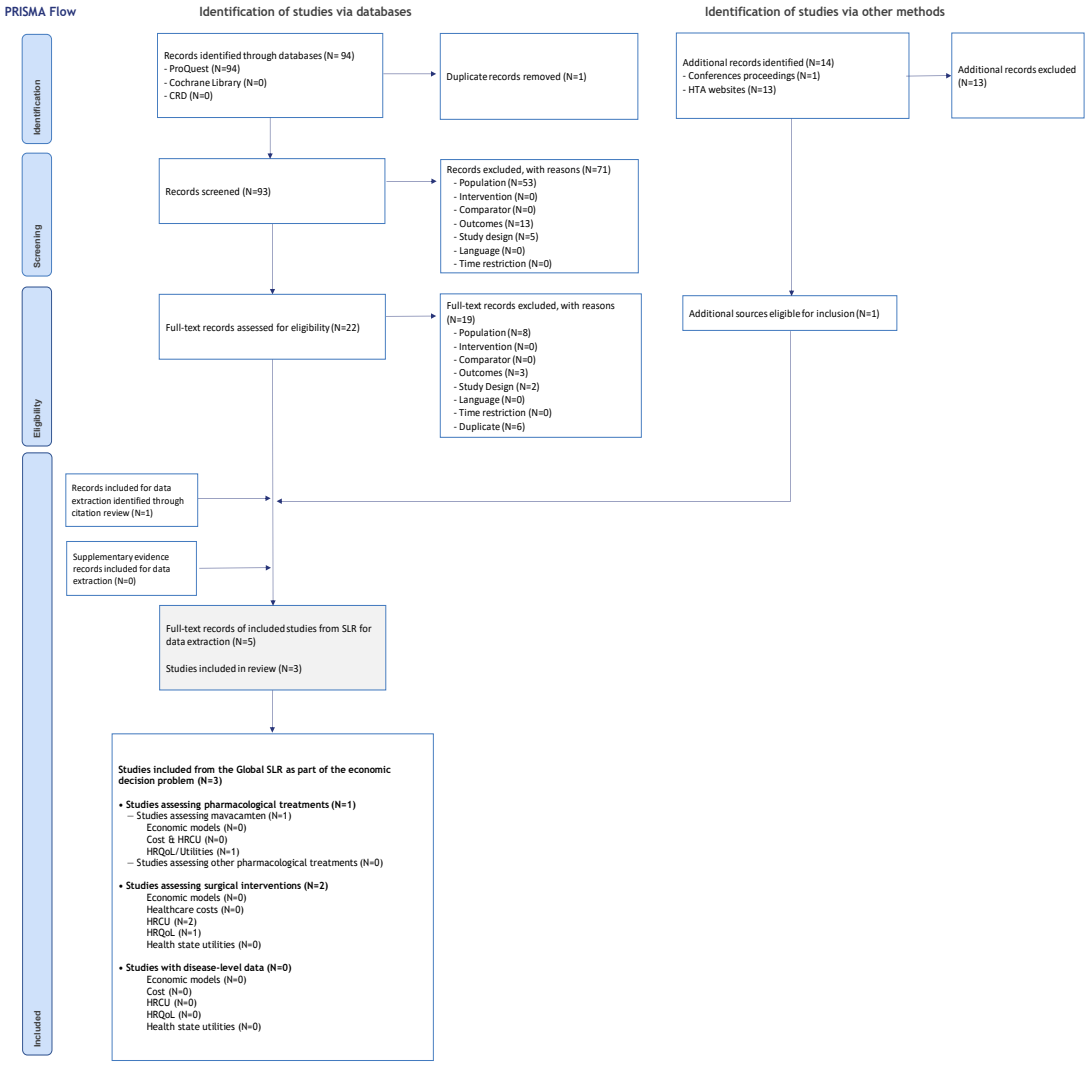
Figure 23. PRISMA flow: 2 August 2021 searches



I.1.5.1.2 3 December 2021 searches

A total of 94 records were identified in the update search. After removing duplicates, the title, and abstracts of 93 records were screened. During the title and abstract review phase, 71 records were excluded. Overall, 22 records were eligible for full-text screening. A total of 19 records were excluded during full-text selection based on the following prespecified criteria: population (n = 8), outcomes (n = 3), study design (n = 2), and duplicate (n = 6). The inclusion of 2 additional records (1 from conference searches and 1 from the clinical SLR) resulted in total of 3 studies from 5 records eligible for data synthesis. Figure 24 summarizes the screening stages of the update SLR.

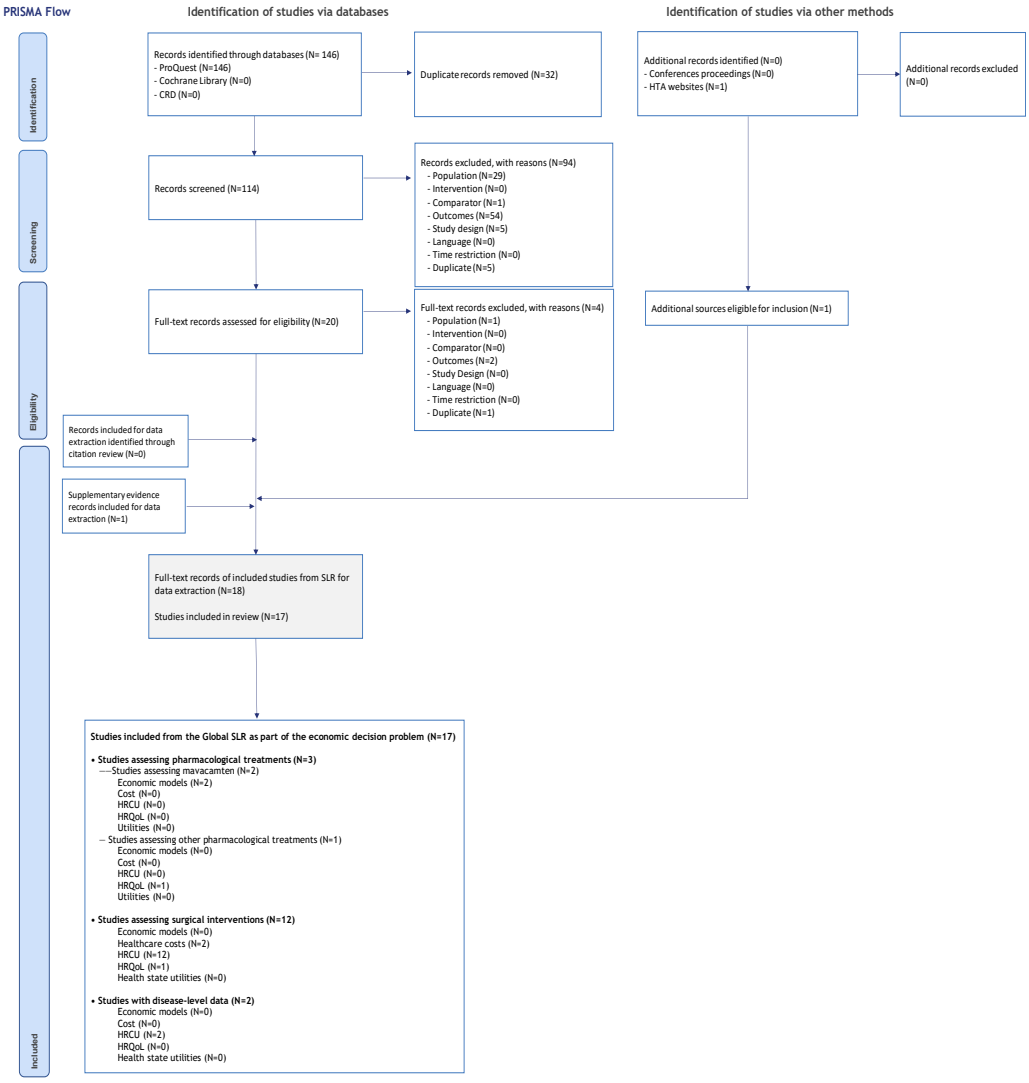
Figure 24. PRISMA flow: 3 December 2021 searches



I.1.5.1.3 23 May 2022 searches

In total, 146 records were identified by the 23 May 2022 search for the global SLR. After removal of duplicates, 114 records were screened for eligibility. During the screening phase, 94 records were excluded. Subsequently, the eligibility of 20 records was assessed during full-text screening. During this stage, 4 full-text records were excluded based on the following prespecified criteria: population (n = 1), outcomes (n = 2), duplicate (n = 1). Two additional records were included for supplementary data extraction. Figure 25 summarizes the screening stages of the update SLR.

Figure 25. PRISMA flow: 23 May 2022 searches



I.1.5.1.4 Combined search results

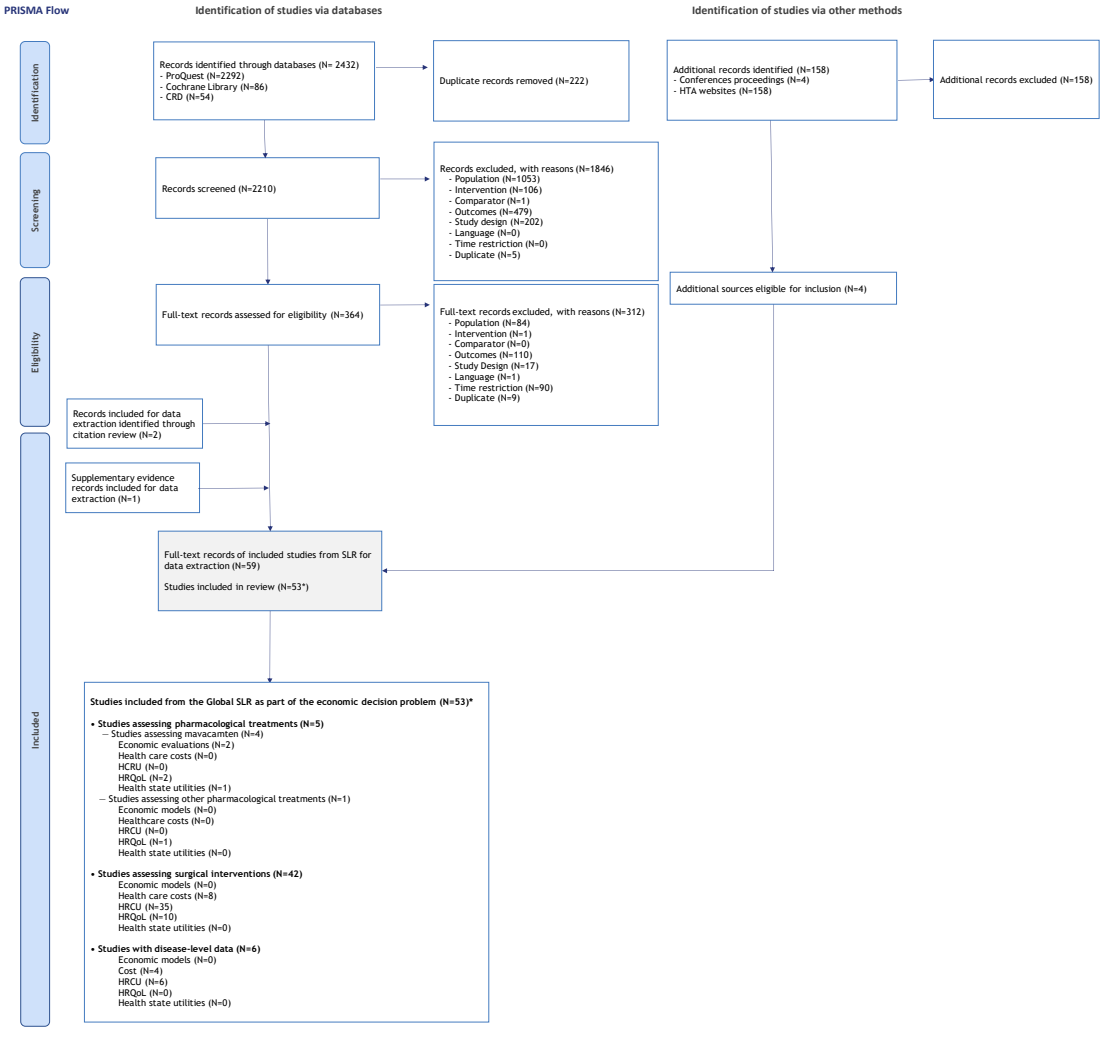
Combined searches added up to a total of 2,432 records from database searches. Following the deduplication, 2,210 records were screened for eligibility. In total, 1,846 records were excluded based on titles and abstracts. The eligibility of the remaining 364 records was assessed through full-text screening. After the exclusion of 312 records and the inclusion of 5 additional records (4 from conference searches and 1 through citation reviews), 53 studies from 59 records met the inclusion criteria and were deemed eligible for data synthesis (Figure 26).

Of note, the searches run on 2 August 2021, 3 December 2021, and 23 May 2022 have identified a total of 5 records reporting on EXPLORER-HCM.[53,63,96,98,159] These 5 records are considered as 1 study included in the combined search counts. In addition, there were 2 economic evaluation studies on mavacamten reported in 3 records,[42,160,161] which were considered as 2 different studies.

Among the 53 included studies, 2 were economic evaluations, 41 reported on HCRU, 12 reported on costs, 12 reported on HRQoL, and 1 on health-state utilities. The economic SLR identified 5 studies from 9 records that assessed pharmacological treatments. Of those, 5 records presented HRQoL and health-state utility results from EXPLORER-HCM, 3 as conference abstracts[96,98,159] and 2 as full-text records,[53,63] and 2 economic evaluation studies, analyzing data from EXPLORER-HCM.[42,160,161] In addition, 1 study reported QoL data for metoprolol.[54]

There were 42 studies reporting on HCRU, healthcare costs, HRQoL, and/ or health-state utility results for SRTs or pacing[99,100,102-105,107,108,111,122,123,138,162-189]; 2 of these studies reported on prophylactic amiodarone with septal myectomy.[101,190] An additional 6 studies reported on disease-level HCRU and cost data.[167,170,191-194] Figure 26 depicts the aggregated flow of information through the stages of global economic SLR.

Figure 26. PRISMA flow: combined searches



*The searches run on 2 August 2021, 3 December 2021 and 23 May 2022 have identified 1 study assessed in 5 different reports. These reports are counted as 1 study in this Global Economic SLR.

I.2 Health-related quality of life and health-state utilities

I.2.1 Health-related quality of life and utility studies

A total of 12 studies reporting on HRQoL and utilities of patients with oHCM were identified. Of those, 10 studies provided HRQoL and utility data of patients who underwent SRTs or pacing,[99-108] 1 study evaluated metoprolol versus placebo,[54] and 1 study (assessed in 5 records) provided HRQoL and utility outcomes from the randomized controlled EXPLORER-HCM trial assessing the effect of mavacamten versus placebo for the treatment of patients with oHCM.[53,63,98,159,195] One of the objectives of the economic SLR was to capture the disutility associated with AEs experienced by patients throughout oHCM treatment. However, no studies were identified reporting on disutility.

The identified studies evaluated and reported HRQoL and utility variables across the US (n = 4),[99-101,108] Spain (n = 2),[104,105] Sweden (n = 1),[106] Japan (n = 1),[107] Germany (n = 1),[103] Denmark (n = 1),[54] and Europe (12 centers) (n = 1),[53,63,98,159,195] and 5 reported on the EXPLORER-HCM trial that was conducted in 13 countries (US, Spain, Poland, Israel, Germany, France, Czech Republic, Denmark, Netherlands, Portugal, Italy, Belgium, UK).[53,63,98,159,195]

The instruments assessing HRQoL and utilities were the EQ-5D (EQ-5D-5L, n = 1)[96] and VAS (Karolinska QoL VAS, n = 2).[102,106] The instruments assessing HRQoL and utilities were the EQ-5D (EQ-5D-5L, n = 1),[96] VAS (Karolinska QoL VAS, n = 2),[102,106] SF-12 Health Survey (SF-12, n = 2[99,103]; SF-36, n = 1,107), Minnesota Living with Heart Failure Questionnaire (MLHFQ, n = 3),[102,106] Kansas City Cardiomyopathy Questionnaire (KCCQ, n = 7),[99,103] Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ, n = 2),[53,159] and Karolinska questionnaire (n = 1).[102]

Olivotto et al. (2020)[53], Xie et al. (2021)[155], Spertus et al. (2021)[63], Naidu et al. (2021)[97], and Jacoby et al. (2021)[98] reported the outcomes from EXPLORER-HCM using EQ-5D.[96] Olivotto et al. (2020)[53], Xie et al. (2021)[96], Spertus et al. (2021)[63], Naidu et al. (2021)[97], and Jacoby et al. (2021)[98] reported the outcomes from EXPLORER-HCM using EQ-5D,[96] VAS,[195] KCCQ,[53,97,98] and HCMSQ[53,97,98] instruments to assess the effects of mavacamten on patient HRQoL.

Among the 10 studies reporting patient HRQoL data for SRTs or pacing, Gadler et al. (1999)[106] and Linde et al. (1999)[102] investigated PROs in patients with drug-refractory oHCM, using EQ VAS instrument and assess the intensity of symptoms like chest pain, dyspnea, palpitation and dizziness. Gadler et al. (1999)[106] reported the results for patients from Sweden, and Linde et al. (1999)[102] reported data for patients included from 12 centers within Europe.

The 3 studies by Serber et al. (2007)[99], Galve et al. (2010)[104], and Boekstegers et al. (2001)[103] reported on the changes in the Short Form Health Survey parameters (physical and mental health) and QoL in patients with oHCM for US,[99] Spain,[104] and Germany,[103] respectively. Serber et al. investigated the outcomes before and after the ASA in patients from US.[99] Boekstegers et al. reported the post-intervention quality-of-life results for German patients with oHCM, who were treated by non-surgical myocardial reduction (NSMR).[103] Furthermore, Galve et al. (2010)[104] examined the Spanish patients'

perception of their QoL who underwent pacemaker implantation for the treatment of oHCM.

Moreover, 3 studies used the Minnesota Living with Heart Failure Questionnaire.[99,100,105] Of those, Serber et al. (2007)[99] reported the change in the cardiac specific quality-of-life score for patients receiving ASA, and Balaram et al. (2012)[100] reported change in global quality-of-life score of patients that underwent anterior mitral leaflet plication for oHCM, both assessed the results for patients from the US. Berruezo et al. (2011)[105] assessed the effectiveness of biventricular pacing and reported changes in quality-of-life scores of oHCM patients from Spain.

