Medicinrådet

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

Vers. 1.0

Bilagsoversigt

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

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29. februar 2024

Rød tekst indikerer rettelser i forhold til 1. vurderingsrapport

Til Medicinrådet

Revideret høringssvar til opdateret vurderingsrapport vedr. Camzyos® (*mavacamten*)

BMS finder, at vurderingsrapporten i sin nuværende form er uegnet som beslutningsgrundlag for Medicinrådets (MR) vurdering af mavacamten. BMS anmoder på det kraftigste om, at alle MRs medlemmer læser denne tilbagemelding på udkastet til vurderingsrapporten for mavacamten igennem og overvejer, hvorvidt vurderingsrapporten udgør et fyldestgørende beslutningsgrundlag.

1) **Hvis MR på trods af de omfattende problemstillinger beskrevet nedenfor vælger at foretage en anbefaling på baggrund af den nuværende vurderingsrapport, vil BMS gøre opmærksom på, at omkostningseffektiviteten i base case ikke er estimeret** for de patienter, der fremhæves som egnede til behandling med mavacamten. Dvs. patienter, som ikke har haft tilstrækkelig gavn af alkohol septal ablation (ASA) og/eller ikke er egnede til at gennemgå de invasive behandlinger. Da de problematiske antagelser omkring ASA ikke er relevante for denne population, er ICER langt lavere end for den samlede population. På baggrund af MRs base case, inklusiv den meget konservative antagelse om ingen påvirkning af mortalitet, vil ICER med den tilbudte aftalepris være på et niveau, der må formodes at være omkostningseffektiv, når ASA udelades af beregningerne. BMS formoder, at scenarie 6 i tabel 18 er en ICER beregnet for populationen, som ikke har haft tilstrækkelig gavn af ASA og/eller ikke er egnede til at gennemgå de invasive behandlinger.

2) **BMS anbefaler, at man konsulterer flere fagspecialister på tværs af landet** for at sikre sig, at rapporten og dens konklusioner ikke møder modstand i det faglige miljø, som overordnet er præget af to modsatrettede holdninger i forhold til effekt/sikkerhed af behandling med ASA, og hvor behandling med mavacamten bør indplaceres. BMS finder det derfor forkert, at man i fagudvalget ikke har fagspecialister med oHCM, som primært speciale, fra andre dele af landet end København/Øst-Danmark. Det forhold, at kun en enkelt oHCM specialist (Formanden), har været med til udarbejdelsen af denne vurdering, er særligt problematisk set i lyset af, at indikationen forslås begrænset i et omfang, der vil udelukke langt de fleste patienter fra adgang til en ny effektiv behandling.

3) **Mavacamten udgør et nyt behandlingsparadigme til oHCM patienter**, der ikke tidligere har haft andre behandlingsmuligheder forud for progression til indikation for invasiv kirurgi. Dette indebærer, at MRs vurdering i højere grad end ved etablerede behandlingsparadigmer vil basere sig på faglige vurderinger. Det er derfor essentielt, at de faglige vurderinger er udtryk for danske specialisters vurderinger på tværs af landet, men også at disse ser patienterne igennem det fulde diagnose- og behandlingsforløb.
   BMS mener, at sammensætningen af fagudvalget ikke repræsenterer disse forskellige synspunkter, og at rapporten derfor fremstår ensidig og biased i sine konklusioner og antagelser.
   Dansk Cardiologisk Selskab har endorset den nyeste ESC guideline 2023 på området og Arbejdsgruppen vurderer, at: ”mavacamten har en dokumenteret klinisk relevant effekt hos symptomatiske patienter med oHCM, men at stoffets plads i behandlingshierakiet er uafklaret”, hvilket understøtter BMS’ pointe om ensidighed.

4) **Samtlige HTA-institutioner, der har evalueret mavacamten, har vurderet, at patientpopulationen svarende til EMA-indikationen er den korrekte.** Mavacamten er således anbefalet til hele patientpopulationen af alle HTA-institutioner, der har færdigbehandlet deres evaluering. Det drejer sig om CADTH (Canada), G-BA (Tyskland), HAS (Frankrig), INESS (Canada), NICE (England) og PBAC (Australien). NICE beregnede eksempelvis en betydelig QALY-gevinst og estimerede en ICER på under 400.000 kr., og G-BA vurderer, at der er betydelig klinisk merværdi af mavacamten sammenlignet med nuværende klinisk praksis. Fagudvalgets vurdering står derfor alene i et internationalt perspektiv.

5) **Effekt og sikkerhed ved alkohol septal ablation (ASA) gennemgås grundlæggende ikke objektivt og systematisk** efter MRs metode. Studierne, der skal belyse effekten af ASA, er ikke udvalgt systematisk, men specifikt af fagudvalget. BMS har i forbindelse med ansøgningen sendt et systematisk litteratur review, der blandt andet gennemgår effekten af ASA baseret på et langt større antal artikler. Det kommenteres der ikke på i rapporten. I rapporten fremlægges ikke evidens for bivirkningsprofilen eller komplikationsraten, herunder risiko for pacemaker og vedligehold af denne og de komplikationer det potentielt kan medføre. Det beskrives heller ikke, at fejlslagen ASA medfører dårligere outcome og højere mortalitetsrisiko. I rapporten fremstilles ASA som en tilnærmelsesvis triviel, kurativ procedure, hvor patienter ikke kræver yderligere behandling/undersøgelser i mange år frem.

6) **Rapporten hævder fejlagtigt, at der i dansk praksis ikke er patienter i NYHA-klasse II, som er behandlingskrævende/symptomatiske** efter standardbehandling med betablokkere (BB). Jf. de netop vedtagne guidelines for oHCM, er det primære terapeutiske mål for behandling af oHCM at nedbringe udløbsgradienten. I BMS' EXPLORER-HCM-studie deltog 3 danske sites, der udelukkende rekrutterede patienter i NYHA-klasse II, som ikke havde optimal effekt af BB. I studiet udgjorde disse patienter ca. 72%. Danske klinikere har desuden rekrutteret samme patientpopulation til et andet dansk studie og et internationalt fase 3 studie med en anden myosinhæmmer, som bl.a. var ledet af Formanden for Fagudvalget. Rekrutteringen har i øvrigt foregået sideløbende med, at Fagudvalget har vurderet mavacamten. BMS undrer sig derfor over, at samtlige danske patienter i NYHA-klasse II i dag skulle være fuldstændig velbehandlede på standardbehandling og uden yderligere behandlingskrævende udløbsgradient eller symptomer. Dermed anfægter BMS det forhold, at den af EMA godkendte indikation ikke skulle gøre sig gældende for i hvert fald en andel af danske patienter i NYHA-klasse II.

7) **Rapporten nævner risiko for pludselig død som følge af behandling med mavacamten. Dette er ikke korrekt.** Risikoen for fald i venstre ventrikels uddrivningsfraktion (LVEF) er omkring 5% og er reversibel ved seponering/pausering af behandling. Rapporten fremhæver også det FDA-godkendte REMS-program, som er irrelevant i Danmark. I USA er produktet godkendt uden CYP2C19-test og uden mulighed for opstart i lav dosis mhp. at minimere risikoen for fald i LVEF hos "dårlige metabolisatorer" (ca. 2% af den kaukasiske befolkning). Inddragelsen af REMS-programmet bidrager ikke til en objektiv og korrekt fremstilling af lægemidlets potentielle bivirkninger eller håndtering af disse. Teksten i den opdaterede vurderingsrapport er nu retvisende.

8) **Det vurderes i rapporten, at alle oHCM patienter har en dødelighed tilsvarende baggrundsbefolkningen.** Dette virker langt fra sandsynligt, når et dansk registerstudie[1] direkte konkluderer en overdødelighed blandt HCM-patienter og andre studier viser, at oHCM er associeret med højere dødelighed end HCM generelt[2,3]. NYHA-klasse blandt oHCM patienter er desuden associeret med højere dødelighed[4]. BMS har desværre ikke adgang til danske data for oHCM patienter, men kan på baggrund af svenske data konkludere, at der i Sverige er en stor overdødelighed blandt nydiagnosticerede oHCM patienter.

Samlet set vil BMS derfor på det kraftigste foreslå, at der foretages en ny vurdering af mavacamten af et bredt sammensat fagudvalg med en bredere repræsentation af oHCM specialister, så begge overordnede faglige holdninger er repræsenteret, diskuteret og vurderet. Der bør ligeledes altid mindst være én patientrepræsentant i fagudvalget, når et lægemiddel bliver vurderet, hvor både livskvalitet og patientpræferencer er aktuelle.

Med venlig hilsen

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Bristol Myers Squibb™

[1] *Jacobsen MHB, Petersen JK, Modin D, Butt JH, Thune JJ, Bundgaard H, et al. Long term mortality in patients with hypertrophic cardiomyopathy – A Danish nationwide study. American Heart Journal Plus: Cardiology Research and Practice. 2023;25.*
2 Maron MS, Olivotto I, Betocchi S, Casey SA, Lesser JR, Losi MA, Cecchi F, Maron BJ. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med. 2003 Jan 23 and 10.1056/NEJMoa02133, 348(4):295-303
[3] *Desai NR, Sutton MB, Xie J, Fine JT, Gao W, Owens AT, Naidu SS. Clinical Outcomes, Resource Utilization, and Treatment Over the Disease Course of Symptomatic Obstructive Hypertrophic Cardiomyopathy in the United States. Am J Cardiol. 2023 Apr 1 and 192:16-23.*
[4] *Yan Wang, Weihua Gao, Xu Han, Jenny Jiang, Belinda Sandler, Xiaoyan Li & Carla Zema (2023) Cardiovascular outcomes by time-varying New York Heart Association class among patients with obstructive hypertrophic cardiomyopathy: A retrospective cohort study, Journal of Medical Economics*

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07.03.2024
CAF/BMC

Forhandlingsnotat

Dato for behandling i Medicinrådet	20.03.2024
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

Prisinformation

Amgros har forhandlet følgende pris på Camzyos (mavacamten):

Tabel 1: Forhandlingsresultat

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

Prisen er betinget af Medicinrådets anbefaling.
[redacted]

Aftaleforhold

Amgros vil indgå en aftale med leverandøren, hvis Medicinrådet anbefaler Camzyos til den ansøgte indikation, som gælder fra den 21.03.2024. Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

[redacted]

Konkurrencesituationen

Der er på nuværende tidspunkt ingen konkurrence på området. Det koster [redacted] for et års behandling med Camzyos uafhængig af dosis.