In addition to the studies reporting quality-of-life results from the EXPLORER trial, the studies by Shalen et al. (2021)[101] and Lin et al. (2019)[108] assessed the changes in KCCQ scores for oHCM patients that underwent septal myectomy in US and Akita et al. (2018)[107] measured the health status of Japanese patients after percutaneous transluminal septal myocardial ablation (PTSMA).

Finally, Linde et al. (1999)[102] used the Karolinska questionnaire to evaluate the QoL of oHCM patients treated in 12 centers across Europe. The parameters assessed were on physical functioning and patient's self-perceived health status of patients with permanent pacemaker.[102]

Table 72 provides a summary of the studies and the HRQoL instruments that were used.

Table 72. Included studies with HRQoL data

Trial name	Country	Reference	Title	Objective	Intervention/comparator	Instruments
EXPLORER-HCM NCT03470545	13 countries: US, Spain, Poland, Israel, Germany, France, Czech Republic, Denmark, Netherlands, Portugal, Italy, Belgium, UK	Olivotto et al. (2020)[53]	Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial	To assess the efficacy and safety of mavacamten, a first-in-class cardiac myosin inhibitor, in symptomatic oHCM	I: Mavacamten C: Placebo	KCCQ-CSS HCMSQ-SoB
		Spertus et al. (2021)[63]	Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): health status analysis of a randomised, double-blind, placebo-controlled, phase 3 trial	To assess the effect of mavacamten, a first-in-class cardiac myosin inhibitor, on patients' health status—i.e., symptoms, physical and social function, and quality of life	I: Mavacamten C: Placebo	KCCQ-CSS KCCQ-OS
		Xie et al. (2021)[96]	Health utilities among patients with obstructive hypertrophic cardiomyopathy (obstructive HCM): an analysis of patient health-related quality of life in the EXPLORER-HCM trial	To assess the effects of mavacamten on patient HRQoL and estimate the utilities for health states defined by NYHA class for these patients	I: Mavacamten C: Placebo	EQ-5D-5L (US value set) EQ VAS
		Naidu et al. (2021)[97]	Mavacamten improves symptoms of shortness of breath in patients with obstructive hypertrophic cardiomyopathy (HCM): analysis of the HCM Symptom Questionnaire in the phase 3 EXPLORER trial	To assess the efficacy and safety of mavacamten, a first-in-class cardiac myosin inhibitor, in symptomatic oHCM	I: Mavacamten C: Placebo	HCMSQ-SoB
		Jacoby et al. (2021)[98]	Efficacy of mavacamten in patients with symptomatic hypertrophic cardiomyopathy: sub-group analyses by background beta-blocker use from the EXPLORER-HCM and MAVA-LTE studies	To examine the effects of mavacamten with and without BB use in patients with symptomatic oHCM	I: Mavacamten +/- BB C: Placebo	KCCQ-CSS
-	US	Serber et al. (2007)[99]	Depression, anxiety, and quality of life in patients with obstructive hypertrophic cardiomyopathy three months after alcohol septal ablation	To examine the changes in psychosocial parameters (i.e., depression, anxiety, satisfaction with life, and optimism) and QoL in	I: ASA C: -	SF-12 Minnesota Living with Heart Failure Questionnaire

Trial name	Country	Reference	Title	Objective	Intervention/comparator	Instruments
				patients with oHCM from before to 3 months after ASA		
-	US	Balaram et al. (2012)[100]	Role of mitral valve plication in the surgical management of hypertrophic cardiomyopathy	To demonstrate the role of mitral valve plication in selected patients through evaluation of clinical outcomes and survival	Mitral valve plication (with or without)	Minnesota Quality of Life score
-	US	Shalen et al. (2021)[101]	Perioperative amiodarone to prevent atrial fibrillation after septal myectomy in obstructive hypertrophic cardiomyopathy	To hypothesize that prophylactic amiodarone would reduce the incidence of post-operative AF following septal myectomy for oHCM.	I: Myectomy C: -	KCCQ score
-	European	Linde et al. (1999)[102]	Placebo effect of pacemaker implantation in obstructive hypertrophic cardiomyopathy	To compare the effects of AV synchronous pacing with an optimal AV delay to inactive pacing in patients with oHCM	I: Inactive Pacing C: Active Pacing	Karolinska questionnaire VAS
-	Germany	Boekstegers et al. (2001)[103]	Pressure-guided non-surgical myocardial reduction induced by small septal infarctions in hypertrophic obstructive cardiomyopathy	To assess the safety and efficacy of pressure-guided NSMR with the induction of small septal infarctions in patients with oHCM	I: Pressure-guided NSMR by small septal infarction C: -	SF-12
-	Spain	Galve et al. (2010)[104]	Late benefits of dual-chamber pacing in obstructive hypertrophic cardiomyopathy: a 10-year follow-up study	To examine the mid-term and long-term outcomes in patients with oHCM submitted to pacing	I: DDD or VDD pacemaker C: -	SF-36
-	Spain	Berruezo et al. (2011)[105]	Biventricular pacing in hypertrophic obstructive cardiomyopathy: a pilot study	To assess the feasibility and effectiveness of LV/biventricular pacing in patients with oHCM and severe LVOT obstruction	I: (Atrio-) biventricular pacing C: -	Minnesota Living with Heart Failure Questionnaire
-	Sweden	Gadler et al. (1999)[106]	Rapid return of left ventricular outflow tract obstruction and symptoms following cessation of long-term atrioventricular synchronous pacing for obstructive hypertrophic cardiomyopathy	To explore the long-term efficacy of cardiac pacing in oHCM	I: Pacemaker C: -	VAS
-	Japan	Akita et al. (2018)[107]	Prognostic significance of repeated brain natriuretic peptide measurements after	To evaluate whether repeated BNP measurements after PTSMA provide	I: PTSMA	KCCQ score

Trial name	Country	Reference	Title	Objective	Intervention/comparator	Instruments
			percutaneous transluminal septal myocardial ablation in patients with drug-refractory hypertrophic obstructive cardiomyopathy	prognostic information regarding the response to PTSMA in patients with drug-refractory oHCM	C: -	
-	US	Lin et al. (2019)[108]	Papillary muscle realignment and septal myectomy for obstructive hypertrophic cardiomyopathy: 1-year outcomes experienced at a single centre	To report the long-term results of combined septal myectomy and PMR and its effects on symptoms, functional capacity, and LV filling pressure	I: Septal myectomy + routine PMR C: -	KCCQ score
NCT03532802	Denmark	Dybro et al. (2021)[54]	Randomised trial of metoprolol in patients with obstructive hypertrophic cardiomyopathy	To investigate the effects of metoprolol on LVOT obstruction, symptoms, and exercise capacity in patients with oHCM.	I: Metoprolol C: Placebo	KCCQ score

ASA = alcohol septal ablation; AV = atrioventricular; BB = beta-blocker; BNP = brain natriuretic peptide; HCMSQ-SoB = Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath; HCM = hypertrophic cardiomyopathy; HRQoL = health-related quality of life; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score; LV = left ventricular; LVOT = left ventricular outflow tract; NSMR = non-surgical myocardial reduction; NYHA = New York Heart Association; oHCM = obstructive hypertrophic cardiomyopathy; PMR = papillary muscle realignment; PTSMA = percutaneous transluminal septal myocardial ablation; QoL = quality of life; SF-12 = SF-12 Health Survey; SF-36 = SF-36 Health Survey; UK = United Kingdom; US = United States; VAS = visual analog scale.

I.2.1.1 Outcomes from HRQoL and utility studies

Table 73 presents the outcomes from the 12 studies reporting on HRQoL and utilities. Of those identified studies, 10 studies provided quality-of-life data of patients treated with SRT[99-108] or pacing,[79-82,129] 1 study compared metoprolol with placebo,[54] and 5 reported on the health status outcomes from the EXPLORER-HCM trial investigating the efficacy and safety of mavacamten versus placebo in patients with oHCM.[53,63,98,159,195]

I.2.1.1.1 Outcomes from HRQoL and utility studies: mavacamten trial (EXPLORER-HCM)

The records by Xie et al. (2022)[196], Spertus et al. (2021)[63], Olivotto et al. (2020)[53], Naidu et al. (2021)[97], and Jacoby et al. (2021)[98] reported the outcomes from EXPLORER-HCM using EQ-5D,[96] KCCQ,[53,63,98] and HCMSQ[53,159] instruments to assess the effects of mavacamten on patient HRQoL.

Xie et al. reported mean utilities by NYHA class for mavacamten and placebo treatment arms were estimated using a generalized estimating equation.[96] Additionally, significant improvement in EQ-5D-5L Index Value and VAS was reported for patients in the mavacamten arm compared with patients in placebo arm ($P < 0.05$).[96]

Three records were identified assessing the changes in KCCQ scores from EXPLORER-HCM.[53,63,98] Spertus et al. (2021)[63] examined the change in KCCQ-overall summary score and KCCQ-clinical summary score from baseline and reported grater change with mavacamten than placebo ($P < 0.0001$). The authors also provided results around total symptom score, physical limitation score, social limitation score and quality-of-life score using KCCQ, for which greater improvements in health status were reported for patients given mavacamten.[63] Scores for each domain ranged from 0 to 100, where scores represents health status from worst to best.[63]

Similarly, improvements in KCCQ scores ($P < 0.0001$) and HCMSQ scores ($P < 0.0001$) favoring mavacamten were reported by Olivotto et al. (2020)[53]. Jacoby et al. (2021)[98] examined the effect of mavacamten with or without BB use (subgroup analysis of EXPLORER-HCM) on patient's symptoms and reported similar improvements in KCCQ scores for both cases.

In addition, Naidu et al. evaluated the changes in HCMSQ scores as a secondary endpoint in EXPLORER-HCM and reported meaningful improvements with mavacamten versus placebo ($P < 0.0001$).[159]

I.2.1.1.2 Outcomes from HRQoL and utility studies: surgical interventions

Ten studies reported the change in quality-of-life scores of patients with oHCM using KCCQ,[101,107,108] VAS,[102,106] SF-12,[99,103] SF-36,[104] Karolinska questionnaire,[102] and the Minnesota Living with Heart Failure[99,100,105] instruments.

For the change in KCCQ scores, Lin et al. (2019)[108] reported long-lasting improvement in patients quality-of-life post-septal myectomy at 1-year ($P < 0.0001$). Similarly, Akita et al. (2018)[107] measured the change in KCCQ score before and after PTSMA and reported

significant results in patients responding to the treatment ($P = 0.007$). Shalen et al. (2021)[101] evaluated the mean change in KCCQ-overall score and reported significant improvement 30 days after surgical myectomy ($P < 0.001$).

The 2 studies by Gadler et al. (1999)[106] and Linde et al. (1999)[102] assessed patients' QoL on a VAS and reported the changes in symptoms of patients induced inactive and active pacing compared with baseline. The one by Linde et al. (1999)[102] obtained significant improvements of symptoms in the active pacing group compared with inactive group, 3 months after baseline. Gadler et al. (1999)[106] reported increase in patient symptoms during inactive pacing compared with active pacing period, namely increase in chest pain ($P < 0.01$) and sensation of palpitations ($P < 0.06$).

The 3 studies by Boekstegers et al. (2001)[103], Serber et al. (2007)[99], and Galve et al. (2010)[104] used the Short Form Health Survey to measure QoL. Mean changes from baseline were recorded in each study. Of those, Serber et al. reported the change before and 3 months after ASA, and the one by Galve et al. included patients with permanent pacemaker implantation into their analysis and reported the change from baseline to 3 months to 1 year. Those studies assessed the change on the physical component ($P = 0.009$[99]; $P = 0.0001$[104]) and mental component $P = 0.143$[99]; $P = 0.02$[104]) from baseline. Additionally, Boekstegers et al.[103] reported improvement in patients' overall QoL after NSMR compared with baseline ($P < 0.001$).

The study by Linde et al. (1999)[102] also assessed patient QoL using Karolinska questionnaire which concerned physical functioning, social, sexual, and cognitive functioning, alertness, sleep, self-perceived health, and emotional state of patients induced inactive and active pacing. The change was compared between baseline and 3 months, for which measurable results were obtained in the group assigned to active pacing.

Finally, the 3 studies by Balaram et al. (2012)[100], Berruezo et al. (2011)[105], and Serber et al. (2007)[99] used the Minnesota Living with Heart Failure Questionnaire to measure QoL. Balaram et al. (2012)[100] compared pre- and post-mitral valve plication and reported improvements in patient quality-of-life scores ($P < 0.001$). The study by Berruezo et al.[105] assessed the effectiveness of biventricular pacing in oHCM patients and reported the changes in QoL in patients from baseline to 3-month ($P < 0.05$) and 1-year ($P < 0.05$). The cardiac specific questionnaire was used by Serber et al. (2007)[99] to assess the change in overall QoL of ASA. An improvement was reported from before to 3 months after ASA ($P < 0.001$).

I.2.1.1.3 Outcomes from HRQoL and utility studies: metoprolol versus placebo

One of the included studies reported response rates and change in KCCQ-CSS scores at 2 weeks for patients receiving metoprolol (n = 29) or placebo (n = 29).[54] The response rate was 100% in both groups, the mean change in KCCQ-CSS scores were 76.2 ± 16.5 and 73.8 ± 19.5 for metoprolol and placebo, respectively.

Table 73. Summary of HRQoL and health-state utility values from included studies

Trial name	Geographic scope	Reference	Population	Treatment arm	Response rate	Instrument	Variable definition	Change in HRQoL/utility outcome values, mean (SD)	Timepoint
Studies reporting on mavacamten									
EXPLORER-HCM NCT03470545	13 countries: US, Spain, Poland, Israel, Germany, France, Czech Republic, Denmark, Netherlands, Portugal, Italy, Belgium, UK	Olivotto et al. (2020)[53]	Patients with HCM with an LVOT gradient of 50 mmHg or greater and NYHA class II-III symptoms	I: Mavacamten (n = 92)	-	KCCQ-CSS	Clinical summary score	13.6 (14.4)	Baseline to 30 weeks
				C: Placebo (n = 88)				4.2 (13.7)	
				Mavacamten vs. Placebo (n = 92 vs. 88)			Difference[a] (95% CI), *P* value	9.1 (5.5-12.7; *P* < 0.0001[c])	
				I: Mavacamten (n = 85)		HCMSQ-SoB	Clinical summary score	−2.8 (2.7)	
				C: Placebo (n = 86)				−0.9 (2.4)	
				Mavacamten vs. Placebo (n = 92 vs. 88)			Difference[a] (95% CI), *P* value	−1.8 (−2.4 to −1.2; *P* < 0.0001[c])	
		Spertus et al. (2021)[63]	Adult patients (≥ 18 years) with symptomatic oHCM	I: Mavacamten (n = 92)	75%	KCCQ (23 item)	Overall summary score	14.9 (15.8)	Baseline to week 30
							Clinical summary score	13.6 (14.4)	

Trial name	Geographic scope	Reference	Population	Treatment arm	Response rate	Instrument	Variable definition	Change in HRQoL/utility outcome values, mean (SD)	Timepoint
			(gradient ≥ 50 mmHg and NYHA class II-III)				Total symptom score	12.4 (15.0)	
							Physical limitation score	14.7 (17.0)	
							Social limitation score	13.5 (22.9)	
							Quality-of-life score	18.8 (21.6)	
					-		Overall summary score	−0.1 (16.5)	Baseline to week 38
							Clinical summary score	1.0 (14.4)	
				C:Placebo (n = 88)	69%	KCCQ (23 item)	Overall summary score	5.4 (13.7)	Baseline to week 30
							Clinical summary score	4.2 (13.9)	
							Total symptom score	4.8 (15.9)	
							Physical limitation score	3.6 (15.4)	
							Social limitation score	5.1 (19.2)	

Trial name	Geographic scope	Reference	Population	Treatment arm	Response rate	Instrument	Variable definition	Change in HRQoL/utility outcome values, mean (SD)	Timepoint
							Quality-of-life score	8.3 (18.8)	
					-		Overall summary score	4.5 (12.7)	Baseline to week 38
							Clinical summary score	3.0 (13.2)	
				Mavacamten vs. Placebo (n = 92 vs. 88)	-	KCCQ-OS	Difference[a] (95% CI), *P* value	9.1 (5.5-12.8; *P* < 0.0001[c])	Baseline to week 30
						KCCQ-CSS	Difference[a] (95% CI), *P* value	9.1 (5.5-12.7; *P* < 0.0001[c])	
						KCCQ-OS	Total symptom score – Difference[a] (95% CI), *P* value	7.7 (3.7-11.5; *P* = 0.0002[c])	
							Physical limitation score - Difference[a] (95% CI), *P* value	10.6 (6.2-14.8; *P* < 0.0001[c])	
							Social limitation score - Difference[a] (95% CI), *P* value	9.3 (4.5-14.1; *P* = 0.0002[c])	
							Quality-of-life score – Difference[a] (95% CI), *P* value	9.6 (4.7-14.5; *P* = 0.0001[c])	

Trial name	Geographic scope	Reference	Population	Treatment arm	Response rate	Instrument	Variable definition	Change in HRQoL/utility outcome values, mean (SD)	Timepoint
		Xie et al. (2021)[96]	Patients with symptomatic oHCM	I: Mavacamten ± BB or CCB monotherapy (n = 96)	-	EQ-5D-5L Tariff: US value set	Index score	0.084 (0.163)	Baseline to week 30
				C: Placebo ± BB or Cobb monotherapy (n = 89)			Index score	0.009 (0.163)	Baseline to week 30
				Mavacamten ± BB or CCB monotherapy vs. Placebo ± BB or CCB monotherapy (n = 96 vs. 89)			Difference – unadjusted (95% CI), *P* value	0.075 (0.028-0.122; *P* = 0.002[c])	
							Difference - adjusted[b] (95 CI%), *P* value	0.073 (0.027-0.118; *P* = 0.002[c])	
				I: Mavacamten ± BB or CCB monotherapy (n = 96)	-	EQ VAS	Score	8.5 (20.3)	
				C: Placebo ± BB or CCB monotherapy (n = 89)			Score	0.7 (20.1)	

Trial name	Geographic scope	Reference	Population	Treatment arm	Response rate	Instrument	Variable definition	Change in HRQoL/utility outcome values, mean (SD)	Timepoint
				Mavacamten ± BB or CCB monotherapy vs. Placebo ± BB or CCB monotherapy (n = 96 vs. 89)			Difference – unadjusted (95% CI), *P* value	7.8 (2.0-13.6; *P* = 0.009) ↑	
							Difference - adjusted[b] (95 CI%), *P* value	7.5 (1.8-13.2; *P* = 0.010) ↑	
				I: Mavacamten ± BB or CCB monotherapy (n = 96)	-	EQ-5D-5L	Mean utility difference NYHA class I vs. II (95% CI)	−0.084 (−0.114 to −0.054)	Baseline to week 30
							Mean utility difference NYHA class III-IV vs. I (95% CI)	−0.242 (−0.336 to −0.147)	
							Mean utility difference NYHA class III-IV vs. II (95% CI)	−0.158 (−0.244 to −0.071)[c]	
				C: Placebo ± BB or CCB monotherapy (n = 89)			Mean utility difference NYHA class I vs. II (95% CI)	−0.102 (−0.139 to −0.065)[c]	

Trial name	Geographic scope	Reference	Population	Treatment arm	Response rate	Instrument	Variable definition	Change in HRQoL/utility outcome values, mean (SD)	Timepoint
							Mean utility difference NYHA class III-IV vs. I (95% CI)	−0.248 (−0.317 to −0.180)[c]	
							Mean utility difference NYHA class III-IV vs. II (95% CI)	−0.146 (−0.212 to −0.081)[c]	
				I: Mavacamten ± BB or CCB monotherapy (n = 96)			Mean health utility by NYHA class I	0.950	
							Mean health utility by NYHA class II	0.866	
							Mean health utility by NYHA class III-IV	0.708	
				C: Placebo ± BB or CCB monotherapy (n = 89)		EQ-5D-5L	Mean health utility by NYHA class I	0.952	Baseline to week 30
							Mean health utility by NYHA class II	0.850	

Trial name	Geographic scope	Reference	Population	Treatment arm	Response rate	Instrument	Variable definition	Change in HRQoL/utility outcome values, mean (SD)	Timepoint
							Mean health utility by NYHA class III-IV	0.704	
				Mavacamten ± BB or CCB monotherapy vs. Placebo ± BB or CCB monotherapy (n = 96 vs. 89)			Mean utility difference (95% CI) – NYHA class I	−0.002 (−0.033 to 0.029)	
							Mean utility difference (95% CI) – NYHA class II	0.016 (−0.023 to 0.054)	
							Mean utility difference (95% CI) – NYHA class III-IV	0.004 (−0.108 to 0.117)	
		Naidu et al. (2021)[97]	Adult patients (≥ 18 years) with symptomatic oHCM (gradient ≥ 50 mmHg and NYHA class II-III)	I: Mavacamten (n = 96)	NR	HCMSQ-SoB	Overall score: mean change from baseline	−1.82 (NR)	4 weeks
				I: Mavacamten (n = 86)	78.8%			−2.13 (NR)	6 weeks
				(n = 72)				−2.76 (NR)	10 weeks
				(n = 89)				−2.60 (NR)	14 weeks
				(n = 86)				−2.84 (NR)	18 weeks

Trial name	Geographic scope	Reference	Population	Treatment arm	Response rate	Instrument	Variable definition	Change in HRQoL/utility outcome values, mean (SD)	Timepoint
				(n = 82)				−2.58 (NR)	22 weeks
				(n = 81)				−2.90 (NR)	26 weeks
				(n = 85/108)	78.7%			−2.82 (2.68); *P* < 0.0001	30 weeks
				(n = 59)	NR			−0.25 (NR)	38 weeks
				C: Placebo (n = 101)	NR		Overall score: mean change from baseline	−0.71	4 weeks
				(n = 89)				−0.72 (NR)	6 weeks
				(n = 58)				−1.09 (NR)	10 weeks
				(n = 87)				−0.98 (NR)	14 weeks
				(n = 93)				−1.15 (NR)	18 weeks
				(n = 90)				−1.02 (NR)	22 weeks
				(n = 89)				−0.85 (NR)	26 weeks
				(n = 86/85)	78.8%			−0.85 (3.24); comparator	30 weeks
				(n = 53)	NR			−1.13 (NR)	38 weeks

Trial name	Geographic scope	Reference	Population	Treatment arm	Response rate	Instrument	Variable definition	Change in HRQoL/utility outcome values, mean (SD)	Timepoint
				Mavacamten vs. placebo	-		Overall score: LS mean difference (95% CI, −2,402 to −1,196); *P* < 0.0001; effect size −0.81	−1.799	30 weeks
EXPLORER-HCM NCT03470545		Jacoby et al. (2021)[98]	Patients with oHCM	I: Mavacamten + BB use (n = 94)	-	KCCQ-CSS	Overall score	14.2 (14.2)	Baseline to week 30
				I: Mavacamten (n = 29)				3.3 (13.7)	
				C: Placebo + BB use (n = 95)				11 (15)	
				C: Placebo (n = 33)				6.3 (13.8)	
MAVA-LTE NCT03723655			Patients with oHCM who had completed EXPLORER-HCM (EXPLORER-HCM cohort)	I:Mavacamten + BB use (n = 122)		KCCQ-CSS	Overall score	ND	Baseline to week 12
				I: Mavacamten + BB use (n = 41)				ND	Baseline to week 48

Trial name	Geographic scope	Reference	Population	Treatment arm	Response rate	Instrument	Variable definition	Change in HRQoL/utility outcome values, mean (SD)	Timepoint
				I: Mavacamten (n = 40)				ND	Baseline to week 12
				I: Mavacamten (n = 8)				ND	Baseline to week 48
Studies reporting on metoprolol									
NCT03532802	Denmark	Dybro et al. (2021)[54]	Patients with oHCM and NYHA functional class II or higher symptoms	I: Metoprolol (n = 29)	100%	KCCQ-CSS	Overall score	76.2 (16.5)	2 weeks
				C: Placebo (n = 29)	100%			73.8 (19.5)	2 weeks
Studies reporting on surgical interventions									
-	US	Serber et al. (2007)[99]	oHCM patients	ASA (n = 14)	100%	SF-12	Physical health summary	30 (7)	Baseline, before ASA
								40 (12)	Baseline to 3 months after ASA
							Mental health summary	43 (13)	Baseline, before ASA
								43 (13)	Baseline to 3 months after ASA

Trial name	Geographic scope	Reference	Population	Treatment arm	Response rate	Instrument	Variable definition	Change in HRQoL/utility outcome values, mean (SD)	Timepoint
				(n = 22)		The Minnesota Living with Heart Failure Questionnaire	Cardiac specific QoL	54 (27)	Baseline, before ASA
								28 (25)	Baseline to 3 months after ASA
		Balaram et al. (2012)[100]	Patients with oHCM	Mitral valve plication (with or without) (n = 124/132)	-	The Minnesota QoL score	Global QoL	39 (23)	Baseline
								27 (22); $P < 0.001$[c]	After treatment, at follow-up (the average time 5.6 + 3.9 years)
		Shalen et al. (2021)[101]	Patients who underwent septal myectomy for symptomatic oHCM	Myectomy: post-intervention amiodarone group (n = 27)	-	KCCQ	Overall score	41.5 (12.5)	Preoperative
					44.2%			40.9 (12.4)	Post-operative at day 30
				Subgroup: patients with a KCCQ score pre- and post-myectomy (n = NR)				40.9 (12.4)	pre-myectomy
								50.8 (11.0); $P = 0.134$[c]	post-myectomy at day 30

Trial name	Geographic scope	Reference	Population	Treatment arm	Response rate	Instrument	Variable definition	Change in HRQoL/utility outcome values, mean (SD)	Timepoint
-	US	Lin et al. (2019)[108]	Patients with oHCM	Septal myectomy + routine papillary muscle realignment (PMR) (n = 39)	-	KCCQ	-	40.7 (12.1)	Preoperative
								55.4 (9.1)	Post-operative (at 1-year)
-	Europe	Linde et al. (1999)[102]	Patients with oHCM	Inactive pacing (n = 40)	-	VAS	Alertness	3.26	Baseline
								3.05	3 months
								Mean difference (%): 0.21 (6); *P* = NS	Change from baseline
							Chest pain	3.54	Baseline
								2.51	3 months
								Mean difference (%): 1.03 (29); *P* < 0.01[d]	Change from baseline
							Dyspnea	5.08	Baseline
								4.07	3 months
								Mean difference (%): 1.01 (20); *P* < 0.01[d]	Change from baseline

Trial name	Geographic scope	Reference	Population	Treatment arm	Response rate	Instrument	Variable definition	Change in HRQoL/utility outcome values, mean (SD)	Timepoint
							Dizziness	3.08	Baseline
								2.26	3 months
								Mean difference (%): 0.82 (27); *P* = NS	Change from baseline
							Palpitations	4.34	Baseline
								2.82	3 months
								Mean difference (%): 1.52 (35); *P* < 0.001[d]	Change from baseline
							Cognitive functioning	2.83	Baseline
								2.07	3 months
								Mean difference (%): 0.75 (27); *P* < 0.05[d]	Change from baseline
							Quality of sleep	3.86	Baseline
								2.79	3 months
								Mean difference (%): 1.07 (28); *P* < 0.05[d]	Change from baseline
					-	VAS	Alertness	3.47	Baseline

Trial name	Geographic scope	Reference	Population	Treatment arm	Response rate	Instrument	Variable definition	Change in HRQoL/utility outcome values, mean (SD)	Timepoint
				Active pacing (n = 41)				2.81	3 months
								Mean difference (%): 0.66 (19); $P < 0.01$[d]	Change from baseline
							Chest pain	3.86	Baseline
								2.2	3 months
								Mean difference (%): 1.66 (43); $P < 0.001$[d]	Change from baseline
							Dyspnea	5.4	Baseline
								3.8	3 months
								Mean difference (%): 1.60 (30); $P < 0.001$[d]	Change from baseline
							Dizziness	3.65	Baseline
								2.37	3 months
								Mean difference (%): 1.28 (35); $P < 0.01$[d]	Change from baseline
							Palpitations	3.75	Baseline
								2.26	3 months

Trial name	Geographic scope	Reference	Population	Treatment arm	Response rate	Instrument	Variable definition	Change in HRQoL/utility outcome values, mean (SD)	Timepoint
								Mean difference (%): 1.49 (40); $P < 0.001$[d]	Change from baseline
							Cognitive functioning	2.82	Baseline
								3.01	3 months
								Mean difference (%): 0.19 (−7); P = NS	Change from baseline
							Quality of sleep	3.11	Baseline
								2.64	3 months
								Mean difference (%): 0.47 (15); P = NS	Change from baseline
				Inactive pacing	-	Karolinska questionnaire	Self-autonomy	1.81	Baseline
								1.69	3 months
								Difference (%): 0.12 (7); P = NS	Change from baseline
							Strenuous activity	2.68	Baseline
								2.6	3 months
								Difference (%): 0.08 (3); P = NS	Change from baseline

Trial name	Geographic scope	Reference	Population	Treatment arm	Response rate	Instrument	Variable definition	Change in HRQoL/utility outcome values, mean (SD)	Timepoint
							Sexual functioning	2.35	Baseline
								2.41	3 months
								Difference (%): −0.02 (−3); *P* = NS	Change from baseline
							Social functioning	1.71	Baseline
								1.57	3 months
								Difference (%): 0.14 (8); *P* = NS	Change from baseline
							Self-perceived restriction in health	2.7	Baseline
								2.26	3 months
								Difference (%): 0.44 (16); *P* = NS	Change from baseline
							Self-perceived health	1.85	Baseline
								1.72	3 months
								Difference (%): 0.13 (7); *P* = NS	Change from baseline
							Depression score	0.69	Baseline
								0.56	3 months

Trial name	Geographic scope	Reference	Population	Treatment arm	Response rate	Instrument	Variable definition	Change in HRQoL/utility outcome values, mean (SD)	Timepoint
								Difference (%): 0.13 (19); *P* = NS	Change from baseline
				Active pacing	-		Self-autonomy	2.13	Baseline
								1.52	3 months
								Difference (%): 0.61 (29); *P* < 0.001[d]	Change from baseline
							Strenuous activity	3.02	Baseline
								2.51	3 months
								Difference (%): 0.51 (17); *P* < 0.001[d]	Change from baseline
							Sexual functioning	2.01	Baseline
								1.86	3 months
								Difference (%): 0.15 (7); *P* = NS	Change from baseline
							Social functioning	1.76	Baseline
								1.44	3 months
								Difference (%): 0.32 (18); *P* < 0.01[d]	Change from baseline

Trial name	Geographic scope	Reference	Population	Treatment arm	Response rate	Instrument	Variable definition	Change in HRQoL/utility outcome values, mean (SD)	Timepoint
							Self-perceived restriction in health	2.66	Baseline
								1.81	3 months
								Difference (%): 0.85 (32); $P < 0.01$[d]	Change from baseline
							Self-perceived health	2.11	Baseline
								1.68	3 months
								Difference (%): 0.39 (18); $P < 0.05$[d]	Change from baseline
							Depression score	0.46	Baseline
								0.38	3 months
								Difference (%): 0.08 (17); P = NS	Change from baseline
-	Germany	Boekstegers et al. (2001)[103]	Patients symptomatic oHCM (NYHA functional class 2.8 +/- 0.6) and an echocardiographically determined LVOT gradient of ≥ 30 mmHg at rest	Pressure-guided NSMR by small septal infarction	-	SF-12	QoL, N = 50	31 (8)	Baseline
							QoL, N = 50	26 (8)	28 days
							QoL, N = 49	25 (9)	4-6 months
							QoL, N = 25	24 (5)	24 months

Trial name	Geographic scope	Reference	Population	Treatment arm	Response rate	Instrument	Variable definition	Change in HRQoL/utility outcome values, mean (SD)	Timepoint
-	Spain	Galve et al. (2010)[104]	Patients with oHCM submitted to pacing	DDD or VDD pacemaker (n = 50)	100%	SF-36 (value digitized)	Physical component	31.32 (6.99)	Baseline
							Physical component	35.98 (8.67)	3-month
							Physical component	37.15 (9.32)	1-year
							Mental component	31.32 (8.8)	Baseline
							Mental component	36.11 (7.89)	3-month
							Mental component	40.38 (9.06)	1-year
		Berruezo et al. (2011)[105]	oHCM patients with significant LV obstruction	(Atrio-) biventricular pacing	100%	The Minnesota Living with Heart Failure Questionnaire	QoL	54 (16)	Baseline
							QoL	28 (13)	3 months
							QoL	27 (15)	1 year
-	Sweden	Gadler et al. (1999)[106]	Patients who were refractory to drugs with oHCM	I: DDD (active pacemaker) (n = 5)	-	Karolinska questionnaire on a VAS	Chest pain	0.89	12 weeks
							Dyspnea	1.53	
							Palpitations	0.32	
							Dizziness	0.27	
							Chest pain	2.44	

Trial name	Geographic scope	Reference	Population	Treatment arm	Response rate	Instrument	Variable definition	Change in HRQoL/utility outcome values, mean (SD)	Timepoint
				C: Inactive (inactive pacemaker) (n = 5)			Dyspnea	2.26	
							Palpitations	0.78	
							Dizziness	0.49	
				DDD vs. Inactive pacemaker (n = 5 vs. 5)			Chest pain	Difference: −1.55; *P* < 0.01[e]	
							Dyspnea	Difference: −0.73; *P*: NS	
							Palpitations	Difference: −0.46; *P* < 0.06[e]	
							Dizziness	Difference: −0.22; *P* = NS	
-	Japan	Akita et al. (2018)[107]	Patients with drug-refractory oHCM	PTSMA (n = 47)	-	KCCQ-12 (value digitized)	-	56 (21.3)	Baseline
							Change in KCCQ score (good responders)	25.77 (20.66)	Before/after PTSMA (change)
							Change in KCCQ score (poor responders)	6.89 (20.28)	Before/after PTSMA (change)

ASA = alcoholic septal ablation; BB = beta-blocker; CCB = calcium channel blocker; HCM = hypertrophic cardiomyopathy; HCMSQ-SoB = Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath; HRQoL = health-related quality of life; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score; LVOT = left ventricular outflow tract; ND = not determined; NR = not reported; NS = not significant; NSMR = non-surgical myocardial reduction; NYHA = New York Heart Association; oHCM = obstructive hypertrophic cardiomyopathy; PTSMA = percutaneous transluminal septal myocardial ablation; SD = standard deviation; SF-12 = SF-12 Health Survey; SRT = septal reduction therapy; US = United States; VAS = visual analog scale.

[a] Model estimated least-square.

[b] Scores were compared between the 2 arms using linear regression, and the proportions of patients with a meaningful improvement were compared using logistic regression. The meaningful change thresholds were estimated using both distribution- and anchor-based approaches.
[c] *P* < 0.05 were considered statistically significant.
[d] *P* value of ≥ 0.05 was considered statistically significant.
[e] Zero millimeters indicated no symptoms. Increasing numbers of millimeters on the VAS indicated progressive severity of symptoms.