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til vurdering
Sverige	Under vurdering	Link til vurdering
England	Anbefalet	Link til anbefaling

Konklusion

Amgros vurderer, at leverandøren på nuværende tidspunkt ikke kan give en bedre pris.

Medicinrådet

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

9 June 2023

[redacted]

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Colour scheme for text highlighting	
Colour of highlighted text	Definition of highlighted text
	Confidential information
[other]	[definition of colour code]

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1 Basic information

Contact information	
Name	**Jens Christensen**
Title	Market Access Manager
Phone number	+45 42 71 40 17
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Overview of the pharmaceutical	
Proprietary name	Camzyos®
Generic name	Mavacamten
Marketing authorisation holder in Denmark	Bristol Myers Squibb Hummeltoftevej 49 2830 Virum Denmark
ATC code	C01EB24
Pharmacotherapeutic group	Cardiac therapy (cardiac myosin inhibitor)
Active substance(s)	2.5/5/10/15 mg of mavacamten
Pharmaceutical form(s)	Hard capsule for oral use.
Mechanism of action	Mavacamten is a novel, selective, allosteric, and reversible cardiac myosin inhibitor developed to target the underlying pathophysiology (exaggerated myosin–actin interaction) of obstructive hypertrophic cardiomyopathy (oHCM). Mavacamten modulates the number of myosin heads that can enter power-generating states, thus reducing (or, in HCM, normalising) the probability of force-producing systolic and residual diastolic cross-bridge formation.
Dosage regimen	*CYP2C19 poor metaboliser 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 left ventricular outflow tract (LVOT) gradient with Valsalva manoeuvre 4 and 8 weeks after treatment initiation. *CYP2C19 intermediate, normal, rapid and ultra-rapid metaboliser phenotype* The recommended starting dose is 5 mg orally once daily. The maximum dose is 15 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 individualised maintenance dose is achieved, patients should be assessed every 12 weeks. If at any visit the patient's LVEF is < 50%, the treatment should be interrupted for 4 weeks and until LVEF returns to ≥ 50%.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Mavacamten is indicated for the treatment of symptomatic (New York Heart Association, NYHA, class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients
Other approved therapeutic indications	None
Will dispensing be restricted to hospitals?	Yes, expected to be categorised as "BEGR"
Combination therapy and/or co-medication	Can be used in combination with beta-blockers and calcium antagonists
Packaging – types, sizes/number of units, and concentrations	28 hard capsules in concentration 2.5/5/10/15 mg mavacamten
Orphan drug designation	Not applicable

2 Abbreviations

Abbreviation	Expansion
AE	adverse event
AF	atrial fibrillation
AHA	American Heart Association
ATC	Anatomical Therapeutic Chemical Classification System
BB	beta-blocker
BMI	body mass index
BMS	Bristol Myers Squibb
CCB	calcium channel blocker
CEM	cost-effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CPET	cardiopulmonary exercise test
CV	cardiovascular
CYP	cytochrome P450
CYP2C19	cytochrome P450 2C19
DKK	Danish krone
DMC	Danish Medicines Council
DRG	diagnosis resource group
DSA	deterministic sensitivity analysis
ECG	echocardiogram
EMA	European Medicines Agency
EMR	electronic medical record
EOS	end of study
ESC	European Society of Cardiology
HCM	hypertrophic cardiomyopathy
HCMSQ	Hypertrophic Cardiomyopathy Symptom Questionnaire
HCMSQ-SoB	Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath
HCRU	healthcare resource utilisation
HR	hazard ratio
HRQOL	health-related quality of life
hs-cTnI	high-sensitivity cardiac troponin I
ICD	implantable cardioverter-defibrillator
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
ITT	intention to treat
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

Abbreviation	Expansion
LV	left ventricular
LVEF	left ventricular ejection fraction
LVOT	left ventricular outflow tract
LY	life-year
MCT	meaningful change threshold
MRI	magnetic resonance imaging
NA	not applicable
NCT	National Clinical Trial
NICE	National Institute for Health and Care Excellence
NT-proBNP	N-terminal pro–B-type natriuretic peptide
NYHA	New York Heart Association
oHCM	obstructive hypertrophic cardiomyopathy
PPPY	per patient per year
PRO	patient-reported outcome
PSA	probabilistic sensitivity analysis
pVO_2	peak oxygen consumption
PY	patient-year
QALY	quality-adjusted life-year
QD	once daily
QOL	quality of life
QTcF	QT interval corrected using Fridericia's formula
RCT	randomised controlled trial
RR	relative risk
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
SHaRe	The Sarcomeric Human Cardiomyopathy Registry
SLR	systematic literature review
SmPC	summary of product characteristics
SRT	septal reduction therapy
TEAE	treatment-emergent adverse event
TP	transitional probability
UK	United Kingdom
US	United States
WTP	willingness to pay

3 Tables and figures

4 Resumé

4.1 Baggrund

Mavacamten (Camzyos®) er et lægemiddel, der er specifikt udviklet til behandling af obstruktiv hypertrofisk kardiomyopati (oHCM), en sjælden, men alvorlig form for kardiomyopati, som kan føre til alvorlige komplikationer som hjertesvigt og pludselig død. Kardiomyopatier er lidelser, der påvirker strukturen og funktionaliteten af hjertemuskulaturen.[1-3] Obstruktiv HCM skyldes en unormal fortykkelse af hjertemusklen (≥ 15 mm, eller 13 mm hvis familiær oHCM) og er særlig karakteriseret ved en dynamisk udløbsobstruktion (LVOT ≥ 30 mmHg) i hvile eller ved provokation.[3,4]

Det er en kronisk progressiv sygdom med en forskelligartet klinisk præsentation. Sygdomsforløbet er kendetegnet ved symptomer såsom træthed, svimmelhed, åndenød, hjertebanken og besvimelser. Obstruktiv HCM medfører alvorlige begrænsninger i patientens funktion og livskvalitet, herunder både fritid og arbejdsliv.[5,6] Mavacamten vil senest den 2. juli 2023 være den første og eneste EC godkendte myosinhæmmer, der specifikt er målrettet årsagen til oHCM. Behandling med mavacamten er godkendt til voksne patienter med symptomatisk oHCM (NYHA II-III). Mavacamten er en selektiv, allosterisk og reversibel kardiel myosinhæmmer, som virker ved at hæmme kardiel myosin, hvormed mavacamten normaliserer kontraktilitet, reducerer dynamisk LVOT-obstruktion og forbereder kardielle fyldningstryk hos patienter med oHCM.

Nuværende behandling og behandlingsbehov

I dag bliver patienter med oHCM typisk behandlet med lægemidler, der ikke specifikt er udviklet til behandling af oHCM, såsom betablokkere (BBs) og calciumantagonister (CCBs). Udfordringen med disse lægemidler er, at de typisk har en begrænset og variabel effekt på symptomerne[5,7] og ikke påvirker den underliggende årsag til eller forhindrer progressionen af sygdommen.[1,3] Patienter som progredierer og ikke har optimal effekt af behandling kan få foretaget septal reduktionsbehandling (SRT), som består af enten kirurgisk myektomi eller transkoronar alkoholablation. Septal reduktionsbehandling er en effektiv behandlingsform til at bedre de strukturelle forandringer i myokardiet, som oHCM medfører,[3,8-10] men de er også ofte associeret med peri- og post-operative komplikationer, ligesom de kan medføre behov for pacemakerimplantation eller re-operation.[11] Derudover vil ca. 20%-30% af patienterne fortsat have behov for farmakologisk behandling efter invasiv behandling.[3]

For patienter med meget svære symptomer og dårlig livskvalitet på trods af behandling kan hjertetransplantation være en mulighed.[12]

Klinisk udviklingsprogram

Mavacamtens effekt og sikkerhed er undersøgt i et stort pivotalt, internationalt, placebo-kontrolleret fase 3 studie, EXPLORER-HCM, designet specifikt til patienter med oHCM i NYHA-klasse II-III. Størstedelen af patienterne (73%) i studiet var i NYHA-klasse II ved studiestart. Patienterne blev randomiseret 1:1 til enten placebobehandling + standardbehandling (BB eller CCB) eller mavacamten + standardbehandling igennem 30 uger. I alt deltog 13 lande, 68 forskellige hospitaler, hvoraf 3 er danske. Da mavacamten er den første selektive, kardielle myosinhæmmer af sin slags, er mavacamten undersøgt overfor placebo. Foruden EXPLORER-HCM har mavacamten været undersøgt i andre kliniske fase 2 og 3 studier, som understøtter behandlingens sikkerhed. Disse er: Et fase 2, multicenter, åben-label, *proof-of-concept* studie, PIONEER-HCM; to åben-label forlængelsesstudier, henholdsvis MAVA-LTE og EXPLORER-LTE; samt et fase 3, multicenter, randomiseret, dobbeltblindet, placebokontrolleret sikkerhedsstudie, VALOR-HCM.

Klinisk effekt og bivirkningsprofil

I det pivotale fase 3 studie, EXPLORER-HCM, forbedrede mavacamten både funktionel status og symptombyrde for voksne patienter med symptomatisk oHCM (NYHA II-III). Studiet viser signifikant effekt af behandling med mavacamten på det primære endepunkt, samt på alle sekundære og eksplorative endepunkter, sammenlignet med placebo + standardbehandling.

- I alt 37 % af patienterne i behandling med mavacamten nåede det primære endepunkt, som var et sammensat endepunkt (forbedring af funktionel kapacitet (pVO_2) og ændring i NYHA-klassen) sammenlignet med 17 % af patienterne i placebogruppen.[13]
- Patienterne i behandling med mavacamten opnåede reduktioner i middelværdier for LVOT-gradienten i hvile og ved provokation allerede i uge 4, og som blev opretholdt i hele studiets varighed på 30 uger.[13]
- Behandling med mavacamten medførte en middelreduktion i LVOT peak gradienten efter træning på 35,6 mmHg sammenlignet med placebo. Desuden var LVOT-obstruktionen (LVOT gradient < 30 mmHg efter træning) ikke længere til stede hos 50% flere patienter og reduceret under tærskelværdien for SRT (LVOT gradient < 50 mmHg efter træning) i 53,5% flere patienter i behandling med mavacamten sammenlignet med placebo.[13]
- 27 % af patienterne opnåede et komplet respons på behandlingen (dvs. alle LVOT-gradienter < 30 mmHg og NYHA-klasse I) med mavacamten sammenlignet med 1 % af patienterne på placebo.[13]
- Endvidere forbedrede behandling med mavacamten signifikant patienternes symptom- og helbredsstatus (KCCQ-CSS, HCMSQ-SoB, EQ-5D-5L og EQ VAS) sammenlignet med placebobehandling, og medførte klinisk relevante forbedringer, hvoraf nogle indtrådte allerede efter 4 ugers behandling.[14,15]

Generelt var behandlingen med mavacamten veltolereret på tværs af de kliniske studier og bivirkningsprofilen forblev acceptabel og konsistent selv med længere behandlingstid.[16] De mest almindeligt rapporterede bivirkninger med mavacamten er svimmelhed (19,7 %), fatigue (15,6%), nasopharyngitis (15,0%), hovedpine (14,6%), dyspnø (13.4 %), AF (12,1%), hypertension (11,1%) og øvre luftvejsinfektion (10,2%).[17]

På tværs af de kliniske studier ses et mindre fald i LVEF (EXPLORER-HCM: gennemsnitlig ændring i LVEF, −3,9%; MAVA-LTE: gennemsnitlig ændring i LVEF ved 84 uger, −9,0% ± 8,1%; VALOR-HCM: gennemsnitlig ændring i LVEF, −3,4%) over tid.[13,16] Denne effekt er forenelig med mavacamtens virkningsmekanisme, som en selektiv, kardiel myosinhæmmer. I alt havde 21 patienter i behandling med mavacamten en måling af LVEF < 50%, som medførte en protokoldrevet midlertidig pause i behandlingen. Hovedparten af patienterne genoptog behandlingen efter en måling af LVEF > 50%, og patienterne kunne fortsætte deres behandling med mavacamten. Ingen af patienterne havde en måling af LVEF < 30%, som ville have medført permanent seponering af behandlingen, og der var heller ingen tilfælde af hjertesvigt.[13]

Den anbefalede startdosis er 5 mg én gang dagligt efterfulgt af ekkokardiogramstyret dosistitrering. For patienter med CYP2C19-fænotype, der er dårlige metabolisatorer, eller med ukendt fænotype, er den anbefalede startdosis 2,5 mg én gang dagligt. Fire og 8 uger efter behandlingsstart skal patienten vurderes for tidligt klinisk respons.

Omkostningseffektivitet og budgetkonsekvenser

Der er gennemført en sundhedsøkonomisk analyse baseret på patient-niveau data fra EXPLORER-HCM studiet og supplerende aggregeret data fra eksterne studier. Analysen er baseret på en Markov model med NYHA-

klasse definerede sygdomsstadier (NYHA I, II, III, IV) og død. Alle patienter starter i enten NYHA II eller III, hvilket reflekterer baseline populationen i EXPLORER-HCM. Analysen viser, at prisen per vunden QALY ved indførelsen af mavacamten er [redacted] På baggrund af det forventede patientoptag estimeres det, at anvendelse af mavacamten vil resultere i en budgetkonsekvens på [redacted] i år 5 for hele landet sammenlignet med nuværende standardbehandling.

Samlet set er mavacamten en effektiv og veltolereret behandling til voksne patienter med symptomatisk oHCM (NYHA II-III), og samtidig en omkostningseffektiv behandlingsmulighed.

5 The patient population, the intervention and choice of comparator(s)

5.1 The medical condition and patient population

Mavacamten is indicated for the treatment of symptomatic (New York Heart Association, NYHA, class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients.

5.1.1 Disease background

HCM is a myocardial disease defined by left ventricular hypertrophy that cannot be explained by another cardiac or systemic disease. It is a chronic progressive disease with a diverse clinical presentation and course. The origin of HCM can be non-genetic or genetic. When genetic, HCM is largely caused by pathogenic variation in genes encoding the cardiac sarcomere. HCM is a complex disease caused by sarcomeric dysfunction. The condition results in excessive cross bridges between myosin and actin, leading to core pathophysiological changes in the structure and function of the heart: disorganised cardiomyocytes, increased myocardial fibrosis, and a small, stiff ventricle with excessive contractility, impaired relaxation, and poor left ventricular compliance.[1-3] 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.[18]

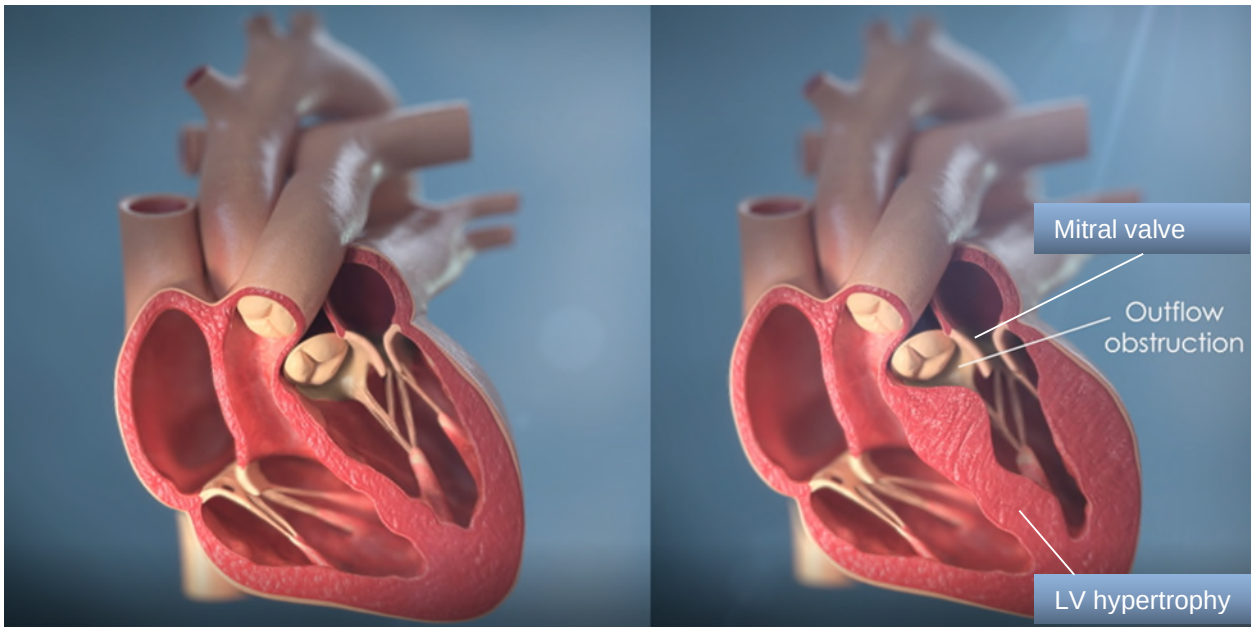
The clinical course and presentation of HCM varies greatly, and symptoms can be debilitating, life-changing, and result in impaired functionality and lower quality of life (QOL). The most common symptoms include shortness of breath (dyspnoea), fatigue, palpitations, light-headedness, chest pain, and syncope.[5,6] However, for some patients, the first symptom is sudden cardiac death (SCD). To reduce the risk of SCD, 5-year risk is assessed for each patient using the ESC HCM risk-SCD calculator, and patients at risk of SCD are offered an implantable cardioverter-defibrillator (ICD) as preventive measure.[3,19,20]

HCM consists of 2 subtypes: non-obstructive and obstructive. The primary difference between the 2 subtypes is the absence or presence of outflow obstruction. In non-obstructive HCM, the thickened heart muscle does not block blood flow out of the left ventricle; this condition is out of scope of the present application and will not be described further.

In oHCM, the thickened septum causes a dynamic narrowing that can obstruct the blood flow from the left ventricle to the aorta (Figure 1) that can be present at rest and/or during physiological provocation. Dynamic narrowing can also involve systolic anterior motion (SAM) of the mitral valve. The obstructive subclassification of HCM is defined by the presence of unexplained left ventricular hypertrophy (wall thickness ≥ 15 mm, or 13 mm if familial HCM) and a LVOT obstruction (peak left ventricular outflow gradient ≥ 30 mmHg at rest or with provocation).[3,4] The presence of LVOT obstruction has been shown to be a strong, independent predictor of disease progression to severe symptoms, such as heart failure, and death.[21]

Figure 1. Obstructive HCM

A. Normal heart **B.** oHCM



HCM = hypertrophic cardiomyopathy; LV = left ventricular; oHCM = obstructive hypertrophic cardiomyopathy.
Adapted from Mayo Clinic (2020)[22]

Obstructive HCM is also associated with an increased risk of long-term cardiovascular (CV) complications.[21] The vast majority of patients with oHCM will have progressive left ventricular remodelling, leading to cardiac dysfunction and, potentially, development of the clinical syndrome of heart failure, which is associated with substantial cardiac morbidity and mortality.[3,6,21,23-26] Other common complications include arrhythmias (atrial fibrillation [AF] or non-sustained ventricular tachycardia in up to 30%-33% of patients). Obstructive HCM affects health-related QOL (HRQOL), including professional life, leisure time activities, mental well-being, and family planning, which means that oHCM can have significant impact on a patient's social life and ability to work.[5] Therefore, patients with oHCM must adapt to severe limitations in daily life due to the burden of symptoms.[27-29]

5.1.1.1 Adverse clinical outcomes and complications

Adverse clinical outcomes and complications of oHCM include AF and stroke, ventricular arrhythmias, and systolic heart failure.[1,21,23] Obstructive HCM–related complications typically occur between 50 and 70 years of age.[21,24] The Sarcomeric Human Cardiomyopathy Registry (SHaRe) reported that the risk of these adverse outcomes, with the exception of ventricular arrhythmias, is increased in patients diagnosed early in life (Table 1) and in patients with pathogenic sarcomeric variations.