I.3 Supplementary information for the SLR

I.3.1 Search syntax

I.3.1.1 Economic search strategy for Embase, MEDLINE, PsychINFO, and EconLit in ProQuest: original search

Table 74. Economic search strategy for Embase, MEDLINE, PsychINFO, and EconLit in ProQuest (searched 4 August 2021)

Set#	Searched for	Results
S1	TI,AB("hypertrophic subaortic stenosis" OR "muscular subaortic stenosis" OR "hypertrophic cardiomyopathy" OR "hypertrophic obstructive cardiomyopathy")	41428*
S2	EMB.EXACT("hypertrophic cardiomyopathy") OR EMB.EXACT("hypertrophic obstructive cardiomyopathy") OR EMB.EXACT("subvalvular aortic stenosis")	30890*
S3	MESH.EXACT("Cardiomyopathy, Hypertrophic") OR MESH.EXACT("Cardiomyopathy, Hypertrophic, Familial")	15621*
S4	S1 OR S2 OR S3	54928*
S5	TI,AB(mavacamten OR MYK461) OR EMB.EXACT("mavacamten")	130°
S6	TI,AB(propanolol OR Inderal OR Corotrend OR Avlocardyl OR Sumial OR InnoPran OR Hemangeol) OR EMB.EXACT("propranolol") OR MESH.EXACT("Propranolol")	135342*
S7	TI,AB(atenolol OR Tenoretic OR Tenormin) OR EMB.EXACT("atenolol") OR MESH.EXACT("atenolol")	41161*
S8	TI,AB(bisoprolol OR Monocor OR Zebeta OR Cardicor OR Congescor) OR EMB.EXACT("bisoprolol") OR MESH.EXACT("bisoprolol")	12609*
S9	TI,AB(metoprolol OR Lopressor OR Toprol OR Metolar OR Betaloc) OR EMB.EXACT("metoprolol") OR MESH.EXACT ("metoprolol")	43846*
S10	TI,AB(nadolol OR corgard) OR EMB.EXACT("nadolol") OR MESH.EXACT ("nadolol")	7094*
S11	TI,AB(pindolol OR Visken) OR EMB.EXACT ("pindolol") OR MESH.EXACT ("pindolol")	6649*
S12	TI,AB(sotalol OR Betapace OR Sotalex OR Sotacor OR Sotylize) OR EMB.EXACT("sotalol") OR MESH.EXACT("Sotalol")	17360*
S13	TI,AB(disopyramide OR Norpace OR Rythmodan) OR EMB.EXACT("disopyramide") OR MESH.EXACT("Disopyramide")	10170*
S14	TI,AB(verapamil OR "Flamon Retard" OR Verapabene OR Falicard OR Isoptin OR Flamon OR Veramil OR verap OR verelan OR verelanpm OR coverahs) OR EMB.EXACT("verapamil") OR MESH.EXACT("Verapamil")	86432*
S15	TI,AB(diltiazem OR cardizem OR Dilacorxr OR Tildiem OR cartiaxt OR diltiaxt OR diltzac OR matzimla OR tiazac) OR EMB.EXACT("diltiazem") OR MESH.EXACT("Diltiazem")	40410*

Set#	Searched for	Results
S16	TI,AB(ventricular septal myectomy OR "septal myectomy" OR "myectomy" OR "morrow procedure" OR "ventricular myotomy")	2708°
S17	TI,AB("septal alcohol ablation" OR "septal ablation" OR "septal reduction therapy" OR "septal therapy" OR (septal NEAR/3 ablation)) OR EMB.EXACT("alcohol septal ablation")	2217°
S18	TI,AB(LCZ696 OR "LCZ 696" OR "LCZ-696" OR "sacubitril valsartan" OR "angiotensin receptor neprilysin inhibitor" OR "entresto")	2351°
S19	TI,AB("CK 274" OR "CK-274" OR "CK 3773274" OR "CK-3773274")	7°
S20	TI,AB("cibenzoline" OR "cifenline") OR EMB.EXACT.EXPLODE("cibenzoline")	939°
S21	S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20	326843*
S22	S4 AND S21	7692*
S23	EMB.EXACT("Cost effectiveness analysis")	166524*
S24	MESH.EXACT("Cost-benefit analysis")	90921*
S25	MESH.EXACT("Economics")	462371*
S26	AB(cost NEAR/1 effectiveness) AND AB(costs or cost)	156225*
S27	TI(cost NEAR/1 effectiveness)	61861*
S28	EMB.EXACT("Cost benefit analysis")	90974*
S29	EMB.EXACT("Economic aspect")	127706*
S30	EMB.EXACT("Socioeconomics")	157237*
S31	MESH.EXACT("Economics, pharmaceutical")	3000°
S32	EMB.EXACT("Health economics")	41089*
S33	MESH.EXACT("Costs and cost analysis")	51663*
S34	MESH.EXACT("Value of life")	6256*
S35	TI,AB(Economic* OR pharmacoeconomic* OR price* OR pricing)	1406010*
S36	TI,AB,IF(monte carlo)	139362*
S37	EMB.EXACT("Probability")	133046*
S38	MESH.EXACT("Decision Theory" OR "Decision Trees")	13251*
S39	EMB.EXACT("Decision Tree")	16335*
S40	MESH.EXACT("Markov chains")	15926*
S41	EMB.EXACT("Statistical Model")	197864*
S42	MESH.EXACT("Monte carlo method")	30878*
S43	EMB.EXACT("Decision Theory")	2817°
S44	EMB.EXACT("Monte carlo method")	45313*

Set#	Searched for	Results
S45	TI,AB,IF(markov)	76938*
S46	AB,IF(cost* NEAR/2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes))	674850*
S47	TI,AB,IF(value NEAR/2 (money or monetary))	10587*
S48	TI,AB,IF(Decision* NEAr/2 (tree* or analy* or model*))	128894*
S49	TI,IF(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed)	2645467*
S50	MESH.EXACT.EXPLODE("Costs and cost analysis")	264036*
S51	EMB.EXACT("Economics")	250168*
S52	EMB.EXACT("Cost")	64312*
S53	AB,IF(economic model*)	248759*
S54	MESH.EXACT("Models, economic")	11430*
S55	EMB.EXACT("Cost utility analysis")	11093*
S56	TI,AB(cost NEAR/2 effectiveness)	173045*
S57	TI,AB(cost NEAR/2 utility)	19650*
S58	TI,AB(cost NEAR/2 benefit)	80096*
S59	S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58	4412514*
S60	S22 AND S59	72°
S61	MESH.EXACT("Economics")	462371*
S62	EMB.EXACT("Economic aspect")	127706*
S63	EMB.EXACT("Socioeconomics")	157237*
S64	MESH.EXACT("Economics, pharmaceutical")	3000°
S65	EMB.EXACT("Health economics")	41089*
S66	MESH.EXACT("Costs and cost analysis")	51663*
S67	MESH.EXACT("Value of life")	6256*
S68	TI,AB(Economic* OR pharmacoeconomic* OR price* OR pricing)	1406010*
S69	MESH.EXACT("Hospital costs")	11804*
S70	MESH.EXACT("Employer health costs")	1094°
S71	MESH.EXACT("Cost savings")	12728*
S72	MESH.EXACT("Direct service costs")	1203°
S73	EMB.EXACT("Financial management")	124069*

Set#	Searched for	Results
S74	EMB.EXACT("Health care financing")	14015*
S75	MESH.EXACT.EXPLODE("Budgets")	14187*
S76	MESH.EXACT.EXPLODE("Economics, medical")	14577*
S77	TI,AB(Low NEAR/1 cost)	224472*
S78	MESH.EXACT("Drug costs")	17499*
S79	MESH.EXACT("Deductibles and Coinsurance")	1779°
S80	EMB.EXACT("Health care cost")	205807*
S81	MESH.EXACT("Health expenditures")	23151*
S82	TI,AB(Cost NEAR/1 variable)	3471°
S83	EMB.EXACT("Cost of illness")	20683*
S84	MESH.EXACT("Capital expenditures")	1996°
S85	MESH.EXACT("Cost allocation")	2016°
S86	EMB.EXACT("Hospital cost")	24026*
S87	MESH.EXACT("Cost control")	22318*
S88	MESH.EXACT.EXPLODE("Economics, hospital")	25653*
S89	MESH.EXACT("Cost sharing")	2611°
S90	MESH.EXACT("Cost of illness")	34442*
S91	TI,AB((Healthcare OR health*care) NEAR/1 cost*)	42701*
S92	TI,AB(Fiscal OR funding OR financial OR finance)	679641*
S93	MESH.EXACT.EXPLODE("Fees and charges")	34302*
S94	EMB.EXACT("Cost minimization analysis")	3801°
S95	TI,AB(Cost NEAR/1 estimate*)	47500*
S96	MESH.EXACT("Health care costs")	44918*
S97	MESH.EXACT("Economics, Nursing")	3975°
S98	MESH.EXACT("Medical savings accounts")	541°
S99	EMB.EXACT("Cost control")	75093*
S100	TI,AB(High NEAR/1 cost)	128202*
S101	TI,AB(Unit NEAR/1 cost*)	13029*
S102	TI,IF(Economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed)	2645467*
S103	MESH.EXACT.EXPLODE("Costs and cost analysis")	264036*
S104	EMB.EXACT("Economics")	250168*

Set#	Searched for	Results
S105	EMB.EXACT("Cost")	64312*
S106	AB,IF(economic model*)	248759*
S107	MESH.EXACT("Models, economic")	11430*
S108	MESH.EXACT("Economics, Dental")	1894°
S109	EMB.EXACT("Budget")	36151*
S110	TI,AB,IF(budget*)	142831*
S111	TI,AB(Productivit*)	214489*
S112	TI,AB("Health care" AND cost*)	159142*
S113	TI,AB("Length of stay")	190253*
S114	TI,AB(Health AND resource)	339559*
S115	TI,AB(Resource NEAR/2 utili*ation)	43069*
S116	TI,AB(Hospitali*ation NEAR/2 (rate OR frequency))	33757*
S117	TI,AB(Hospitali*ation)	441563*
S118	EMB.EXACT("Productivity")	56303*
S119	TI,AB(Resource NEAR/3 use)	75745*
S120	TI,AB(Visit NEAR/3 (inpatient OR outpatient OR ER OR emergency OR GP))	82463*
S121	TI,AB(Lost AND work* AND day*)	8997*
S122	S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92 OR S93 OR S94 OR S95 OR S96 OR S97 OR S98 OR S99 OR S100 OR S101 OR S102 OR S103 OR S104 OR S105 OR S106 OR S107 OR S108 OR S109 OR S110 OR S111 OR S112 OR S113 OR S114 OR S115 OR S116 OR S117 OR S118 OR S119 OR S120 OR S121	5233732*
S123	S4 AND S122	1114°
S124	MESH.EXACT("Quality-Adjusted Life Years") OR EMB.EXACT("quality adjusted life year")	45468*
S125	TI,AB,SU("quality adjusted" OR "adjusted life year*")	65599*
S126	TI,AB,SU(qaly OR qald OR qale OR qtime)	36215*
S127	TI,AB,SU("illness state$1" OR "health state$1")	21895*
S128	TI,AB,SU(health$1 year$1 equivalent$1)	22003*
S129	TI,AB,SU(hui OR hui1 OR hui2 OR hui3)	7430*
S130	TI,AB,SU(multiattribute OR "multi attribute$1")	2728°

Set#	Searched for	Results
S131	TI,AB,SU(utility NEAR/3 (score$1 OR value$2 or valuation or valuing or health OR cost or costing OR measure$2 or measurement or measuring OR disease$2 OR mean OR gain or gains OR index$2 or indexing))	71696*
S132	TI,AB,SU(utilities)	665655*
S133	TI,AB,SU(eq-5d OR eq5d OR eq-5 OR eq5 OR "euro qual" OR euroqual OR "euro qual5d" OR euroqual5d OR "euro qol" OR euroqol OR "euro qol5d" OR euroqol5d OR "euro quol" OR euroquol OR "euro quol5d" OR euroquol5d OR "eur qol" OR eurqol OR "eur qol5d" OR "eur qol5d" OR eur?qul OR eur?qul5d OR "euro* quality of life" OR "european qol")	42542*
S134	TI,AB,SU((euro or euroqol or "Euro QOL" or EQ) NEAR/3 (5-d OR 5d OR 5-dimension OR 5dimension* OR 5-domain OR 5domain))	34264*
S135	TI,AB(sf6 OR "sf 6" OR sf6d OR "sf 6d" OR "sf six" OR sfsix OR sf8 OR "sf 8" OR "sf eight" OR sfeight)	7922*
S136	TI,AB(sf12 OR "sf 12" OR "sf twelve" OR sftwelve)	15475*
S137	TI,AB(15D OR 15-D OR "15 dimension")	12231*
S138	TI,AB(sf16 OR "sf 16" OR "sf sixteen" OR sfsixteen)	61°
S139	TI,AB(sf20 OR "sf 20" OR "sf twenty" OR sftwenty)	466°
S140	TI,AB,SU(sf36* OR "sf 36*" OR "sf thirtysix" OR "sf thirty six")	69650*
S141	TI,AB("standard gamble$1" OR sg)	31074*
S142	TI,AB,SU("time trade off$1" OR "time tradeoff$1" OR tto OR timetradeoff$1)	5800*
S143	TI,AB("rating scal*")	204770*
S144	TI,AB("linear scal*")	2002°
S145	TI,AB("linear analog*")	1492°
S146	TI,AB("visual analog*" OR "VAS")	228275*
S147	(MESH.EXACT("Quality of Life") OR EMB.EXACT("quality of life")) AND TI,AB,IF(quality of life OR qol NEAR (score[*1] or measure[*1]))	588536*
S148	(MESH.EXACT("Quality of Life") OR EMB.EXACT("quality of life")) AND TI,AB,IF(health NEAR/3 status)	67258*
S149	TI,AB,SU(quality of life OR qol) AND (MESH.EXACT("Cost-Benefit Analysis") OR EMB.EXACT("cost benefit analysis"))	27916*
S150	(TI,AB,SU((qol OR hrqol OR quality of life) OR (EMB.EXACT(*quality of life)) OR MESH.EXACT(*Quality of Life))) AND (AB(qol OR hrqol* OR quality of life NEAR/2 (increas* OR decrease* OR improv* OR declin* OR reduc* OR high* OR low* OR effect OR effects OR worse OR score OR scores OR change[*1] OR impact[*1] OR impacted OR deteriorat*)))	359221*
S151	(MESH.EXACT("Cost-Benefit Analysis") OR EMB.EXACT("cost benefit analysis")) AND TI,AB,IF(cost-effectiveness ratio* AND (perspective* OR life expectanc*))	5887*
S152	(MESH.EXACT("Quality of Life") OR EMB.EXACT("quality of life")) AND TI(quality of life OR qol)	189384*

Set#	Searched for	Results
S153	(MESH.EXACT("Quality of Life") OR EMB.EXACT("quality of life")) AND TI,AB,IF(quality of life OR qol NEAR/3 (improv* or chang*))	588793*
S154	(MESH.EXACT("Quality of Life") OR EMB.EXACT("quality of life")) AND TI,AB,IF(health-related quality of life)	115839*
S155	EMB.EXACT("economic model") OR MESH.EXACT("Models, Economic")	14053*
S156	Ti,AB("Kansas City Cardiomyopathy Questionnaire" OR "KCCQ")	1275°
S157	Ti,AB("Symptom Questionnaire Shortness of Breath" OR "HCMSQ-SoB")	2°
S158	S124 OR S125 OR S126 OR S127 OR S128 OR S129 OR S130 OR S131 OR S132 OR S133 OR S134 OR S135 OR S136 OR S137 OR S138 OR S139 OR S140 OR S141 OR S142 OR S143 OR S144 OR S145 OR S146 OR S147 OR S148 OR S149 OR S150 OR S151 OR S152 OR S153 OR S154 OR S155 OR S156 OR S157	1897130*
S159	S4 AND S158	1006°
S160	S60 OR S123 OR S159	2052°

* Duplicates are removed from the search, but included in the result count.
° Duplicates are removed from the search and from the result count.

I.3.1.2 Economic search strategy for Embase, MEDLINE, PsychINFO, and EconLit in ProQuest: update search

Table 75. Economic search strategy for Embase, MEDLINE, PsychINFO, and EconLit in ProQuest (searched 3 December 2021)

Set#	Searched for	Results
S1	TI,AB("hypertrophic subaortic stenosis" OR "muscular subaortic stenosis" OR "hypertrophic cardiomyopathy" OR "hypertrophic obstructive cardiomyopathy")	42240*
S2	EMB.EXACT("hypertrophic cardiomyopathy") OR EMB.EXACT("hypertrophic obstructive cardiomyopathy") OR EMB.EXACT("subvalvular aortic stenosis")	31614*
S3	MESH.EXACT("Cardiomyopathy, Hypertrophic") OR MESH.EXACT("Cardiomyopathy, Hypertrophic, Familial")	15968*
S4	S1 OR S2 OR S3	56029*
S5	TI,AB(mavacamten OR MYK461) OR EMB.EXACT("mavacamten")	142°
S6	TI,AB(propanolol OR Inderal OR Corotrend OR Avlocardyl OR Sumial OR InnoPran OR Hemangeol) OR EMB.EXACT("propranolol") OR MESH.EXACT("Propranolol")	136082*
S7	TI,AB(atenolol OR Tenoretic OR Tenormin) OR EMB.EXACT("atenolol") OR MESH.EXACT("atenolol")	41443*
S8	TI,AB(bisoprolol OR Monocor OR Zebeta OR Cardicor OR Congescor) OR EMB.EXACT("bisoprolol") OR MESH.EXACT("bisoprolol")	13007*
S9	TI,AB(metoprolol OR Lopressor OR Toprol OR Metolar OR Betaloc) OR EMB.EXACT("metoprolol") OR MESH.EXACT ("metoprolol")	44461*

Set#	Searched for	Results
S10	TI,AB(nadolol OR corgard) OR EMB.EXACT("nadolol") OR MESH.EXACT ("nadolol")	7151*
S11	TI,AB(pindolol OR Visken) OR EMB.EXACT ("pindolol") OR MESH.EXACT ("pindolol")	6652*
S12	TI,AB(sotalol OR Betapace OR Sotalex OR Sotacor OR Sotylize) OR EMB.EXACT("sotalol") OR MESH.EXACT("Sotalol")	17522*
S13	TI,AB(disopyramide OR Norpace OR Rythmodan) OR EMB.EXACT("disopyramide") OR MESH.EXACT("Disopyramide")	10212*
S14	TI,AB(verapamil OR "Flamon Retard" OR Verapabene OR Falicard OR Isoptin OR Flamon OR Veramil OR verap OR verelan OR verelanpm OR coverahs) OR EMB.EXACT("verapamil") OR MESH.EXACT("Verapamil")	86978*
S15	TI,AB(diltiazem OR cardizem OR Dilacorxr OR Tildiem OR cartiaxt OR diltiaxt OR diltzac OR matzimla OR tiazac) OR EMB.EXACT("diltiazem") OR MESH.EXACT("Diltiazem")	40702*
S16	TI,AB(ventricular septal myectomy OR "septal myectomy" OR "myectomy" OR "morrow procedure" OR "ventricular myotomy")	2785°
S17	TI,AB("septal alcohol ablation" OR "septal ablation" OR "septal reduction therapy" OR "septal therapy" OR (septal NEAR/3 ablation)) OR EMB.EXACT("alcohol septal ablation")	2256°
S18	TI,AB(LCZ696 OR "LCZ 696" OR "LCZ-696" OR "sacubitril valsartan" OR "angiotensin receptor neprilysin inhibitor" OR "entresto")	2638°
S19	TI,AB("CK 274" OR "CK-274" OR "CK 3773274" OR "CK-3773274")	8°
S20	TI,AB("cibenzoline" OR "cifenline") OR EMB.EXACT.EXPLODE("cibenzoline")	948°
S21	S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20	329886*
S22	S4 AND S21	7881*
S23	EMB.EXACT("Cost effectiveness analysis")	169385*
S24	MESH.EXACT("Cost-benefit analysis")	92877*
S25	MESH.EXACT("Economics")	465631*
S26	AB(cost NEAR/1 effectiveness) AND AB(costs or cost)	159878*
S27	TI(cost NEAR/1 effectiveness)	63228*
S28	EMB.EXACT("Cost benefit analysis")	92030*
S29	EMB.EXACT("Economic aspect")	128652*
S30	EMB.EXACT("Socioeconomics")	159635*
S31	MESH.EXACT("Economics, pharmaceutical")	3037°
S32	EMB.EXACT("Health economics")	41351*
S33	MESH.EXACT("Costs and cost analysis")	52072*
S34	MESH.EXACT("Value of life")	6276*

Set#	Searched for	Results
S35	TI,AB(Economic* OR pharmacoeconomic* OR price* OR pricing)	1437695*
S36	TI,AB,IF(monte carlo)	142281*
S37	EMB.EXACT("Probability")	136706*
S38	MESH.EXACT("Decision Theory" OR "Decision Trees")	13416*
S39	EMB.EXACT("Decision Tree")	17142*
S40	MESH.EXACT("Markov chains")	16210*
S41	EMB.EXACT("Statistical Model")	199677*
S42	MESH.EXACT("Monte carlo method")	31479*
S43	EMB.EXACT("Decision Theory")	2826°
S44	EMB.EXACT("Monte carlo method")	46378*
S45	TI,AB,IF(markov)	78809*
S46	AB,IF(cost* NEAR/2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes))	688953*
S47	TI,AB,IF(value NEAR/2 (money or monetary))	10806*
S48	TI,AB,IF(Decision* NEAr/2 (tree* or analy* or model*))	133115*
S49	TI,IF(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed)	2681438*
S50	MESH.EXACT.EXPLODE("Costs and cost analysis")	268546*
S51	EMB.EXACT("Economics")	251220*
S52	EMB.EXACT("Cost")	64802*
S53	AB,IF(economic model*)	255467*
S54	MESH.EXACT("Models, economic")	11628*
S55	EMB.EXACT("Cost utility analysis")	11330*
S56	TI,AB(cost NEAR/2 effectiveness)	176907*
S57	TI,AB(cost NEAR/2 utility)	20220*
S58	TI,AB(cost NEAR/2 benefit)	81468*
S59	S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58	4488968*
S60	S22 AND S59	72°
S61	MESH.EXACT("Economics")	465631*
S62	EMB.EXACT("Economic aspect")	128652*
S63	EMB.EXACT("Socioeconomics")	159635*

Set#	Searched for	Results
S64	MESH.EXACT("Economics, pharmaceutical")	3037°
S65	EMB.EXACT("Health economics")	41351*
S66	MESH.EXACT("Costs and cost analysis")	52072*
S67	MESH.EXACT("Value of life")	6276*
S68	TI,AB(Economic* OR pharmacoeconomic* OR price* OR pricing)	1437695*
S69	MESH.EXACT("Hospital costs")	11946*
S70	MESH.EXACT("Employer health costs")	1096°
S71	MESH.EXACT("Cost savings")	12894*
S72	MESH.EXACT("Direct service costs")	1210°
S73	EMB.EXACT("Financial management")	124831*
S74	EMB.EXACT("Health care financing")	14081*
S75	MESH.EXACT.EXPLODE("Budgets")	14256*
S76	MESH.EXACT.EXPLODE("Economics, medical")	14611*
S77	TI,AB(Low NEAR/1 cost)	232335*
S78	MESH.EXACT("Drug costs")	17710*
S79	MESH.EXACT("Deductibles and Coinsurance")	1796°
S80	EMB.EXACT("Health care cost")	209407*
S81	MESH.EXACT("Health expenditures")	23789*
S82	TI,AB(Cost NEAR/1 variable)	3542°
S83	EMB.EXACT("Cost of illness")	20930*
S84	MESH.EXACT("Capital expenditures")	1997°
S85	MESH.EXACT("Cost allocation")	2019°
S86	EMB.EXACT("Hospital cost")	24413*
S87	MESH.EXACT("Cost control")	22345*
S88	MESH.EXACT.EXPLODE("Economics, hospital")	25833*
S89	MESH.EXACT("Cost sharing")	2639°
S90	MESH.EXACT("Cost of illness")	35303*
S91	TI,AB((Healthcare OR health*care) NEAR/1 cost*)	44298*
S92	TI,AB(Fiscal OR funding OR financial OR finance)	700519*
S93	MESH.EXACT.EXPLODE("Fees and charges")	34462*
S94	EMB.EXACT("Cost minimization analysis")	3855°
S95	TI,AB(Cost NEAR/1 estimate*)	48554*
S96	MESH.EXACT("Health care costs")	45748*

Set#	Searched for	Results
S97	MESH.EXACT("Economics, Nursing")	3979°
S98	MESH.EXACT("Medical savings accounts")	541°
S99	EMB.EXACT("Cost control")	75926*
S100	TI,AB(High NEAR/1 cost)	132248*
S101	TI,AB(Unit NEAR/1 cost*)	13268*
S102	TI,IF(Economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed)	2681438*
S103	MESH.EXACT.EXPLODE("Costs and cost analysis")	268546*
S104	EMB.EXACT("Economics")	251220*
S105	EMB.EXACT("Cost")	64802*
S106	AB,IF(economic model*)	255467*
S107	MESH.EXACT("Models, economic")	11628*
S108	MESH.EXACT("Economics, Dental")	1896°
S109	EMB.EXACT("Budget")	36457*
S110	TI,AB,IF(budget*)	145119*
S111	TI,AB(Productivit*)	219857*
S112	TI,AB("Health care" AND cost*)	161950*
S113	TI,AB("Length of stay")	196829*
S114	TI,AB(Health AND resource)	350837*
S115	TI,AB(Resource NEAR/2 utili*ation)	44521*
S116	TI,AB(Hospitali*ation NEAR/2 (rate OR frequency))	35024*
S117	TI,AB(Hospitali*ation)	457156*
S118	EMB.EXACT("Productivity")	57141*
S119	TI,AB(Resource NEAR/3 use)	77749*
S120	TI,AB(Visit NEAR/3 (inpatient OR outpatient OR ER OR emergency OR GP))	85481*
S121	TI,AB(Lost AND work* AND day*)	9149*
S122	S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92 OR S93 OR S94 OR S95 OR S96 OR S97 OR S98 OR S99 OR S100 OR S101 OR S102 OR S103 OR S104 OR S105 OR S106 OR S107 OR S108 OR S109 OR S110 OR S111 OR S112 OR S113 OR S114 OR S115 OR S116 OR S117 OR S118 OR S119 OR S120 OR S121	5347284*
S123	S4 AND S122	1167°

Set#	Searched for	Results
S124	MESH.EXACT("Quality-Adjusted Life Years") OR EMB.EXACT("quality adjusted life year")	46857*
S125	TI,AB,SU("quality adjusted" OR "adjusted life year*")	67630*
S126	TI,AB,SU(qaly OR qald OR qale OR qtime)	37279*
S127	TI,AB,SU("illness state$1" OR "health state$1")	22386*
S128	TI,AB,SU(health$1 year$1 equivalent$1)	22711*
S129	TI,AB,SU(hui OR hui1 OR hui2 OR hui3)	7650*
S130	TI,AB,SU(multiattribute OR "multi attribute$1")	2786°
S131	TI,AB,SU(utility NEAR/3 (score$1 OR value$2 or valuation or valuing or health OR cost or costing OR measure$2 or measurement or measuring OR disease$2 OR mean OR gain or gains OR index$2 or indexing))	73642*
S132	TI,AB,SU(utilities)	682285*
S133	TI,AB,SU(eq-5d OR eq5d OR eq-5 OR eq5 OR "euro qual" OR euroqual OR "euro qual5d" OR euroqual5d OR "euro qol" OR euroqol OR "euro qol5d" OR euroqol5d OR "euro quol" OR euroquol OR "euro quol5d" OR euroquol5d OR "eur qol" OR eurqol OR "eur qol5d" OR "eur qol5d" OR eur?qul OR eur?qul5d OR "euro* quality of life" OR "european qol")	44382*
S134	TI,AB,SU((euro or euroqol or "Euro QOL" or EQ) NEAR/3 (5-d OR 5d OR 5-dimension OR 5dimension* OR 5-domain OR 5domain))	35675*
S135	TI,AB(sf6 OR "sf 6" OR sf6d OR "sf 6d" OR "sf six" OR sfsix OR sf8 OR "sf 8" OR "sf eight" OR sfeight)	8114*
S136	TI,AB(sf12 OR "sf 12" OR "sf twelve" OR sftwelve)	15882*
S137	TI,AB(15D OR 15-D OR "15 dimension")	12427*
S138	TI,AB(sf16 OR "sf 16" OR "sf sixteen" OR sfsixteen)	61°
S139	TI,AB(sf20 OR "sf 20" OR "sf twenty" OR sftwenty)	473°
S140	TI,AB,SU(sf36* OR "sf 36*" OR "sf thirtysix" OR "sf thirty six")	71013*
S141	TI,AB("standard gamble$1" OR sg)	31936*
S142	TI,AB,SU("time trade off$1" OR "time tradeoff$1" OR tto OR timetradeoff$1)	5924*
S143	TI,AB("rating scal*")	209540*
S144	TI,AB("linear scal*")	2054°
S145	TI,AB("linear analog*")	1505°
S146	TI,AB("visual analog*" OR "VAS")	234135*
S147	(MESH.EXACT("Quality of Life") OR EMB.EXACT("quality of life")) AND TI,AB,IF(quality of life OR qol NEAR (score[*1] or measure[*1]))	609652*
S148	(MESH.EXACT("Quality of Life") OR EMB.EXACT("quality of life")) AND TI,AB,IF(health NEAR/3 status)	68613*

Set#	Searched for	Results
S149	TI,AB,SU(quality of life OR qol) AND (MESH.EXACT("Cost-Benefit Analysis") OR EMB.EXACT("cost benefit analysis"))	28861*
S150	(TI,AB,SU((qol OR hrqol OR quality of life) OR (EMB.EXACT(*quality of life)) OR MESH.EXACT(*Quality of Life))) AND (AB(qol OR hrqol* OR quality of life NEAR/2 (increas* OR decrease* OR improv* OR declin* OR reduc* OR high* OR low* OR effect OR effects OR worse OR score OR scores OR change[*1] OR impact[*1] OR impacted OR deteriorat*)))	370617*
S151	(MESH.EXACT("Cost-Benefit Analysis") OR EMB.EXACT("cost benefit analysis")) AND TI,AB,IF(cost-effectiveness ratio* AND (perspective* OR life expectanc*))	6260*
S152	(MESH.EXACT("Quality of Life") OR EMB.EXACT("quality of life")) AND TI(quality of life OR qol)	194943*
S153	(MESH.EXACT("Quality of Life") OR EMB.EXACT("quality of life")) AND TI,AB,IF(quality of life OR qol NEAR/3 (improv* or chang*))	609909*
S154	(MESH.EXACT("Quality of Life") OR EMB.EXACT("quality of life")) AND TI,AB,IF(health-related quality of life)	120044*
S155	EMB.EXACT("economic model") OR MESH.EXACT("Models, Economic")	14332*
S156	Ti,AB("Kansas City Cardiomyopathy Questionnaire" OR "KCCQ")	1370°
S157	Ti,AB("Symptom Questionnaire Shortness of Breath" OR "HCMSQ-SoB")	3°
S158	S124 OR S125 OR S126 OR S127 OR S128 OR S129 OR S130 OR S131 OR S132 OR S133 OR S134 OR S135 OR S136 OR S137 OR S138 OR S139 OR S140 OR S141 OR S142 OR S143 OR S144 OR S145 OR S146 OR S147 OR S148 OR S149 OR S150 OR S151 OR S152 OR S153 OR S154 OR S155 OR S156 OR S157	1949595*
S159	S4 AND S158	1039°
S160	S60 OR S123 OR S159	2135°
S161	S160 and pd(>20210802)	94°

* Duplicates are removed from the search, but included in the result count.
° Duplicates are removed from the search and from the result count.

I.3.1.3 Economic search strategy for Embase, MEDLINE, PsychINFO, and EconLit in ProQuest: update search

Table 76. Economic search strategy for Embase, MEDLINE, PsychINFO, and EconLit in ProQuest (searched 23 May 2022)

Set#	Searched for	Results
S1	TI,AB(hypertrophic subaortic stenosis OR muscular subaortic stenosis OR "hypertrophic cardiomyopathy" OR hypertrophic obstructive cardiomyopathy)	44626
S2	EMB.EXACT("hypertrophic cardiomyopathy") OR EMB.EXACT("hypertrophic obstructive cardiomyopathy") OR EMB.EXACT("subvalvular aortic stenosis")	33529
S3	MESH.EXACT("Cardiomyopathy, Hypertrophic") OR MESH.EXACT("Cardiomyopathy, Hypertrophic, Familial")	16577

Set#	Searched for	Results
S4	S1 OR S2 OR S3	59063
S5	TI,AB(mavacamten OR MYK461) OR EMB.EXACT("mavacamten")	272
S6	TI,AB(propanolol OR Inderal OR Corotrend OR Avlocardyl OR Sumial OR InnoPran OR Hemangeol) OR EMB.EXACT("propranolol") OR MESH.EXACT("Propranolol")	136579
S7	TI,AB(atenolol OR Tenoretic OR Tenormin) OR EMB.EXACT("atenolol") OR MESH.EXACT("atenolol")	41972
S8	TI,AB(bisoprolol OR Monocor OR Zebeta OR Cardicor OR Congescor) OR EMB.EXACT("bisoprolol") OR MESH.EXACT("bisoprolol")	13936
S9	TI,AB(metoprolol OR Lopressor OR Toprol OR Metolar OR Betaloc) OR EMB.EXACT("metoprolol") OR MESH.EXACT ("metoprolol")	45861
S10	TI,AB(nadolol OR corgard) OR EMB.EXACT("nadolol") OR MESH.EXACT ("nadolol")	7235
S11	TI,AB(pindolol OR Visken) OR EMB.EXACT ("pindolol") OR MESH.EXACT ("pindolol")	6341
S12	TI,AB(sotalol OR Betapace OR Sotalex OR Sotacor OR Sotylize) OR EMB.EXACT("sotalol") OR MESH.EXACT("Sotalol")	17980
S13	TI,AB(disopyramide OR Norpace OR Rythmodan) OR EMB.EXACT("disopyramide") OR MESH.EXACT("Disopyramide")	10308
S14	TI,AB(verapamil OR "Flamon Retard" OR Verapabene OR Falicard OR Isoptin OR Flamon OR Veramil OR verap OR verelan OR verelanpm OR coverahs) OR EMB.EXACT("verapamil") OR MESH.EXACT("Verapamil")	87702
S15	TI,AB(diltiazem OR cardizem OR Dilacorxr OR Tildiem OR cartiaxt OR diltiaxt OR diltzac OR matzimla OR tiazac) OR EMB.EXACT("diltiazem") OR MESH.EXACT("Diltiazem")	41243
S16	TI,AB(ventricular septal myectomy OR "septal myectomy" OR "myectomy" OR "morrow procedure" OR "ventricular myotomy")	4740
S17	TI,AB("septal alcohol ablation" OR "septal ablation" OR "septal reduction therapy" OR "septal therapy" OR (septal NEAR/3 ablation)) OR EMB.EXACT("alcohol septal ablation")	3593
S18	TI,AB(LCZ696 OR "LCZ 696" OR "LCZ-696" OR "sacubitril valsartan" OR "angiotensin receptor neprilysin inhibitor" OR "entresto")	4719
S19	TI,AB("CK 274" OR "CK-274" OR "CK 3773274" OR "CK-3773274")	14
S20	TI,AB("cibenzoline" OR "cifenline") OR EMB.EXACT.EXPLODE("cibenzoline")	1251
S21	S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 S15 OR S16 OR S17 OR S18 OR S19 OR S20	254195
S22	S4 AND S21	7705
S23	TI,AB(clinical AND (trial or study or studies))	5905746
S24	TI,AB(random*) OR TI,AB,IF(placebo*) OR TI,AB(double NEAR/1 blind*)	3469290

Set#	Searched for	Results
S25	TI,AB(random*) OR TI,AB,IF(placebo*) OR TI,AB(sham)	3597445
S26	TI,AB("RCT")	78269
S27	TI,AB(random*AND (trial or study or studies))	14
S28	TI,AB(open-label)	152572
S29	TI,AB((singl* OR doubl* OR treb* or tripl*) NEAR/1 (blind[*3] OR mask[*3]))	468507
S30	TI,AB((singl* OR doubl* OR treb* or tripl*) NEAR/1 (blind[*3] OR mask[*3] OR dumm*))	468895
S31	TI,AB(placebo[*1])	593810
S32	TI,AB(random* NEAR/2 allocated)	86791
S33	EMB.EXACT.EXPLODE("Clinical trial")	1928212
S34	EMB.EXACT("Controlled clinical trial")	536803
S35	EMB.EXACT("Randomized controlled trial")	774547
S36	EMB.EXACT.EXPLODE("Randomization")	107089
S37	EMB.EXACT("Single blind procedure")	52572
S38	EMB.EXACT("Double blind procedure")	205725
S39	EMB.EXACT("Crossover procedure")	76252
S40	EMB.EXACT("Placebo")	432041
S41	EMB.EXACT("Triple blind procedure")	405
S42	EMB.EXACT("Multicenter study" OR "Phase 3 clinical trial" OR "Phase 4 clinical trial")	408445
S43	EMB.EXACT("Prospective study")	831118
S44	MESH.EXACT.EXPLODE("Randomized Controlled Trials as Topic" OR "Randomized Controlled Trial") OR MESH.EXACT.EXPLODE("Clinical Trials as Topic")	377004
S45	MESH.EXACT.EXPLODE("Random Allocation")	106880
S46	MESH.EXACT.EXPLODE("Double-Blind Method")	173031
S47	MESH.EXACT.EXPLODE("Single-Blind Method")	32189
S48	MESH.EXACT.EXPLODE("Placebos")	39331
S49	MESH.EXACT.EXPLODE("Cross-Over Studies")	54049
S50	MESH.EXACT.EXPLODE("Prospective Studies")	638963
S51	RTYPE("Clinical trial, phase i")	24234
S52	RTYPE("Clinical trial, phase ii")	38603
S53	RTYPE("Clinical trial, phase iii")	20946
S54	RTYPE("Clinical trial, phase iv")	2361