Table 1. **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 transplantation, implantable cardioverter-defibrillator 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; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

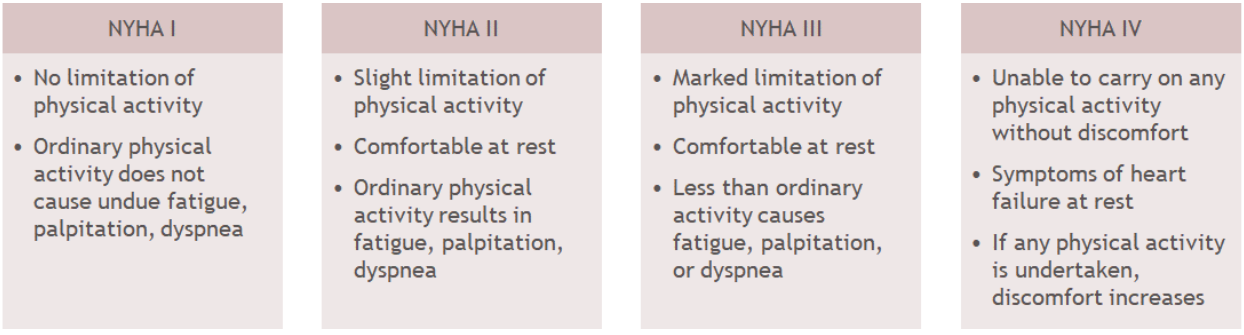
5.1.1.2 Patient population

Based on the European Medicines Agency (EMA) label, mavacamten is indicated for the treatment of symptomatic (NYHA class II-III) oHCM in adult patients. In Denmark, BBs and non-dihydropyridine CCBs have been the mainstay of treatment for decades but offer only limited and variable relief in symptoms and/or functional status.[5] In addition to inadequate symptom relief, these treatments are often poorly tolerated.[30] Mavacamten's position in the treatment pathway is for those patients with persisting symptoms in NYHA class II-III.

To assess the severity of symptoms for patients with oHCM, the NYHA functional classification system can be used in clinical practice.

The NYHA functional classification system is widely used to categorise heart failure according to the severity of symptoms while an individual is performing physical activity (Figure 2); worse symptoms equate to higher NYHA classes and correlate to a greater risk of all-cause mortality.[8,31]

Figure 2. **Overview of NYHA classes**



NYHA = New York Heart Association.
Adapted from AHA (2021)[31]

An increased symptomatic burden, as measured by NYHA class, has been demonstrated in 2 large register-based studies to be associated with an increased risk of mortality in patients with oHCM.

Wang et al.[32] 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 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.[32] Table 2 presents the HRs by NYHA class.

[redacted] Table 2 presents the HRs by NYHA class.

Table 2. Hazard ratios for each NYHA class compared with NYHA I

NYHA class	HR (95% CI) from Wang et al. [32]	HR (95% CI) from SHaRe analysis[33]
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.

5.1.1.3 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,[34-36] whereas diagnosed prevalence of symptomatic HCM is estimated to be 1 in 1,500 people.[3,8,37-43] 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.[3,8] 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.[44] In the study, all Danish residents aged 18 years or older with a hospitalisation 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.[45] Table 3 presents the incidence of oHCM in Denmark from 2014-2018.

Table 3. Incidence of oHCM in Denmark (2014-2018)

Year	2014	2015	2016	2017	2018
Incidence in Denmark	138	128	139	133	103

oHCM = obstructive hypertrophic cardiomyopathy.

Source: Zoerner et al. (2022)[45]

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.[45] 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,[45] 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.[45] Based on an expert elicitation study from the United Kingdom (UK),[46] 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 4 presents the calculations and assumptions.

Table 4. 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)[45]	
Number of patients with oHCM and still alive in 2018, including patients diagnosed before 2005	+25%	1,443	Zoerner et al. (2022)[45]	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)[45] 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 3). 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 5 consider mortality as described in Section 8.4.7; 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 5. Estimated number of patients eligible for treatment in Denmark

Year	2023	2024	2025	2026	2027
Number of patients with oHCM in Denmark who are eligible for mavacamten	244	270	296	322	348

oHCM = obstructive hypertrophic myocardiopathy.

5.1.1.4 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.[26,47] 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.[48] In SHaRe, a global registry, the median age of diagnosis was 45.8 years.[24] 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.[49] 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.[18] The Danish registry study reported a median age of 68.4 years at the time of diagnosis for all patients with oHCM.[45] In the EXPLORER-HCM trial, the mean age was 58.5 years in both the mavacamten group and the placebo group.[13] Most patients had NYHA class II symptoms (73%) and were taking BBs or CCBs (92%).[13] 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.

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

Currently recommended pharmacological treatments address only the symptoms of oHCM and do not target the underlying pathophysiology or aetiology of the disease or disease progression.[1,3] The relevant guidelines for the treatment of oHCM in Denmark are primarily the guideline on myocardial diseases by Dansk Cardiologisk Selskab[19] and the 2014 ESC guideline.[3] 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, randomised controlled trials (RCT).[3] 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.[5,7] In addition to inadequate symptom relief, these treatments are often poorly tolerated.[30] Potential side effects of BBs that may affect daily life include fatigue, chronotropic incompetence, and asthma; potential side effects of CCBs are atrioventricular conduction decrease and ankle oedema.[30] It is estimated that 20% of patients will undergo SRT, either myectomy[i] or alcohol septal ablation,[ii] which can treat cardiac structural changes caused by the disease[3,8-10,50] but is associated with peri-procedural and potentially severe post-surgery complications, as well as the potential need for pacemaker implantation

[i] Myectomy is open heart surgery to remove a section of the thickened heart tissue and, therefore, reduce outflow obstruction.

[ii] 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.

and re-intervention.[11] In Denmark, alcohol septal ablation is the preferred treatment in comparison to ventricular septal myectomy. Additionally, approximately 20% to 30% of patients still require treatment following invasive therapy.[3] As a final resort, patients may undergo a heart transplant.[12]

5.2.2 Choice of comparator(s)

On the basis of 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.

5.3 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. Mavacamten offers a novel treatment option for symptomatic oHCM and constitutes an effective and safe, once-daily oral therapy. During the EMA process the CYP2C19 genotype testing was introduced to the label and the recommended starting dose for the CYP2C19 poor metaboliser phenotype and unknown phenotype was changed to 2.5 mg orally once daily, although the test and starting dose have not been part of the clinical program for mavacamten. The incidence of CYP2C19 poor metaboliser phenotype ranges from approximately 2% in Caucasian to 18% in Asian populations. [51] Table 6 summarises the use of mavacamten as indicated. Full details of the prescribing information for mavacamten are available from the summary of product characteristics (SmPC).[51]

Table 6. Description of mavacamten

	Description
Dosing	*CYP2C19 poor metaboliser phenotype 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 left ventricular outflow tract (LVOT) gradient with Valsalva manoeuvre 4 and 8 weeks after treatment initiation. *CYP2C19 intermediate, normal, rapid and ultra-rapid metaboliser phenotype* The recommended starting dose is 5 mg orally once daily. The maximum dose is 15 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 individualised maintenance dose is achieved, patients should be assessed every 12 weeks. If at any visit the patient's LVEF is < 50%, the treatment should be interrupted for 4 weeks and until LVEF returns to ≥ 50%.
Method of administration	Oral use (capsule), once daily
Treatment duration/criteria for treatment discontinuation	Consideration should be given to discontinuing treatment in patients who have shown no response (e.g., no improvement in symptoms, quality of life, 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.
Should the pharmaceutical be administered with other medicines?	Can be used in combination with BBs and CCBs

	Description
Necessary monitoring, during administration, during the treatment period and after the end of the treatment	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 should return to monitoring every 12 weeks. Once an individualised maintenance dose is achieved, patients should be monitored every 12 weeks for the first 12 months of treatment and hereafter every 6 months.
Need for diagnostic or other test	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 metaboliser phenotype have increased mavacamten exposures (up to 3 times) that can lead to an increased risk of systolic dysfunction compared with normal metabolisers.[51]

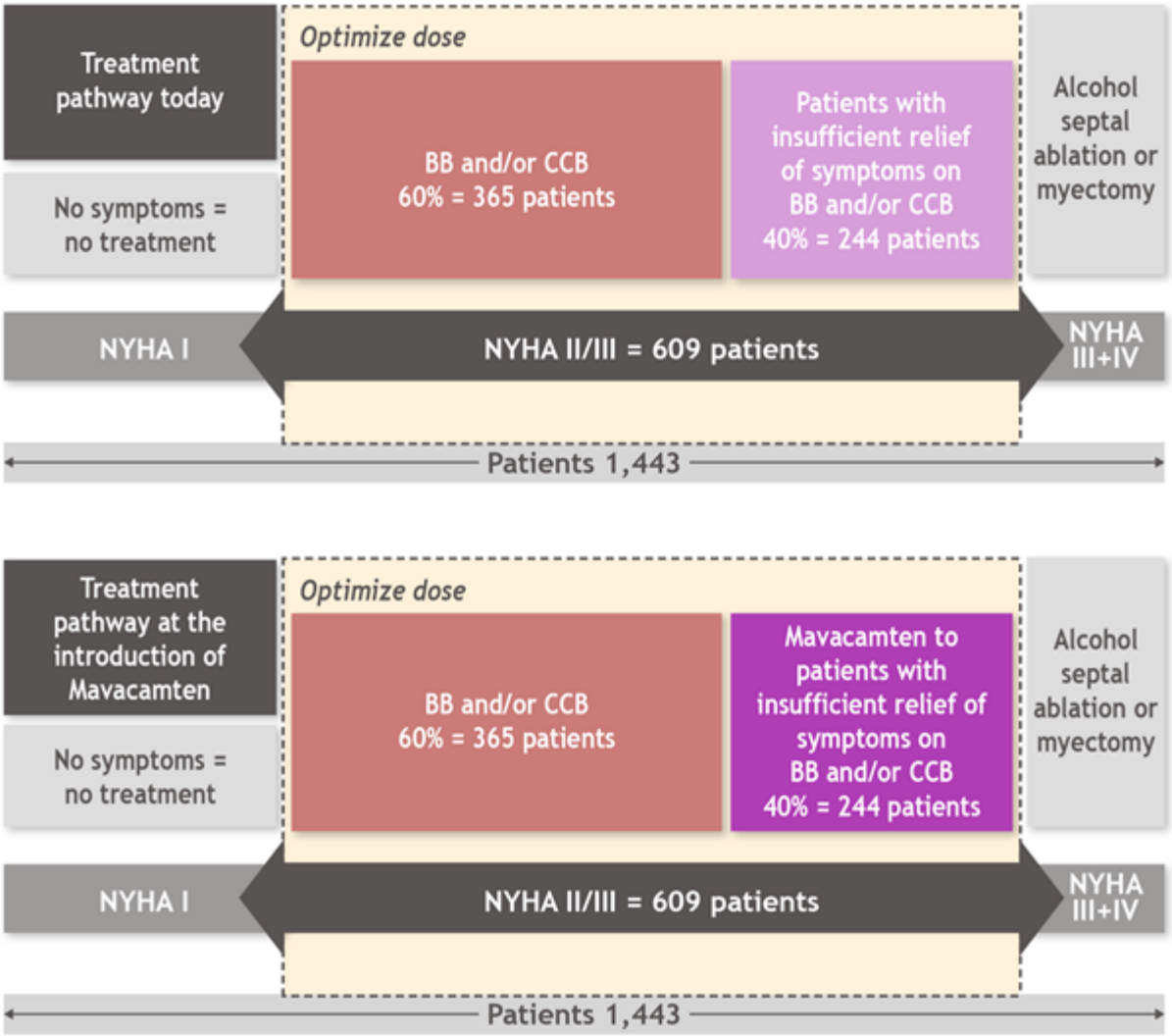
LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract.

In Denmark, genetic testing of patients presenting with symptoms of oHCM and suspicion of genetic/familiar disposition is standard practice.[19] This means that family members of the proband might be carriers of a disease-causing genetic variation, even though they might be asymptomatic.[18] Genetic testing of patients as well as relatives has been part of standard clinical care in Denmark for several years, and it is therefore 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.

5.3.1 Position in the treatment pathway

The current clinical treatment pathway for patients with oHCM in Denmark is shown in Figure 3, which includes the proposed placement of mavacamten. The estimates for patient numbers are presented and explained in Section 5.1.2.

Figure 3. Overview of the oHCM treatment pathway in Denmark and mavacamten's anticipated position



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

Sources: Mølgaard et al. (2022)[19]; Elliott et al. (2014)[3]; Ommen et al. (2020)[1]; Zoerner et al. (2022)[45]; and BMS estimate

6 Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

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, a systematic literature review (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.[13]
- The phase 2 trial, PIONEER-HCM, investigated the safety, tolerability, and dosing of mavacamten in patients with oHCM.[52]

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 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 only briefly summarised in this submission.

PIONEER-HCM was a phase 2, open-label study[52] and was not considered to represent the best available evidence, given that data are available from the pivotal phase 3 EXPLORER-HCM trial.[13] PIONEER-HCM[53] and the associated long-term extension (LTE) study, PIONEER-OLE,[53] are therefore not described further in the main submission.

6.2 List of relevant studies

Table 7 presents the relevant studies included in this assessment. Table 8 presents ongoing studies.

Table 7. Summary of randomised controlled trials 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)[13]
					Spertus et al. (2021)[14]
					Xie et al. (2021)[15]
					Ho et al. (2020)[54]
					Saberi et al. (2020)[55]
					Hegde et al. (2021)[56]
MAVA-LTE (contains EXPLORER-LTE cohort)	NCT03723655	2/3	October 2018 to April 2026	None	Rader et al. (2022)[16]
VALOR-HCM	NCT04349072	3	July 2020 to June 2024	Placebo	Desai et al. (2021)[57]
					Desai et al. (2022)[58]

NCT = National Clinical Trial.

[a] Included for safety results only.

Table 8. Summary of ongoing randomised controlled trials

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)[16]
VALOR-HCM	NCT04349072	3	July 2020 to June 2024	Placebo	Desai et al. (2021)[57]
					Desai et al. (2022)[58]
PIONEER-OLE	NCT03496168	2	April 2018 to November 2023	None	Heitner et al. (2019)[52]

NCT = National Clinical Trial.

For detailed information about included studies, see Appendix B.

7 Efficacy and safety

The pivotal trial for this application is EXPLORER-HCM (MYK-461-005), described in Table 9. 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.[16,59] 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 interim analysis based on the August 2021 database lock.[16] In addition supporting evidence from VALOR-HCM (MYK-461-017) is presented.[57,58]

For detailed study characteristics, see Appendix B. For baseline characteristics of patients included in each study, see Appendix C.

7.1 Relevant studies

7.1.1 EXPLORER-HCM

Table 9. EXPLORER-HCM: summary of trial methodology

Study 1	EXPLORER-HCM[13-15]
Sample size (n)	251
Study design	Double-blind, multicentre, randomised, 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
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 health-related quality of life 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; LVOT = left ventricular outflow tract; NYHA = New York Heart Association; oHCM = obstructive hypertrophic cardiomyopathy; pVO_2 = peak oxygen consumption.

7.1.1.1 EXPLORER-HCM: study design

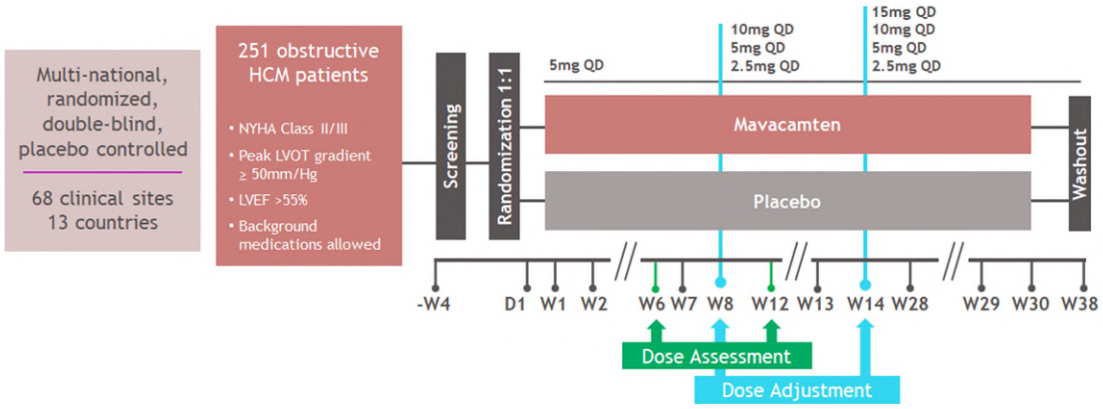
The primary objective of EXPLORER-HCM was to evaluate the efficacy and safety of mavacamten compared with placebo in patients with symptomatic oHCM (NYHA class II-III).[13] The study was an international, parallel-group, multicentre study conducted at 68 sites, including 31 sites in Europe, of which 3 sites were in Denmark.[60]

Figure 4 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 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.[13]

Figure 4. 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)[54]

The inclusion and exclusion criteria for this study were designed not only to prioritise safety, including the ability of patients to safely perform the cardiopulmonary exercise test (CPET) but also to represent patients with real-world, symptomatic oHCM.[13]

7.1.1.2 Key inclusion criteria

- ≥ 18 years of age, body weight > 45 kg at screening
- Has adequate acoustic windows to enable accurate transthoracic echocardiogram (ECG)
- Diagnosed oHCM
- LVEF ≥ 55%
- NYHA II-III symptoms
- 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

7.1.1.3 Key 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 of screening
- History of resuscitated sudden cardiac arrest or appropriate ICD discharge for life-threatening ventricular arrhythmia
- QT interval corrected using Fridericia's formula (QTcF) > 500 ms at screening
- Paroxysmal or intermittent AF present at screening
- Persistent or permanent AF and not receiving anti-coagulation treatment for ≥ 4 weeks before screening and/or not adequately rate controlled within 6 months before screening
- Treatment (within 14 days prior to screening) or planned treatment with disopyramide, ranolazine, or a combination of BBs and CCBs; previous treatment with cardiotoxic agents
- LVOT gradient with Valsalva manoeuvre < 30 mmHg at screening
- Underwent SRT within 6 months or plans to have SRT during study
- ICD placement within 2 months before screening or planned ICD placement during the study

7.1.1.4 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 (pVO_2 measured by CPET) and subjective assessments of symptom burden (NYHA class).[13] 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.[54] In addition, pVO_2 has been shown to correlate with NYHA functional class, patient-reported outcomes (PROs), and QOL.[54] Hence, the goal of the trial was to investigate both improvement in functional capacity and symptom burden.[54] The primary efficacy endpoint was a composite functional endpoint, which could be achieved through either composite 1 or composite 2 (see definition below).[13] It is not possible to power randomised trials in HCM to identify benefit for hard endpoints because of the low rates of mortality, stroke, transplant, and hospitalisation. 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.[54]

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

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 (N-terminal pro–B-type natriuretic peptide [NT-proBNP], high-sensitivity cardiac troponin I), from baseline to week 30
- ECG 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

7.1.1.5 EXPLORER-HCM: Statistical testing

Efficacy and safety analyses were conducted on the intention-to-treat (ITT) population, defined as all patients who were randomly assigned and received ≥ 1 dose of study medication. The primary efficacy endpoint and improvement in NYHA class were analysed with the Cochran-Mantel-Haenszel test for stratified categorical data. Continuous variables in secondary efficacy endpoints were compared between treatment groups by analysis of covariance or by mixed-effect model repeated measures. Safety data were analysed as descriptive statistics. Additionally, efficacy was also assessed in prespecified subgroups based on observed baseline demographic and disease characteristics.[13]