Set#	Searched for	Results
S55	RTYPE("Controlled clinical trial")	95041
S56	RTYPE("Randomized controlled trial")	581272
S57	RTYPE("Multicenter study")	325652
S58	RTYPE("Clinical trial")	631962
S59	RTYPE("Pragmatic Clinical Trial")	2141
S60	S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59	10820329
S61	S22 AND S60	1714
S62	TI,AB("Case control") OR TI,AB(case control NEAR/1 (study OR studies))	350218
S63	Cohort NEAR/1 (study OR studies)	1011353
S64	TI,AB(Cohort analys*)	911937
S65	TI,AB(Follow up NEAR/1 (study OR studies))	153587
S66	TI,AB(Observational NEAR/1 (study OR studies))	448340
S67	TI,AB("Cross sectional") OR TI,AB(cross sectional NEAR/1 (study OR studies))	1082649
S68	TI,AB(Epidemiologic[*1] NEAR/1 (study OR studies))	66598
S69	TI,AB(Longitudinal)	715564
S70	TI,AB(Retrospective)	1833746
S71	EMB.EXACT("Clinical study")	311615
S72	EMB.EXACT("Family study")	45351
S73	EMB.EXACT("Longitudinal study")	191581
S74	EMB.EXACT("Retrospective study")	1337067
S75	EMB.EXACT("Prospective study") NOT EMB.EXACT("Randomized controlled trials")	831118
S76	EMB.EXACT("Cohort analysis")	928116
S77	EMB.EXACT("Case control study")	208136
S78	EMB.EXACT("Follow up")	2050357
S79	EMB.EXACT("Observational study")	306417
S80	EMB.EXACT("Epidemiology")	1468829
S81	EMB.EXACT("Cross-sectional study")	519670
S82	EMB.EXACT("Disease registry")	19606
S83	MESH.EXACT("Epidemiologic studies")	9174

Set#	Searched for	Results
S84	MESH.EXACT.EXPLODE("Case control studies")	323562
S85	MESH.EXACT("Cross-sectional studies")	440624
S86	MESH.EXACT("Longitudinal Studies")	160452
S87	MESH.EXACT("Retrospective Studies")	1060280
S88	MESH.EXACT("Prospective Studies")	638963
S89	MESH.EXACT("Follow-Up Studies")	687459
S90	MESH("Observational Studies")	8139
S91	S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 ORS85 OR S85 OR S86 OR S87 OR S88 OR S89 OR S90	10473196
S92	S22 AND S91	2666
S93	S61 OR S92	3418
S94	TI,AB(case NEAR/1 (stud* OR report))	2043558
S95	EMB.EXACT("Case study")	143999
S96	EMB.EXACT("Abstract report" OR "Letter")	1257872
S97	RTYPE("Case reports")	2293313
S98	RTYPE("Letter")	2439380
S99	RTYPE("Historical article")	368724
S100	PSTYPE("Conference proceedings")	4329
S101	RTYPE("Conference abstract")	4560297
S102	RTYPE("Editorial")	1362872
S103	RTYPE("Note")	911699
S104	S94 OR S95 OR S96 OR S97 OR S98 OR S99 OR S100 OR S101 OR S102 OR S103	13151779
S105	S93 NOT S104	2470
S106	S105 and pd(>20211203)	159°
S107	(TI,AB("hypertrophic subaortic stenosis" OR "muscular subaortic stenosis" OR "hypertrophic cardiomyopathy" OR "hypertrophic obstructive cardiomyopathy")) and (ud(20211203-20220523))	1836°
S108	(EMB.EXACT("hypertrophic cardiomyopathy") OR EMB.EXACT("hypertrophic obstructive cardiomyopathy") OR EMB.EXACT("subvalvular aortic stenosis")) and (ud(20211203-20220523))	1624°
S109	(MESH.EXACT("Cardiomyopathy, Hypertrophic") OR MESH.EXACT("Cardiomyopathy, Hypertrophic, Familial")) and (ud(20211203-20220523))	822°

Set#	Searched for	Results
S110	(S1 OR S2 OR S3) and (ud(20211203-20220523))	2484°
S111	(TI,AB(mavacamten OR MYK461) OR EMB.EXACT("mavacamten")) and (ud(20211203-20220523))	54°
S112	(TI,AB(propanolol OR Inderal OR Corotrend OR Avlocardyl OR Sumial OR InnoPran OR Hemangeol) OR EMB.EXACT("propranolol") OR MESH.EXACT("Propranolol")) and (ud(20211203-20220523))	1512°
S113	(TI,AB(atenolol OR Tenoretic OR Tenormin) OR EMB.EXACT("atenolol") OR MESH.EXACT("atenolol")) and (ud(20211203-20220523))	689°
S114	(TI,AB(bisoprolol OR Monocor OR Zebeta OR Cardicor OR Congescor) OR EMB.EXACT("bisoprolol") OR MESH.EXACT("bisoprolol")) and (ud(20211203-20220523))	754°
S115	(TI,AB(metoprolol OR Lopressor OR Toprol OR Metolar OR Betaloc) OR EMB.EXACT("metoprolol") OR MESH.EXACT ("metoprolol")) and (ud(20211203-20220523))	1299°
S116	(TI,AB(nadolol OR corgard) OR EMB.EXACT("nadolol") OR MESH.EXACT ("nadolol")) and (ud(20211203-20220523))	135°
S117	(TI,AB(pindolol OR Visken) OR EMB.EXACT ("pindolol") OR MESH.EXACT ("pindolol")) and (ud(20211203-20220523))	23°
S118	(TI,AB(sotalol OR Betapace OR Sotalex OR Sotacor OR Sotylize) OR EMB.EXACT("sotalol") OR MESH.EXACT("Sotalol")) and (ud(20211203-20220523))	434°
S119	(TI,AB(disopyramide OR Norpace OR Rythmodan) OR EMB.EXACT("disopyramide") OR MESH.EXACT("Disopyramide")) and (ud(20211203-20220523))	74°
S120	(TI,AB(verapamil OR "Flamon Retard" OR Verapabene OR Falicard OR Isoptin OR Flamon OR Veramil OR verap OR verelan OR verelanpm OR coverahs) OR EMB.EXACT("verapamil") OR MESH.EXACT("Verapamil")) and (ud(20211203-20220523))	1216°
S121	(TI,AB(diltiazem OR cardizem OR Dilacorxr OR Tildiem OR cartiaxt OR diltiaxt OR diltzac OR matzimla OR tiazac) OR EMB.EXACT("diltiazem") OR MESH.EXACT("Diltiazem")) and (ud(20211203-20220523))	648°
S122	(TI,AB(ventricular septal myectomy OR "septal myectomy" OR "myectomy" OR "morrow procedure" OR "ventricular myotomy")) and (ud(20211203-20220523))	248°
S123	(TI,AB("septal alcohol ablation" OR "septal ablation" OR "septal reduction therapy" OR "septal therapy" OR (septal NEAR/3 ablation)) OR EMB.EXACT("alcohol septal ablation")) and (ud(20211203-20220523))	144°
S124	(TI,AB(LCZ696 OR "LCZ 696" OR "LCZ-696" OR "sacubitril valsartan" OR "angiotensin receptor neprilysin inhibitor" OR "entresto")) and (ud(20211203-20220523))	578°
S125	(TI,AB("CK 274" OR "CK-274" OR "CK 3773274" OR "CK-3773274")) and (ud(20211203-20220523))	2°

Set#	Searched for	Results
S126	(TI,AB("cibenzoline" OR "cifenline") OR EMB.EXACT.EXPLODE("cibenzoline")) and (ud(20211203-20220523))	20°
S127	(S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20) and (ud(20211203-20220523))	7309*
S128	(S4 AND S21) and (ud(20211203-20220523))	408°
S129	(EMB.EXACT("Cost effectiveness analysis")) and (ud(20211203-20220523))	6858*
S130	(MESH.EXACT("Cost-benefit analysis")) and (ud(20211203-20220523))	5003*
S131	(MESH.EXACT("Economics")) and (ud(20211203-20220523))	9099*
S132	(AB(cost NEAR/1 effectiveness) AND AB(costs or cost)) and (ud(20211203-20220523))	11712*
S133	(TI(cost NEAR/1 effectiveness)) and (ud(20211203-20220523))	3330°
S134	(EMB.EXACT("Cost benefit analysis")) and (ud(20211203-20220523))	2626°
S135	(EMB.EXACT("Economic aspect")) and (ud(20211203-20220523))	2705°
S136	(EMB.EXACT("Socioeconomics")) and (ud(20211203-20220523))	4645°
S137	(MESH.EXACT("Economics, pharmaceutical")) and (ud(20211203-20220523))	49°
S138	(EMB.EXACT("Health economics")) and (ud(20211203-20220523))	735°
S139	(MESH.EXACT("Costs and cost analysis")) and (ud(20211203-20220523))	960°
S140	(MESH.EXACT("Value of life")) and (ud(20211203-20220523))	40°
S141	(TI,AB(Economic* OR pharmacoeconomic* OR price* OR pricing)) and (ud(20211203-20220523))	65850*
S142	(TI,AB,IF(monte carlo)) and (ud(20211203-20220523))	6826*
S143	(EMB.EXACT("Probability")) and (ud(20211203-20220523))	7870*
S144	(MESH.EXACT("Decision Theory" OR "Decision Trees")) and (ud(20211203-20220523))	367°
S145	(EMB.EXACT("Decision Tree")) and (ud(20211203-20220523))	1854°
S146	(MESH.EXACT("Markov chains")) and (ud(20211203-20220523))	692°
S147	(EMB.EXACT("Statistical Model")) and (ud(20211203-20220523))	3076°
S148	(MESH.EXACT("Monte carlo method")) and (ud(20211203-20220523))	1367°
S149	(EMB.EXACT("Decision Theory")) and (ud(20211203-20220523))	30°
S150	(EMB.EXACT("Monte carlo method")) and (ud(20211203-20220523))	2177°
S151	(TI,AB,IF(markov)) and (ud(20211203-20220523))	3651°
S152	(AB,IF(cost* NEAR/2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes))) and (ud(20211203-20220523))	39925*

Set#	Searched for	Results
S153	(TI,AB,IF(value NEAR/2 (money or monetary))) and (ud(20211203-20220523))	421°
S154	(TI,AB,IF(Decision* NEAr/2 (tree* or analy* or model*))) and (ud(20211203-20220523))	11110*
S155	(TI,IF(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed)) and (ud(20211203-20220523))	63050*
S156	(MESH.EXACT.EXPLODE("Costs and cost analysis")) and (ud(20211203-20220523))	10887*
S157	(EMB.EXACT("Economics")) and (ud(20211203-20220523))	1129°
S158	(EMB.EXACT("Cost")) and (ud(20211203-20220523))	1129°
S159	(AB,IF(economic model*)) and (ud(20211203-20220523))	13718*
S160	(MESH.EXACT("Models, economic")) and (ud(20211203-20220523))	484°
S161	(EMB.EXACT("Cost utility analysis")) and (ud(20211203-20220523))	560°
S162	(TI,AB(cost NEAR/2 effectiveness)) and (ud(20211203-20220523))	12458*
S163	(TI,AB(cost NEAR/2 utility)) and (ud(20211203-20220523))	1222°
S164	(TI,AB(cost NEAR/2 benefit)) and (ud(20211203-20220523))	2572°
S165	(S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58) and (ud(20211203-20220523))	708727*
S166	(S22 AND S59) and (ud(20211203-20220523))	0°
S167	(MESH.EXACT("Economics")) and (ud(20211203-20220523))	9099*
S168	(EMB.EXACT("Economic aspect")) and (ud(20211203-20220523))	2705°
S169	(EMB.EXACT("Socioeconomics")) and (ud(20211203-20220523))	4645°
S170	(MESH.EXACT("Economics, pharmaceutical")) and (ud(20211203-20220523))	49°
S171	(EMB.EXACT("Health economics")) and (ud(20211203-20220523))	735°
S172	(MESH.EXACT("Costs and cost analysis")) and (ud(20211203-20220523))	960°
S173	(MESH.EXACT("Value of life")) and (ud(20211203-20220523))	40°
S174	(TI,AB(Economic* OR pharmacoeconomic* OR price* OR pricing)) and (ud(20211203-20220523))	65850*
S175	(MESH.EXACT("Hospital costs")) and (ud(20211203-20220523))	334°
S176	(MESH.EXACT("Employer health costs")) and (ud(20211203-20220523))	2°
S177	(MESH.EXACT("Cost savings")) and (ud(20211203-20220523))	331°

Set#	Searched for	Results
S178	(MESH.EXACT("Direct service costs")) and (ud(20211203-20220523))	17°
S179	(EMB.EXACT("Financial management")) and (ud(20211203-20220523))	1915°
S180	(EMB.EXACT("Health care financing")) and (ud(20211203-20220523))	256°
S181	(MESH.EXACT.EXPLODE("Budgets")) and (ud(20211203-20220523))	181°
S182	(MESH.EXACT.EXPLODE("Economics, medical")) and (ud(20211203-20220523))	76°
S183	(TI,AB(Low NEAR/1 cost)) and (ud(20211203-20220523))	20717*
S184	(MESH.EXACT("Drug costs")) and (ud(20211203-20220523))	609°
S185	(MESH.EXACT("Deductibles and Coinsurance")) and (ud(20211203-20220523))	41°
S186	(EMB.EXACT("Health care cost")) and (ud(20211203-20220523))	8466*
S187	(MESH.EXACT("Health expenditures")) and (ud(20211203-20220523))	1252°
S188	(TI,AB(Cost NEAR/1 variable)) and (ud(20211203-20220523))	150°
S189	(EMB.EXACT("Cost of illness")) and (ud(20211203-20220523))	468°
S190	(MESH.EXACT("Capital expenditures")) and (ud(20211203-20220523))	3°
S191	(MESH.EXACT("Cost allocation")) and (ud(20211203-20220523))	13°
S192	(EMB.EXACT("Hospital cost")) and (ud(20211203-20220523))	927°
S193	(MESH.EXACT("Cost control")) and (ud(20211203-20220523))	115°
S194	(MESH.EXACT.EXPLODE("Economics, hospital")) and (ud(20211203-20220523))	412°
S195	(MESH.EXACT("Cost sharing")) and (ud(20211203-20220523))	77°
S196	(MESH.EXACT("Cost of illness")) and (ud(20211203-20220523))	1744°
S197	(TI,AB((Healthcare OR health*care) NEAR/1 cost*)) and (ud(20211203-20220523))	3059°
S198	(TI,AB(Fiscal OR funding OR financial OR finance)) and (ud(20211203-20220523))	42047*
S199	(MESH.EXACT.EXPLODE("Fees and charges")) and (ud(20211203-20220523))	360°
S200	(EMB.EXACT("Cost minimization analysis")) and (ud(20211203-20220523))	104°
S201	(TI,AB(Cost NEAR/1 estimate*)) and (ud(20211203-20220523))	2460°
S202	(MESH.EXACT("Health care costs")) and (ud(20211203-20220523))	1875°
S203	(MESH.EXACT("Economics, Nursing")) and (ud(20211203-20220523))	13°
S204	(MESH.EXACT("Medical savings accounts")) and (ud(20211203-20220523))	5°
S205	(EMB.EXACT("Cost control")) and (ud(20211203-20220523))	1827°

Set#	Searched for	Results
S206	(TI,AB(High NEAR/1 cost)) and (ud(20211203-20220523))	10640*
S207	(TI,AB(Unit NEAR/1 cost*)) and (ud(20211203-20220523))	533°
S208	(TI,IF(Economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed)) and (ud(20211203-20220523))	63050*
S209	(MESH.EXACT.EXPLODE("Costs and cost analysis")) and (ud(20211203-20220523))	10887*
S210	(EMB.EXACT("Economics")) and (ud(20211203-20220523))	1129°
S211	(EMB.EXACT("Cost")) and (ud(20211203-20220523))	1129°
S212	(AB,IF(economic model*)) and (ud(20211203-20220523))	13718*
S213	(MESH.EXACT("Models, economic")) and (ud(20211203-20220523))	484°
S214	(MESH.EXACT("Economics, Dental")) and (ud(20211203-20220523))	2°
S215	(EMB.EXACT("Budget")) and (ud(20211203-20220523))	903°
S216	(TI,AB,IF(budget*)) and (ud(20211203-20220523))	3337°
S217	(TI,AB(Productivit*)) and (ud(20211203-20220523))	12199*
S218	(TI,AB("Health care" AND cost*)) and (ud(20211203-20220523))	8194*
S219	(TI,AB("Length of stay")) and (ud(20211203-20220523))	18740*
S220	(TI,AB(Health AND resource)) and (ud(20211203-20220523))	30189*
S221	(TI,AB(Resource NEAR/2 utili*ation)) and (ud(20211203-20220523))	3017°
S222	(TI,AB(Hospitali*ation NEAR/2 (rate OR frequency))) and (ud(20211203-20220523))	2381°
S223	(TI,AB(Hospitali*ation)) and (ud(20211203-20220523))	39600*
S224	(EMB.EXACT("Productivity")) and (ud(20211203-20220523))	2453°
S225	(TI,AB(Resource NEAR/3 use)) and (ud(20211203-20220523))	5257*
S226	(TI,AB(Visit NEAR/3 (inpatient OR outpatient OR ER OR emergency OR GP))) and (ud(20211203-20220523))	7901*
S227	(TI,AB(Lost AND work* AND day*)) and (ud(20211203-20220523))	352°
S228	(S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92 OR S93 OR S94 OR S95 OR S96 OR S97 OR S98 OR S99 OR S100 OR S101 OR S102 OR S103 OR S104 OR S105 OR S106 OR S107 OR S108 OR S109 OR S110 OR S111 OR S112 OR S113 OR S114 OR S115 OR S116 OR S117 OR S118 OR S119 OR S120 OR S121) and (ud(20211203-20220523))	1109416*
S229	(S4 AND S122) and (ud(20211203-20220523))	191°
S230	(MESH.EXACT("Quality-Adjusted Life Years") OR EMB.EXACT("quality adjusted life year")) and (ud(20211203-20220523))	2884°