7.1.1.6 EXPLORER-HCM: Baseline characteristics

A total of 251 patients were randomly assigned and included in the ITT and safety population (mavacamten, n = 123; placebo, n = 128). Patients had expected features of oHCM (e.g., left ventricular wall thickness, positive family history for the condition, ICD). The mean age of patients was 58.5 years, with most having NYHA II symptoms (73%) and taking a BB or CCB (92%). Eleven patients treated with mavacamten and 8 patients treated with placebo underwent prior SRT. Baseline characteristics are presented in Table 10 and were similar between study groups, except for the mavacamten group had a smaller percentage of men and patients with a history of AF, a higher percentage of patients taking a CCB, and higher baseline NT-proBNP concentration than the placebo group.[13]

Table 10. EXPLORER-HCM: baseline demographic and disease characteristics

Characteristic	Mavacamten (n = 123)	Placebo (n = 128)
Age (years), mean (SD)	58.5 (12.2)	58.5 (11.8)
Male sex, n (%)	66 (54)	83 (65)
Female sex, n (%)	57 (46)	45 (35)
NYHA		
Class II	88 (72)	95 (74)
Class III	35 (28)	33 (26)
Medical history, n (%)		
Family history of HCM	33 (27)	36 (28)
AF	12 (10)	23 (18)
Septal reduction therapy	11 (9)	8 (6)
pVO_2, mL/kg/min, mean (SD)	18.9 (4.9)	19.9 (4.9)
NT-proBNP, ng/L, geometric mean (coefficient of variation %)[a]	777 (136)	616 (108)
Background therapy, n (%)		
BB	94 (76)	95 (74)
CCB	25 (20)	17 (13)
HCM genetic testing performed, n (%)		
Pathogenic/likely pathogenic HCM gene variant, n/N tested (%)	28/90 (31)	22/100 (22)
Echocardiographic parameters		
LVEF, %	74 (6)	74 (6)
Maximum left ventricular wall thickness, mm	20 (4)	20 (3)
LVOT gradient, rest mmHg	52 (29)	51 (32)
LVOT gradient, Valsalva manoeuvre, mmHg	72 (32)	74 (32)
LVOT gradient, post-exercise, mmHg	86 (34)	84 (36)
Left atrial volume index, mL/m^2	40 (12)	41 (14)
Left atrial diameter, mm	42 (5)	42 (6)

AF = atrial fibrillation; BB = beta-blocker; CCB = calcium channel blocker; 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; pVO_2 = peak oxygen consumption; SD = standard deviation.

[a] Coefficient of variation % is defined as the ratio of the SD to the mean.

Source: Olivotto et al. (2020)[13]

7.1.2 EXPLORER-LTE

7.1.2.1 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.

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%.[16]

This multicentre study enrolled participants who completed EXPLORER-HCM through week 38 (n = 244), following the same randomisation, 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 5).[13,16,61,62]

Figure 5. EXPLORER-LTE: study design

Because patients in EXPLORER-LTE were previously enrolled in EXPLORER-HCM, the inclusion and exclusion criteria were the same for both trials (see Section 7.1.1.1).[13]

7.1.2.2 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 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

7.1.2.3 EXPLORER-LTE: statistical testing

The analysis populations defined for this interim analysis were:

- 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 summarised by number of patients, mean, SD, median, minimum, and maximum; categorical variables were summarised 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.[63] 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.[64]

7.1.2.4 EXPLORER-LTE: Baseline characteristics

Baseline patient characteristics from the EXPLORER-LTE cohort are summarised in Table 11 (based on interim analysis from the data cut-off date of 31 August 2021).

Table 11. EXPLORER-LTE: baseline demographic and disease characteristics

Characteristic	EXPLORER-LTE cohort (n = 231)
Age (years), mean (SD)	60.0 (11.9)
Female sex, n (%)	91 (39.4)
Background HCM therapy, n (%)	
BB	175 (75.8)
CCB	38 (16.5)
NYHA	
Class I	14 (6.1)
Class II	152 (65.8)
Class III	65 (28.1)
NT-proBNP, ng/L, Median NT-proBNP, ng/L (interquartile range)	783 (326, 1593)
Echocardiographic parameters (SD)	
LVEF, %	74.0 (5.9)
LVOT gradient, rest mmHg	48.3 (31.9)
LVOT gradient, Valsalva manoeuvre, mmHg	69.5 (33.3)

BB = beta-blocker; CCB = calcium channel blocker; 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; SD = standard deviation.

Source: Rader et al. (2022)[16]

7.1.3 VALOR-HCM

7.1.3.1 VALOR-HCM: study design

VALOR-HCM is a 136-week, phase 3, multicentre, randomised, double-blind, placebo-controlled trial to evaluate the efficacy, safety, and tolerability of mavacamten in adults with symptomatic oHCM who are eligible for SRT as defined by the 2011 American College of Cardiology/American Heart Association (ACC/AHA) guideline criteria and who are willing to undergo the procedure.[57] Table 12 presents details of the study methodology.

Table 12. VALOR-HCM: summary of trial methodology

Study	VALOR-HCM[57]
Sample size (n)	112
Study design	Double-blind, multicentre, randomised, placebo-controlled, phase 3 trial
Patient population	Adults with oHCM in NYHA III or IV, or class II with exertional syncope or near syncope who meet 2011 ACC/AHA guideline criteria for SRT
Intervention(s)	Mavacamten 5 mg once daily + BB/CCB monotherapy, with possible dose adjustment
Comparator(s)	Placebo + BB/CCB monotherapy
Follow-up period	Study duration: 128 weeks Follow-up: 136 weeks
Is the study used in the health economic model?	Yes, in a scenario analysis
Reasons for use/non-use of the study in the model	This study is not the pivotal study; it is a supportive study for this application
Primary endpoints reported	Week 16 SRT status
Other outcomes reported	Change in LVOT gradient; NYHA class; KCCQ-23; NT-proBNP; cardiac troponin

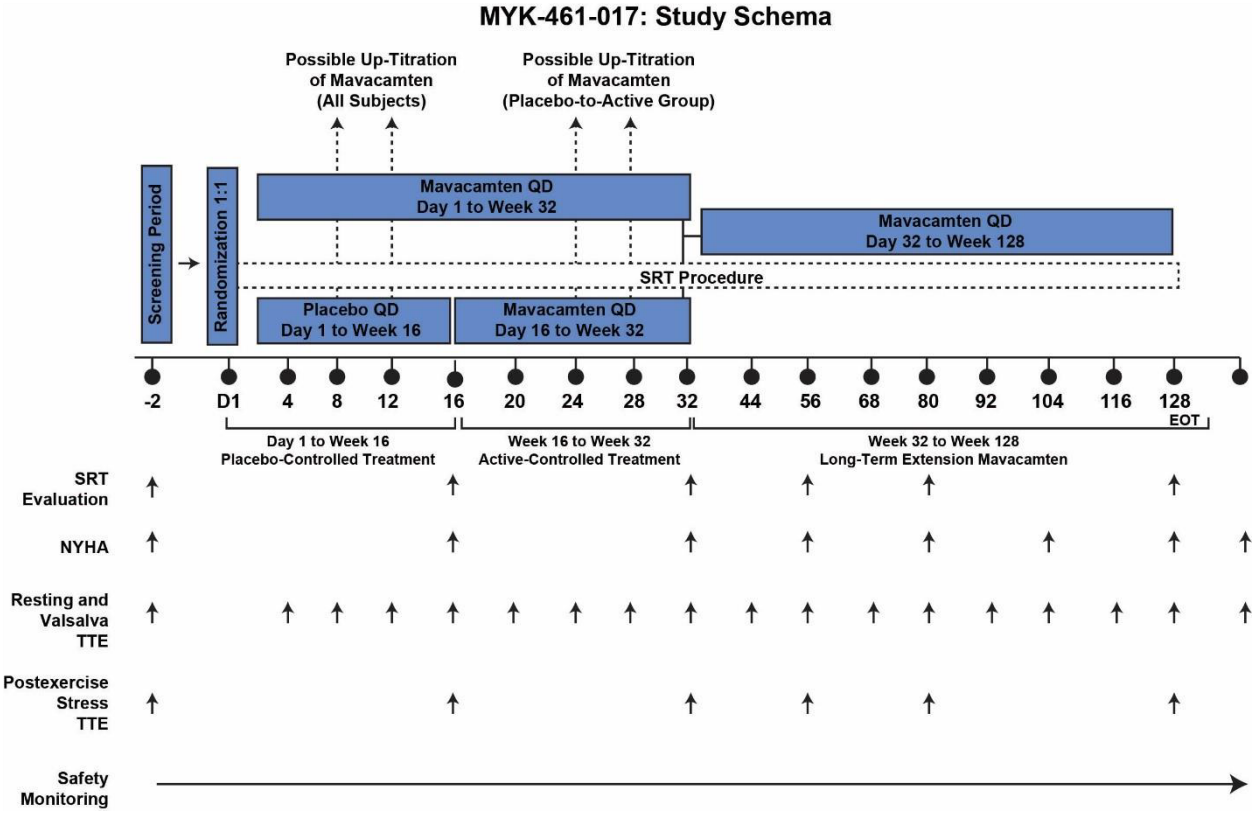
ACC/AHA = American College of Cardiology/American Heart Association; BB = beta-blocker; CCB = calcium channel blocker; HCM = hypertrophic cardiomyopathy; KCCQ-23 = 23-item Kansas City Cardiomyopathy Questionnaire; LVOT = left ventricular outflow tract; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; SRT = septal reduction therapy.

Study visits occur at screening, day 1, every 4 weeks through week 32, every 12 weeks thereafter until week 128 (end of trial), and at week 136 (end of study). A variety of general, cardiopulmonary, laboratory, biomarker, patient-reported outcome, and symptom assessments are scheduled to be performed at screening, day 1, and all subsequent study visits.[57]

On day 1, eligible patients began placebo-controlled dosing with mavacamten 5 mg or placebo once daily for 16 weeks. Randomisation was performed using an interactive voice/web-response system in a 1:1 ratio to receive double-blind treatment with mavacamten or matching placebo. Randomisation was stratified by the type of SRT recommended (myectomy or alcohol ablation) and NYHA class.[58]

Throughout the study, all necessary dose adjustments occured in a blinded manner via integration of LVOT gradient and LVEF from echocardiography into the interactive voice/web-response system.[58] Figure 6 presents the study design of VALOR-HCM.

Figure 6. VALOR-HCM: study design



EOT = end of treatment; NYHA = New York Heart Association; QD = once daily; SRT = septal reduction therapy; TTE = transthoracic echocardiogram.

Sources: Desai et al. (2021)[57]; Desai et al. (2022)[58]

7.1.3.2 VALOR-HCM: key inclusion criteria[57]

- Adults with symptomatic oHCM consistent with 2011 ACC/AHA and/or 2014 ESC guidelines who have met recommendations for invasive therapies within the past 12 months and are willing to undergo the procedure
- Despite maximally tolerated drug therapy, have severe dyspnoea or chest pain (NYHA III or IV) or class II with exertional symptoms, such as exertion-induced syncope or near syncope
- Dynamic LVOT gradient at rest or with provocation (i.e., Valsalva manoeuvre or exercise) ≥ 50 mmHg associated with septal hypertrophy (read by the core echocardiography laboratory)
- Documented LVEF ≥ 60% and oxygen saturation at rest ≥ 90% at screening
- Maximum septal wall thickness ≥ 15 mm or ≥ 13 mm with family history of HCM
- Weight > 45 kg
- Referred or under active consideration within 12 months for, and willing to undergo, SRT procedure

7.1.3.3 VALOR-HCM: key exclusion criteria[57]

- Persistent or permanent atrial fibrillation without anticoagulation for ≥ 4 weeks and/or not adequately rate-controlled ≤ 6 months before screening
- Prior SRT
- Any recent or anticipated dose change of beta-blockers, calcium channel blockers, or disopyramide

- Conditions precluding upright exercise stress testing or others considered a risk to patient safety
- Paroxysmal or intermittent atrial fibrillation
- Prior treatment with cardiotoxic agents

7.1.3.4 VALOR-HCM: endpoints[57]

Primary endpoints

- Week 16 SRT status.
- A composite of the decision to proceed with SRT before or at week 16 or be considered eligible for SRT at week 16 per guidelines. Early dropouts or patients whose response status cannot be assessed at the end of the 16-week dosing period will be classified as eligible for SRT.

Secondary endpoints

- Change from baseline to week 16 in NYHA class
- Change from baseline to week 16 in 23-item Kansas City Cardiomyopathy Questionnaire (KCCQ-23) score
- Change from baseline to week 16 in NT-proBNP
- Change from baseline to week 16 in cardiac troponin
- Change from baseline to week 16 in LVOT gradient

Exploratory endpoints

- A composite of the outcomes at weeks 32, 56, 80, and 128:
  - Decision to proceed with SRT before the end of each period; or eligible for SRT at the end of each period per guidelines

7.1.3.5 VALOR-HCM: Baseline characteristics

The baseline demographic and disease characteristics for patients in VALOR-HCM are presented in Table 13.

Table 13. VALOR-HCM: baseline demographic and disease characteristics

Characteristic	Mavacamten (n = 56)	Placebo (n = 56)
Age (years), mean (SD)	59.8 (14.2)	60.9 (10.5)
Male sex, n (%)	29 (51.8)	28 (50)
Female sex, n (%)	27 (48.2)	28 (50)
NYHA class, n (%)		
II with exertional syncope	4 (7.1)	4 (7.1)
III or higher	52 (92.9)	52 (92.9)
Medical history, n (%)		
Family history of HCM	17 (30.4)	15 (26.8)
Atrial fibrillation	11 (19.6)	8 (14.3)
Hypertension	36 (64.3)	34 (60.7)
Syncope or presyncope	29 (51.8)	30 (53.6)

Characteristic	Mavacamten (n = 56)	Placebo (n = 56)
Implantable cardioverter-defibrillator	9 (16.1)	10 (17.9)
Type of SRT, n (%)		
Alcohol septal ablation	8 (14.3)	7 (12.5)
Myectomy	48 (85.7)	49 (87.5)
NT-proBNP, ng/L, geometric mean (CV%)	724 (291-1913)	743 (275-1196)
Background therapy, n (%)		
BB monotherapy	26 (46.4)	25 (44.6)
CCB monotherapy	7 (12.5)	10 (17.9)
BB/CCB	6 (10.7)	10 (17.9)
Disopyramide (monotherapy or in combination)	14 (25)	8 (14.4)
None, medication intolerance	3 (5.4)	3 (5.4)
Echocardiographic parameters, n (SD)		
LVEF, %	67.9 (3.7)	68.3 (3.2)
LVOT gradient, rest mmHg	51.2 (31.4)	51 (32)
LVOT gradient, Valsalva manoeuvre, mmHg	75.3 (30.8)	76.2 (29.9)
LVOT gradient, after exercise, mmHg	82.5 (34.7)	85.2 (37.0)
LAVI, mL/m^2	41.3 (16.5)	40.9 (15.2)

BB = beta-blocker; CCB = calcium channel blocker; CV = coefficient of variation; HCM = hypertrophic cardiomyopathy; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; SD = standard deviation; SRT = septal reduction therapy.

Source: Desai et al. (2022)[58]

7.2 Efficacy results

7.2.1 EXPLORER-HCM: efficacy results

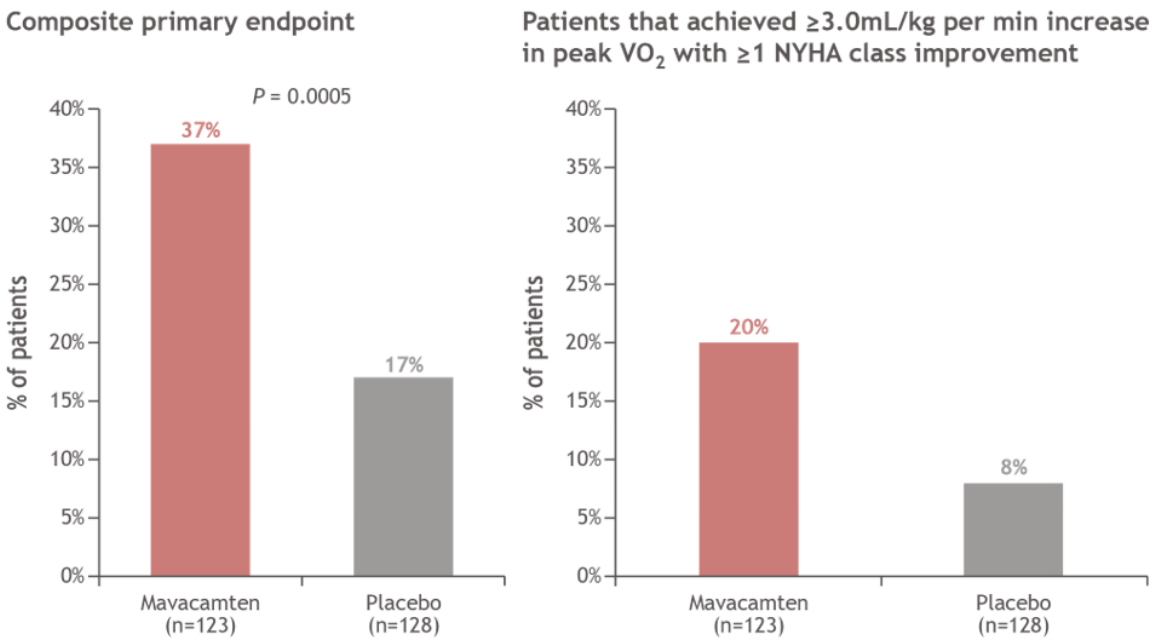
This section presents results from analyses of the primary efficacy endpoints and secondary/exploratory endpoints from the pivotal study EXPLORER-HCM and the LTE study EXPLORER-LTE. Currently, no comparable treatment exists; therefore, the EXPLORER-HCM trial evaluating mavacamten versus placebo is the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

For detailed efficacy and safety results, see Appendices D and E.

7.2.1.1 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 7). 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.[13] Hence, treatment with mavacamten provided clinically relevant improvements in functional capacity concomitant with a reduction in symptom burden compared with placebo.

Figure 7. **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)[13]

The between-group difference for patients who achieved the composite functional endpoint was statistically significant based on the primary analysis (Table 14).[13]

Table 14. **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.