Set#	Searched for	Results
S231	(TI,AB,SU("quality adjusted" OR "adjusted life year*")) and (ud(20211203-20220523))	6194*
S232	(TI,AB,SU(qaly OR qald OR qale OR qtime)) and (ud(20211203-20220523))	2440°
S233	(TI,AB,SU("illness state$1" OR "health state$1")) and (ud(20211203-20220523))	1124°
S234	(TI,AB,SU(health$1 year$1 equivalent$1)) and (ud(20211203-20220523))	1480°
S235	(TI,AB,SU(hui OR hui1 OR hui2 OR hui3)) and (ud(20211203-20220523))	296°
S236	(TI,AB,SU(multiattribute OR "multi attribute$1")) and (ud(20211203-20220523))	149°
S237	(TI,AB,SU(utility NEAR/3 (score$1 OR value$2 or valuation or valuing or health OR cost or costing OR measure$2 or measurement or measuring OR disease$2 OR mean OR gain or gains OR index$2 or indexing))) and (ud(20211203-20220523))	5402*
S238	(TI,AB,SU(utilities)) and (ud(20211203-20220523))	45371*
S239	(TI,AB,SU(eq-5d OR eq5d OR eq-5 OR eq5 OR "euro qual" OR euroqual OR "euro qual5d" OR euroqual5d OR "euro qol" OR euroqol OR "euro qol5d" OR euroqol5d OR "euro quol" OR euroquol OR "euro quol5d" OR euroquol5d OR "eur qol" OR eurqol OR "eur qol5d" OR "eur qol5d" OR eur?qul OR eur?qul5d OR "euro* quality of life" OR "european qol")) and (ud(20211203-20220523))	5165*
S240	(TI,AB,SU((euro or euroqol or "Euro QOL" or EQ) NEAR/3 (5-d OR 5d OR 5-dimension OR 5dimension* OR 5-domain OR 5domain))) and (ud(20211203-20220523))	3014°
S241	(TI,AB(sf6 OR "sf 6" OR sf6d OR "sf 6d" OR "sf six" OR sfsix OR sf8 OR "sf 8" OR "sf eight" OR sfeight)) and (ud(20211203-20220523))	377°
S242	(TI,AB(sf12 OR "sf 12" OR "sf twelve" OR sftwelve)) and (ud(20211203-20220523))	920°
S243	(TI,AB(15D OR 15-D OR "15 dimension")) and (ud(20211203-20220523))	410°
S244	(TI,AB(sf16 OR "sf 16" OR "sf sixteen" OR sfsixteen)) and (ud(20211203-20220523))	4°
S245	(TI,AB(sf20 OR "sf 20" OR "sf twenty" OR sftwenty)) and (ud(20211203-20220523))	13°
S246	(TI,AB,SU(sf36* OR "sf 36*" OR "sf thirtysix" OR "sf thirty six")) and (ud(20211203-20220523))	3002°
S247	(TI,AB("standard gamble$1" OR sg)) and (ud(20211203-20220523))	1722°
S248	(TI,AB,SU("time trade off$1" OR "time tradeoff$1" OR tto OR timetradeoff$1)) and (ud(20211203-20220523))	278°
S249	(TI,AB("rating scal*")) and (ud(20211203-20220523))	12966*
S250	(TI,AB("linear scal*")) and (ud(20211203-20220523))	108°

Set#	Searched for	Results
S251	(TI,AB("linear analog*")) and (ud(20211203-20220523))	54°
S252	(TI,AB("visual analog*" OR "VAS")) and (ud(20211203-20220523))	18770*
S253	((MESH.EXACT("Quality of Life") OR EMB.EXACT("quality of life")) AND TI,AB,IF(quality of life OR qol NEAR (score[*1] or measure[*1]))) and (ud(20211203-20220523))	45668*
S254	((MESH.EXACT("Quality of Life") OR EMB.EXACT("quality of life")) AND TI,AB,IF(health NEAR/3 status)) and (ud(20211203-20220523))	2526°
S255	(TI,AB,SU(quality of life OR qol) AND (MESH.EXACT("Cost-Benefit Analysis") OR EMB.EXACT("cost benefit analysis"))) and (ud(20211203-20220523))	2191°
S256	((TI,AB,SU((qol OR hrqol OR quality of life) OR (EMB.EXACT(*quality of life)) OR MESH.EXACT(*Quality of Life))) AND (AB(qol OR hrqol* OR quality of life NEAR/2 (increas* OR decrease* OR improv* OR declin* OR reduc* OR high* OR low* OR effect OR effects OR worse OR score OR scores OR change[*1] OR impact[*1] OR impacted OR deteriorat*)))) and (ud(20211203-20220523))	30811*
S257	((MESH.EXACT("Cost-Benefit Analysis") OR EMB.EXACT("cost benefit analysis")) AND TI,AB,IF(cost-effectiveness ratio* AND (perspective* OR life expectanc*))) and (ud(20211203-20220523))	719°
S258	((MESH.EXACT("Quality of Life") OR EMB.EXACT("quality of life")) AND TI(quality of life OR qol)) and (ud(20211203-20220523))	11859*
S259	((MESH.EXACT("Quality of Life") OR EMB.EXACT("quality of life")) AND TI,AB,IF(quality of life OR qol NEAR/3 (improv* or chang*))) and (ud(20211203-20220523))	45652*
S260	((MESH.EXACT("Quality of Life") OR EMB.EXACT("quality of life")) AND TI,AB,IF(health-related quality of life)) and (ud(20211203-20220523))	9214*
S261	(EMB.EXACT("economic model") OR MESH.EXACT("Models, Economic")) and (ud(20211203-20220523))	689°
S262	(Ti,AB("Kansas City Cardiomyopathy Questionnaire" OR "KCCQ")) and (ud(20211203-20220523))	264°
S263	(Ti,AB("Symptom Questionnaire Shortness of Breath" OR "HCMSQ-SoB")) and (ud(20211203-20220523))	4°
S264	(S124 OR S125 OR S126 OR S127 OR S128 OR S129 OR S130 OR S131 OR S132 OR S133 OR S134 OR S135 OR S136 OR S137 OR S138 OR S139 OR S140 OR S141 OR S142 OR S143 OR S144 OR S145 OR S146 OR S147 OR S148 OR S149 OR S150 OR S151 OR S152 OR S153 OR S154 OR S155 OR S156 OR S157) and (ud(20211203-20220523))	167418*
S265	(S4 AND S158) and (ud(20211203-20220523))	0°
S266	(S60 OR S123 OR S159) and (ud(20211203-20220523))	719501*
S267	(S160 and pd(>20210802)) and (ud(20211203-20220523))	149°
S268	(S160 and pd(>20210802)) and (ud(20211203-20220522))	149°
S269	(S160 and pd(>20210802)) and (ud(20211203-20220522) and (pd(20211203-20220523)))	95°

Set#	Searched for	Results
S270	(S160 and pd(>20210802)) and (ud(20211203-20220522) and (pd(20211203-20220523)))	95
S271	(S160 and pd(>20210802)) and (ud(20211203-20220522))	149
S272	(S160 and pd(>20210802)) and (ud(20211203-20220522))	149°

I.3.1.4 Economic search strategy for CRD database search

Table 77. DARE, NHS EED, and HTA search strategy (searched 4 August 2021, 3 December 2021, 23 May 2022)

Search type	Search string	CRD database	4 Aug 2021	3 Dec 2021	23 May 2022
Title	Cardiomyopathy	DARE	31	0	0
Title	Cardiomyopathy	NHS EED	9	0	0
Title	Cardiomyopathy	HTA	14	0	0
Total			**54**	**0**	**0**

CRD = Centre for Reviews and Dissemination; DARE = Database of Abstracts of Reviews of Effects; NHS EED = National Health Service Economic Evaluation Database; HTA = health technology assessment.

I.3.1.5 HTA and other grey literature websites

Table 78. Overview of searches: HTA and other grey literature websites (searched 4 August 2021, 3 December 2021, 23 May 2022)

HTA	Search terms	4 Aug 2021	3 Dec 2021	23 May 2022
Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)/Agencia de Evaluación de Tecnologías Sanitarias (AETS)	"cardiomyopathy"	0	0	0
Canadian Agency for Drugs and Technologies in Health (CADTH)	"cardiomyopathy"	35	3	0
Gemeinsamer Bundesausschuss (G-BA)	"Hypertrophe Kardiomyopathie" In Nutzenbewertungsverfahren	19	3	3
Haute Autorité de Santé (HAS)	"Cardiomyopathie hypertrophique" In Les médicaments	31	1	1
Institute for Clinical and Economic Review (ICER)	"cardiomyopathy"	4	1	1
National Centre for Pharmacoeconomics Ireland (NCPE)	"cardiomyopathy"	1	0	0

HTA	Search terms	4 Aug 2021	3 Dec 2021	23 May 2022
National Institute for Health and Care excellence (NICE)	"cardiomyopathy"; Technology appraisal guidance	29	4	0
Pharmaceutical Benefits Advisory Committee (PBAC)	"cardiomyopathy"	9	0	0
Scottish Medicines Consortium (SMC)	"cardiomyopathy"	1	0	0
Tandvårds- och läkemedelsförmånsverket (TLV)	"cardiomyopathy" or "kardiomyopati"	11	2	0

AEMPS = Agencia Española de Medicamentos y Productos Sanitarios; AETS = Agencia de Evaluación de Tecnologías Sanitarias; CADTH = Canadian Agency for Drugs and Technologies in Health; G-BA = Gemeinsamer Bundesausschuss; HAS = Haute Autorité de Santé; ICER = Institute for Clinical and Economic Review; NCPE = National Centre for Pharmacoeconomics; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium; TLV = Tandvårds- och läkemedelsförmånsverket.

I.4 Included studies by region and outcomes

Table 79. Included studies by region and outcomes

Pharmacological treatments (5 studies)	Study location	EE	HCRU	Costs	HRQoL	Utilities
EXPLORER-HCM Olivotto, 2020[53] Spertus, 2021[63] Xie, 2021[96] Naidu, 2021[159] **EXPLORER-HCM and MAVA-LTE** Jacoby, 2021[98]	Multi-regional				✓	✓
EXPLORER-HCM Desai, 2022[161]	Multi-regional	✓				
TEMPO Dybro, 2021[54]	Denmark				✓	
ICER Study Wasfy, 2021[160] Beinfeld, 2022[42]	US	✓				
Surgical interventions (42 studies)	**Study location**	**EE**	**HCRU**	**Costs**	**HRQoL**	**Utilities**
Afanasyev, 2022[162]	Russia		✓			
Akita, 2018[107]	Japan		✓		✓	

Pharmacological treatments (5 studies)	Study location	EE	HCRU	Costs	HRQoL	Utilities
Bahaa, 2021[163]	Iraq		✓			
Balaram, 2012[100]	US		✓		✓	
Balaram, 2005[164]	US		✓			
Balaram, 2008[165]	US		✓			
Berruezo, 2011[105]	Spain				✓	
Boekstegers, 2001[103]	Germany				✓	
Bourque, 2022[166]	France		✓			
Butzner, 2021[167]	US		✓	✓		
Chothani, 2016[168]	US		✓	✓		
Collis, 2017[169]	UK		✓			
Collis, 2018[138]	UK		✓			
Gadler, 1999[106]	Sweden				✓	
Galve, 2010[104]	Spain				✓	
Holst, 2019[122]	US		✓			
Jain, 2019[171]	US		✓	✓		
Javidgonbadi, 2021[172]	Sweden		✓	✓		
Kim, 2016[111]	US		✓	✓		
Lin, 2019[108]	US				✓	
Linde, 1999[102]	EU				✓	
Mani, 2021[173]	India		✓			
Meng, 2022[174]	China		✓			
Morita, 2021[175]	US		✓			

Pharmacological treatments (5 studies)	Study location	EE	HCRU	Costs	HRQoL	Utilities
Osman, 2022[176]	US		✓	✓		
Panaich, 2014[123]	US		✓	✓		
Pruna-Guillen, 2021[177]	Spain		✓			
Serber, 2007[99]	US				✓	
*Shalen, 2019[190]	US		✓			
*PAPA-SMURPH Shalen, 2021[101]	US		✓		✓	
Singh, 2017[178]	US		✓			
Song, 2018[179]	US		✓			
Sun, 2022[180]	US		✓			
Sun, 2022[181]	US		✓			
Valdigem, 2021[182]	Brazil		✓			
Van der Merwe, 2018[183]	Belgium		✓			
Vassileva, 2011[184]	US		✓			
Verdugo, 2019[185] Cataldo, 2021[197]	Chile		✓			
Wei, 2022[186]	China		✓			
Wong, 2021[187]	US		✓			
Yandrapalli, 2022[188]	US		✓	✓		
Yatabe, 2019 (non-cardiac surgery)[189]	Japan		✓			
Disease level (6 studies)	**Study location**	**EE**	**HCRU**	**Costs**	**HRQoL**	**Utilities**
Akhtar, 2020[191]	US		✓	✓		
Butzner, 2022[198]	US		✓			
Butzner, 2022[194]	US		✓			

Pharmacological treatments (5 studies)	Study location	EE	HCRU	Costs	HRQoL	Utilities
Desai, 2019[192]	US		✓	✓		
Jain, 2021[170,195]	US		✓	✓		
Rungatscher, 2016[193]	US		✓	✓		

EE = economic evaluation; HCRU = healthcare resource utilization; HRQoL = health-related quality of life.
Note: Color coding: no color, original search; light green, December 2021 update; dark green, May 2022 update
*Studies focus on prophylactic amiodarone with septal myectomy.

Appendix J. Literature searches for input to the health economic model

Not applicable.

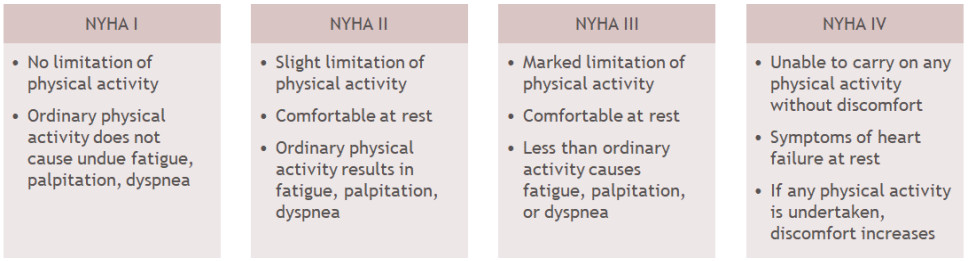
Appendix K. Additional information

Table 80. Cumulative incidence of adverse outcomes in patients with HCM diagnosed aged < 40 years, compared with > 60 years

	Diagnosed with HCM aged < 40 years—cumulative incidence assessed at age 60 years	Diagnosed with HCM aged > 60 years—cumulative incidence assessed at age 70 years
Cumulative incidence (95% CI) of cardiac arrest, cardiac transplant, ICD therapy, all-cause death, AF, stroke, disease progression (NYHA functional class III-IV) symptoms, LVEF < 35%	77% (72%-80%)	32% (29%-36%)

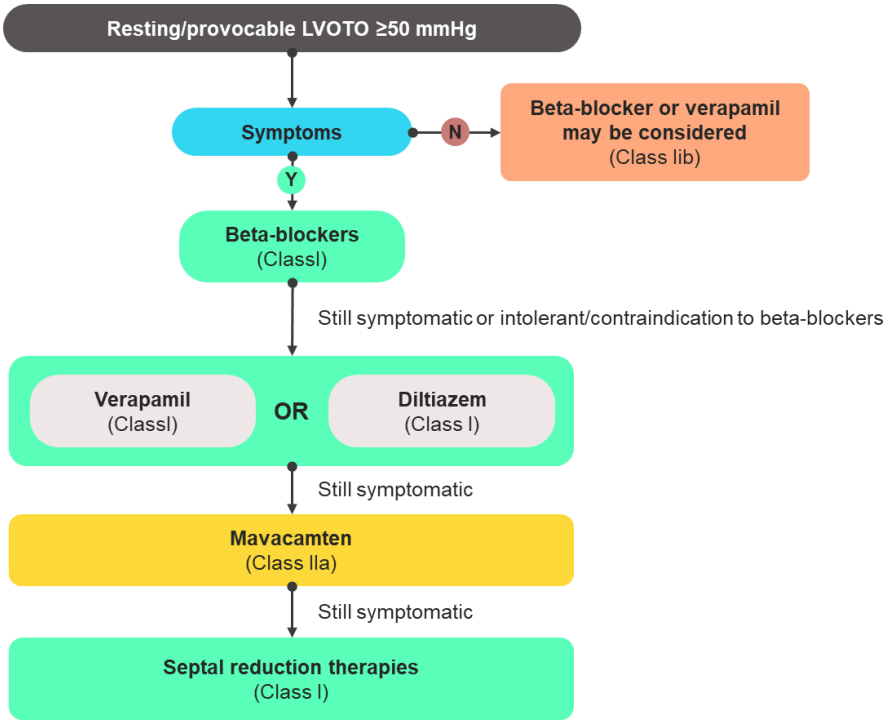
AF = atrial fibrillation; CI = confidence interval; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

Figure 27. Overview of NYHA classes



NYHA = New York Heart Association.
Adapted from AHA (2021)[32]

Figure 28. Overview of the oHCM treatment pathway in Denmark and mavacamten's anticipated position



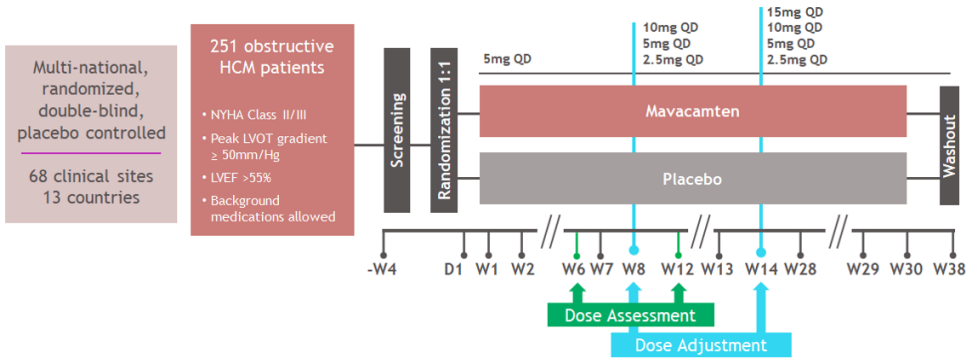
LVOTO = left ventricular outflow tract obstruction; oHCM = obstructive hypertrophic cardiomyopathy.
Adapted from: Arbelo et al. (2023)[9]

Table 81. HRs for each NYHA class compared with NYHA I

NYHA class	HR (95% CI) from Wang et al. (2023)[34]	HR (95% CI) from SHaRe analysis[6]
I	Reference class; as per all-cause mortality; HR, 1.00	
II vs. I	1.80 (1.40-2.32)	1.48 (0.829-2.64)
III vs. I	4.12 (3.24-5.25)	3.17 (1.70-5.92)[a]
IV vs. I	10.90 (8.28-14.4)	

CI = confidence interval; HR = hazard ratio; NYHA = New York Heart Association.
[a] Composite NYHA class III-IV HR applied to both class III and IV separately.

Figure 29. EXPLORER-HCM: study design



D = day; HCM = hypertrophic cardiomyopathy; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; NYHA = New York Heart Association; QD = once daily; W = week.
Adapted from Ho et al. (2020)[66]

Figure 30. EXPLORER-LTE: study design

EOS = end of study; QD = once daily.
Notes: If the dose was decreased to 2.5 mg at week 4, it should remain unchanged and not be increased at week 8 or week 12. For all women of childbearing potential, a pregnancy test would be taken every 4 weeks at home, the site, or a local laboratory when no clinic visit was scheduled.
Assessments from the EXPLORER-HCM week 38 (EOS) visit could serve as screening assessments if the participant began screening into study MYK-461-007 within 28 days of the week 38 visit.
Participants would receive mavacamten immediate-release capsules at a starting dosage of 5 mg QD unless otherwise noted in Section 7 of the protocol.
[a] Dose adjustments were based on site-read echocardiography measures for only Valsalva LVOT gradient and LVEF.
[b] Dose adjustment was also possible at week 24 after site-read echocardiography assessment of post-exercise LVOT gradient. Subsequent to week 24, dose adjustment was possible if site-read Valsalva LVOT gradient was > 30 mmHg and LVEF was ≥ 50%.
Sources: Garcia-Pavia et al. (2024)[92]; Rader et al. (2022)[91]

Appendix L. Additional safety results

L.1.1 Safety: VALOR-HCM

L.1.1.1 VALOR-HCM: summary of safety data

These safety data include the primary analysis of the double-blind period (day 1 to week 16) in patients treated with either mavacamten (n = 56) or placebo (n = 55) and data from the long-term follow-up period in the all-mavacamten exposure group (n = 108) for timepoints reached up to week 80 and from week 56 to week 128. Long-term safety up to week 80 is summarized based on the total time that patients have received mavacamten. Table 82 summarizes the safety data from the double-blind period and the long-term follow-up.

In the VALOR-HCM trial during the double-blind period, the overall proportions of patients with on-treatment SAEs were slightly higher in the mavacamten group through week 16 than in the placebo group. However, in both treatment groups, the frequency of SAEs was low (3 patients [5.4%] in the mavacamten group vs. 1 patient [1.8%] in the placebo group) (Table 82). For further description of VALOR-HCM study design, see Table 65 in Appendix A.

Table 82. VALOR-HCM: safety summary

	Number of patients (%)			
	Double blind[a]		Long-term follow-up[b]	Long-term follow-up (week 56-128)[c]
	Mavacamten (n = 56)	Placebo (n = 55)	Overall mavacamten (n = 108)	Overall mavacamten (n = 108)
[redacted]	[redacted]	[redacted]	[redacted]	NR
[redacted]	[redacted]	[redacted]	[redacted]	15 (13.9)
[redacted]	[redacted]	[redacted]	[redacted]	2 (1.9)[d]
[redacted]	[redacted]	[redacted]	[redacted]	0
[redacted]	[redacted]	[redacted]	[redacted]	0
[redacted]	[redacted]	[redacted]	[redacted]	6 (5.6)[e]
[redacted]				

[c] Long-term follow-up data were collected from week 56 until end of treatment at week 128 for the all-mavacamten exposure group, including the group that transitioned from placebo to mavacamten.
[d] Recorded as drug-related SAE.
[e] Recorded as treatment interruption due to left ventricular ejection fraction < 50%.
[redacted] Desai et al. (2025)[95]

L.1.1.2 VALOR-HCM: summary of SAE safety data

Two patients on mavacamten (vs. none on placebo) experienced cardiac disorders attributed to AF. Both patients had a prior history of AF. One patient in the mavacamten group had acute COVID-19 infection. One patient in the placebo group had acute alcohol poisoning. No patients in the double-blind period experienced SAEs of congestive cardiac failure, syncope, or SCD. Drug-related SAEs, corresponding to cardiac disorders, were observed in 1 patient in the mavacamten group (Table 83).

During long-term follow-up (from the transition of placebo to mavacamten at week 16 until the end of treatment and for the previous mavacamten group from day 1 until end of treatment, up to 80 weeks), 9 patients (8.3%) had SAEs. There was 1 patient (0.9%) with a fatal SAE due to SCD, 1 (0.9%) with severe AF, 2 (1.9%) with moderate AF, and 1 (0.9%) with moderate congestive cardiac failure. One patient (0.9%) was reported to have an SAE due to COVID-19 (Table 83). Between week 56 and week 128 during the long-term follow-up, 15 patients (13.9%) experienced SAEs. Four patients (3.7%) experienced major cardiac events (Table 83).

Table 83. VALOR-HCM: SAE safety summary

	Number of patients (%)			
	Double blind		Long-term follow-up	Long-term follow-up (week 56 to 128)
	Mavacamten (n = 56)	Placebo (n = 55)	Overall mavacamten (n = 108)	Overall mavacamten (n = 108)
[redacted]				
[redacted]				15 (13.9)
[redacted]				
[redacted]				
[redacted]				4 (3.7)
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

	Number of patients (%)			
	Double blind		Long-term follow-up	Long-term follow-up (week 56 to 128)
	Mavacamten (n = 56)	Placebo (n = 55)	Overall mavacamten (n = 108)	Overall mavacamten (n = 108)
[redacted]				

	Number of patients (%)			
	Double blind		Long-term follow-up	Long-term follow-up (week 56 to 128)
	Mavacamten (n = 56)	Placebo (n = 55)	Overall mavacamten (n = 108)	Overall mavacamten (n = 108)
[redacted]				

Desai et al. (2025)[95]

L.1.1.3 VALOR-HCM: common AE data

During the double-blind period, 125 on-treatment AEs were reported in the mavacamten group and 95 were reported in the placebo group. A greater proportion of patients in the mavacamten group than in the placebo group experienced any on-treatment AE (73.2% vs. 61.8%). Table 84 presents on-treatment AEs that occurred in ≥ 5% of patients.

Table 84. VALOR-HCM: overview of common AEs, double-blind period

	Mavacamten (n = 56)	Placebo (n = 55)
[redacted]		

	Mavacamten (n = 56)	Placebo (n = 55)
[redacted]		

For the long-term follow-up period up to 80 weeks, 347 TEAEs were reported for patients treated with mavacamten (TEAEs that occurred from day 1 in previous mavacamten arm and TEAEs from week 16 in the previous placebo arm), 239 for patients with previous mavacamten treatment, and 108 for patients on previous placebo treatment. As mavacamten exposure for patients previously randomly assigned to mavacamten starts earlier than exposure for patients previously randomly assigned to placebo, the duration of exposure is longer for patients who previously received mavacamten than for those who previously received placebo. The longer duration of exposure may result in a greater number of safety events in patients who previously received mavacamten than in those who previously received placebo.

Table 85 presents TEAEs that occurred in ≥ 5% of patients treated with mavacamten. A total of 75% of patients in the total mavacamten group reported a TEAE. The most frequently reported TEAEs were fatigue (9.3%), dizziness (8.3%), and headache (7.4%). One patient previously treated with mavacamten experienced AF; this was a post-operative complication of septal myectomy, and the patient had been off mavacamten for 3 weeks when it occurred.

Table 85. VALOR-HCM: overview of common adverse reactions, long-term follow-up period (up to week 80)

Preferred term	Previous mavacamten (n = 56)	Previous placebo (n = 52)	Total mavacamten (n = 108)
[redacted]			

Preferred term	Previous mavacamten (n = 56)	Previous placebo (n = 52)	Total mavacamten (n = 108)
[redacted]			

Table 86 presents new AEs that occurred in ≥ 5% of patients treated with mavacamten between weeks 56 and 128. The most frequent newly reported events were COVID-19 (25.0%), urinary tract infection (9.3%), and upper respiratory tract infection (8.3%).

Table 86. VALOR-HCM: overview of common adverse reactions, long-term follow-up period (week 56 to week 128)

Preferred term	Total mavacamten (n = 108)
New onset AF	7 (6.5)
Fatigue	7 (6.5)
COVID-19	27 (25.0)
Urinary tract infection	10 (9.3)
Ejection fraction 30%-50%	6 (5.6)
Upper respiratory tract infection	9 (8.3)
Anxiety	6 (5.6)

AE = adverse event; AF = atrial fibrillation.
Source: Desai et al. (2025)[95]

L.1.1.4 VALOR-HCM: deaths

No patients in the mavacamten or placebo groups died during the double-blinded period. One patient who received disopyramide and verapamil as background HCM medications and received placebo during the double-blinded period who transitioned to

mavacamten treatment at week 16 had a TEAE of SCD at week 56, which was 5 days after discontinuing mavacamten.[139]

Appendix M. Additional summary of the model update

M.1.1 Modeling the Effect of Mavacamten After Treatment Discontinuation – DMC request to allow patients to move back to their baseline NYHA functional class after discontinuation

M.1.1.1 Background

This document summarizes the approach used to model the clinical outcomes of patients who discontinue treatment with mavacamten in the cost-effectiveness model for symptomatic obstructive hypertrophic cardiomyopathy (oHCM). In the original model structure, patients who discontinued mavacamten were assumed to remain in the NYHA functional class they had achieved during treatment. From that point onward, they were assumed to follow the natural disease progression associated with that NYHA class. This assumption effectively allowed patients to maintain treatment-related improvements even after therapy had been discontinued.

Evidence from the EXPLORER-HCM Study, particularly the 30-week follow-up data, suggests that improvements in functional status observed during treatment may not be sustained once therapy is stopped. Based on this evidence, DMC recommended that patients who discontinue mavacamten should revert to the NYHA class they had at baseline before initiating treatment. To address this concern, a “back-to-baseline” approach was implemented in the model. Under this approach, once treatment is discontinued, the patient returns to their baseline NYHA functional class rather than remaining in the improved health state achieved during treatment.

M.1.1.2 Model implementation

This modification was incorporated within the existing Markov modeling framework and applied consistently across all patients who discontinue mavacamten treatment due to adverse events (AEs) or lack of efficacy. Two baseline populations were simulated separately in the model: patients starting treatment in NYHA class II and III. Patients who experience an improvement during treatment revert to their baseline NYHA class when treatment is discontinued. In contrast, patients who experience disease progression during treatment remain in their current NYHA class after discontinuation, reflecting the clinical assumption that worsening disease states are unlikely to reverse.

For patients who enter the model with NYHA II, when treatment discontinuation occurs, patients who are in NYHA class I revert to their baseline NYHA class II. Patients who remained in NYHA class II retain that status after discontinuation. Patients who progressed to NYHA class III or IV remain in those states.

Table 87. Transition Rules After Discontinuation for Patients with Baseline NYHA class II

NYHA Class at Discontinuation	Reason for Discontinuation	Reason for Discontinuation

NYHA I	AE	Transition to NYHA II
NYHA II	AE or lack of efficacy	Remain in NYHA II
NYHA III	AE or lack of efficacy	Remain in NYHA III
NYHA IV	AE or lack of efficacy	Remain in NYHA IV

Abbreviation: AE, adverse event

For patients who enter the model with NYHA III, when treatment discontinuation occurs, patients who are in NYHA class I and II revert to their baseline NYHA class III. Patients who remain in NYHA class III during treatment retain this classification after discontinuation. Similarly, patients who experience disease progression to NYHA class IV remain in that state.

Table 88. Transition Rules After Discontinuation for Patients with Baseline NYHA class III

NYHA Class at Discontinuation	Reason for Discontinuation	Reason for Discontinuation
NYHA I	AE	Transition to NYHA III
NYHA II	AE	Transition to NYHA III
NYHA III	AE or lack of efficacy	Remain in NYHA III
NYHA IV	AE or lack of efficacy	Remain in NYHA IV

Abbreviation: AE, adverse event

When implementing the back-to-baseline assumption, baseline population characteristics were kept consistent with the global values used in the model. Introducing separate baseline parameters for patients with NYHA class II and III was considered impractical within the existing Markov trace framework and would likely have only a very limited impact on the overall model results.

The implementation of this approach primarily affects the distribution of patients across NYHA functional classes following treatment discontinuation. Because patients revert to their baseline functional status rather than maintaining treatment-related improvements, a larger proportion of patients remain in NYHA classes II and III over time (rather than NYHA I).

This change leads to a reduction in both life years and quality-adjusted life years in the mavacamten treatment arm compared with the original model structure. The reduction in outcomes is primarily driven by fewer patients remaining in NYHA class I, which is associated with better survival and higher health-related quality of life. In contrast, the impact on costs is minimal. The revised assumption does not substantially alter treatment duration or resource use patterns but mainly affects the health state distribution within the model.

Overall, the adoption of this assumption results in a more conservative estimate of mavacamten's clinical benefits while maintaining consistency between the modeled costs and health outcomes.

Tables and Figures

Abbreviations

Abbreviation	Definition
ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
AD	absolute difference
AE	adverse event
AF	atrial fibrillation
AHA	American Heart Association
AIC	Akaike information criterion
ANCOVA	analysis of covariance
ASA	alcohol septal ablation
ATC	Anatomical Therapeutic Chemical Classification System
ATMP	Advanced Therapy Medicinal Products
ATPase	adenosine triphosphatase
AV	Atrioventricular
BB	beta-blocker
BIC	Bayesian information criterion
BMI	body mass index
BMS	Bristol Myers Squibb
BNP	brain natriuretic peptide
CCB	calcium channel blocker
CEM	cost-effectiveness model
CHF	congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CPET	cardiopulmonary exercise test
CRD	Centre for Reviews and Dissemination
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
CYP	cytochrome P450
DARE	Database of Abstracts of Reviews of Effects
DKK	Danish krone

DMC	Danish Medicines Council
DRG	diagnosis-related group
EC	ethics committee
ECG	electrocardiogram
EE	economic evaluation
EED	Economic Evaluation Database
EMA	European Medicines Agency
EOS	end of study
ESC	European Society of Cardiology
FDA	Food and Drug Administration
HCM	hypertrophic cardiomyopathy
HCM-LVSD	hypertrophic cardiomyopathy left ventricular systolic dysfunction
HCMSQ-SoB	Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath
HCRU	healthcare resource utilization
HR	hazard ratio
HRQoL	health-related quality of life
hs-cTnI	high-sensitivity cardiac troponin I
hs-cTnT	high-sensitivity cardiac troponin T
HSUV	health state utility value
HTA	health technology assessment
ICD	implantable cardioverter-defibrillator
ICER	incremental cost-effectiveness ratio
ITT	intention to treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-23	23-item Kansas City Cardiomyopathy Questionnaire
KCCQ-CSS	Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score
KCCQ-OS	Kansas City Cardiomyopathy Questionnaire–Overall Summary
LS	least squares
LTE	long-term extension
LV	left ventricular
LVEF	left ventricular ejection fraction
LVOT	left ventricular outflow tract
LVOTO	left ventricular outflow tract obstruction

LVSD	left ventricular systolic dysfunction
LY	life-year
MCT	meaningful change threshold
MeSH	Medical Subject Headings
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MRI	magnetic resonance imaging
N/A	not applicable
NA	not available
NBV	National kardiologisk behandlingsvejledning (National cardiological treatment guideline)
NCT	National Clinical Trial
ND	not determined
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	not reported
NS	not significant
NSMR	non-surgical myocardial reduction
NT-proBNP	N-terminal pro–B-type natriuretic peptide
NYHA	New York Heart Association
oHCM	obstructive hypertrophic cardiomyopathy
PICOS	population, intervention, comparison, outcomes, and study
PMR	papillary muscle realignment
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	patient-reported outcome
PTSMA	percutaneous transluminal septal myocardial ablation
pVO_2	peak oxygen consumption
QALY	quality-adjusted life-year
QD	once daily
QoL	quality of life
QTcF	QT interval corrected using Fridericia's formula
RCT	randomized controlled trial
RD	risk difference
REMS	risk evaluation and mitigation strategy
RWE	real-world evidence

SAE	serious adverse event
SAM	systolic anterior motion
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCD	sudden cardiac death
SD	standard deviation
SE	standard error
SF-12	SF-12 Health Survey
SF-36	SF-36 Health Survey
SHaRe	Sarcomeric Human Cardiomyopathy Registry
SLR	systematic literature review
SmPC	summary of product characteristics
SRT	septal reduction therapy
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
TP	transition probability
UK	United Kingdom
US	United States
UTI	urinary tract infection
VAS	visual analog scale
vLVOT	Valsalva manoeuvre left ventricular outflow tract
ZIN	Zorginstituut Nederland (National Health Care Institute)

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