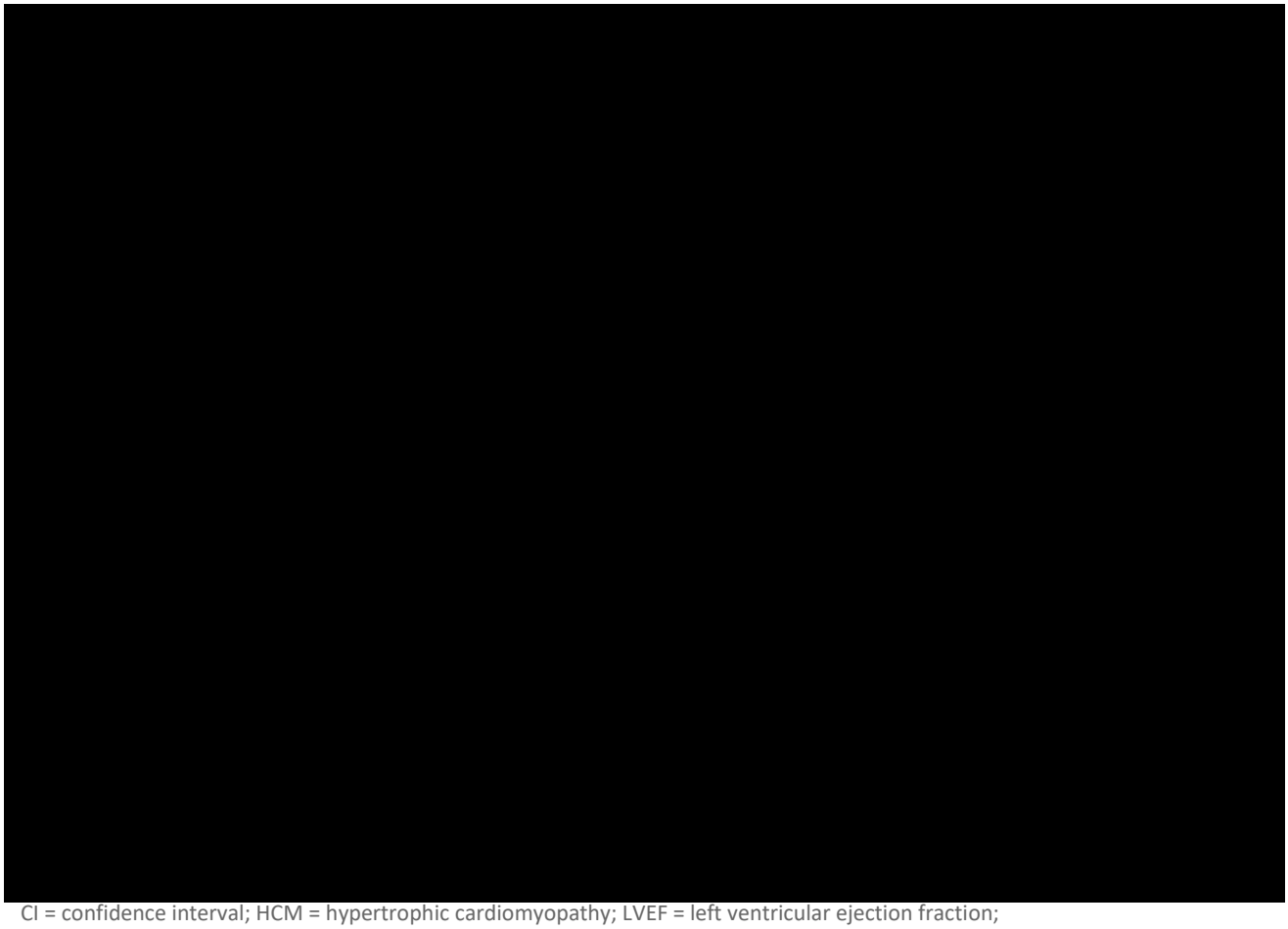
Note: The primary composite endpoint was defined as achieving an improvement of ≥ 1.5 mL/kg/min pVO_2 and a reduction of ≥ 1 class in NYHA class (Composite 1) or an improvement of ≥ 3.0 mL/kg/min in pVO_2 with no worsening in NYHA class (Composite 2). Patients with a non-evaluable primary endpoint and 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)[13]

Prespecified subgroup analyses found that the effect of mavacamten on the primary composite endpoint was generally consistent across subgroups (Figure 8).[13] 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.[13] Olivotto et al. (2020)[13] 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.[65]

Figure 8. EXPLORER-HCM: treatment effect on primary composite endpoint by subgroup



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 favouring mavacamten treatment, and a negative mean percentage difference indicative of favouring placebo.

Source: Olivotto et al. (2020)[13]

7.2.1.2 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.[13] Across multiple measures of symptoms and function evaluated in EXPLORER-HCM, the results demonstrate that myosin inhibition with mavacamten normalises contractility, reduces dynamic LVOT obstruction, improves cardiac filling pressures, and reduces biomarkers of cardiac stress, improving symptoms and exercise capacity.[13]

All secondary endpoints showed consistent benefit for mavacamten across prespecified subgroups, irrespective of BB use.[13]

Physician-reported outcomes

Patients treated with mavacamten showed decreased LVOT gradient, increased pVO_2, and improved symptoms as evaluated by physicians (NYHA class; Table 15).[13]

Table 15. 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 analysable for secondary endpoints based on availability of both baseline and week 30 values.

[a] Mavacamten (n = 117), placebo (n = 122).

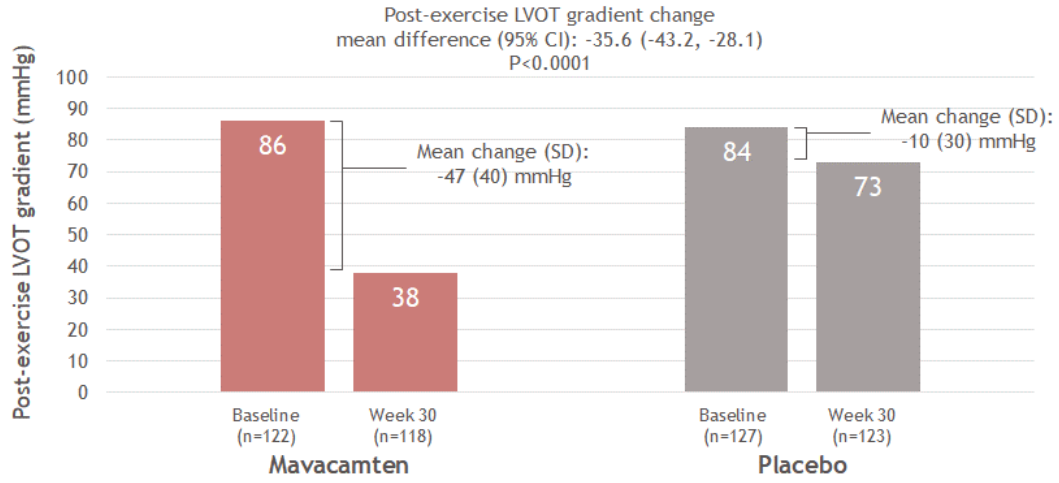
[b] Mavacamten (n = 120), placebo (n = 125).

[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)[13]

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 9).[13]

Figure 9. EXPLORER-HCM: post-exercise left ventricular outflow tract gradient change



CI = confidence interval; LVOT = left ventricular outflow tract; SD = standard deviation.

Adapted from Olivotto et al. (2020)[13]

Prespecified subgroup analyses found that the benefit of mavacamten extended across subgroups when assessing post-exercise LVOT gradient (Figure 10).[13]

Figure 10. EXPLORER-HCM: treatment effect on post-exercise left ventricular outflow tract gradient by subgroup

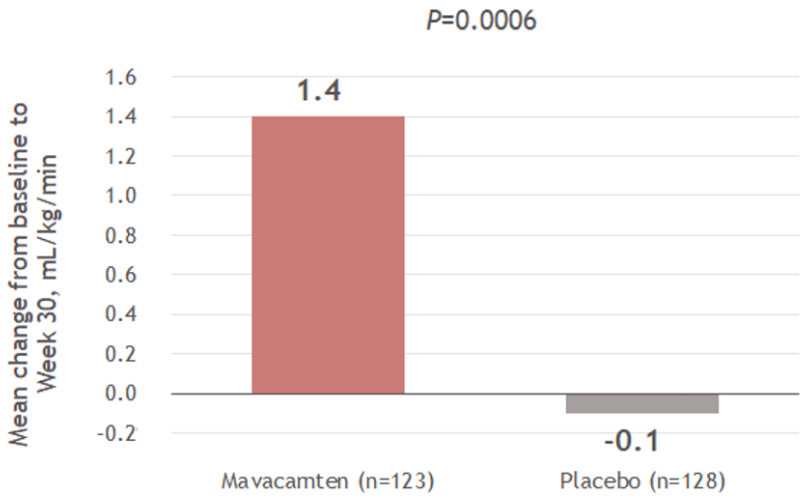
CI = confidence interval; HCM = hypertrophic cardiomyopathy; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association.

Note: No treatment effect is at 0, with a positive mean difference indicative of favouring placebo, and a negative mean difference indicative of favouring mavacamten treatment.

Source: Olivotto et al. (2020)[13]

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 11).[13]

Figure 11. Improvement in exercise capacity, measured by peak oxygen consumption (pVO_2)

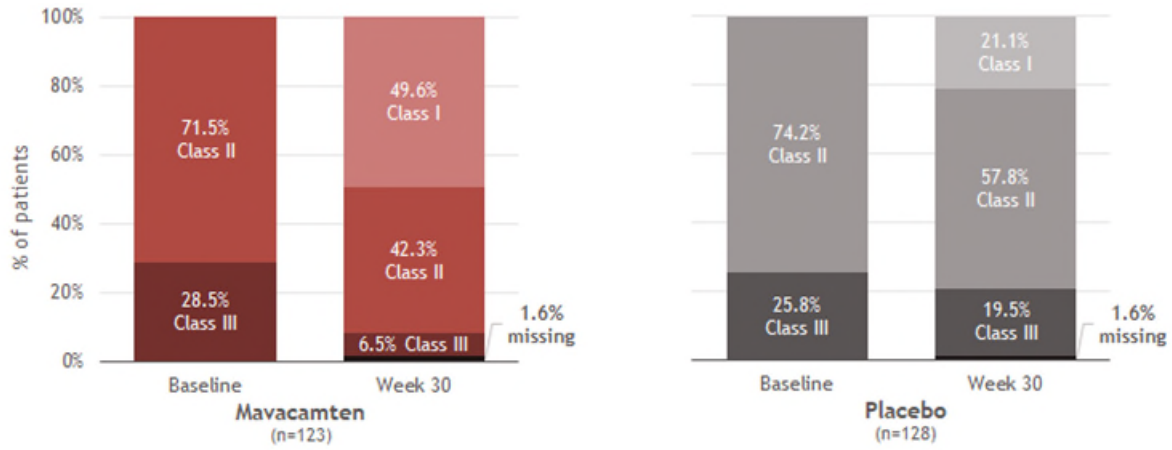


Adapted from Olivotto et al. (2020)[13]

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).[59]

In the mavacamten group, 80 out of 123 patients (65%) had at least 1 NYHA class improvement compared with 40 out of 128 patients (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% of patients (27 of 128) reached NYHA class I status with placebo (Figure 12).[13] 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 12. Change in NYHA class from baseline to week 30



NYHA = New York Heart Association.
Adapted from Olivotto et al. (2020)[13]

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).[59]

Patient-reported outcomes

Improvements in symptoms as evaluated by PROs were also observed with mavacamten compared with placebo (Table 16).[14,15] 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).[59]

Table 16. EXPLORER-HCM: secondary endpoints, patient-reported outcomes

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 analysable 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 unfavourable outcomes for mavacamten and favourable 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)[14]; Xie et al. (2021)[15]; Olivotto et al. (2020)[13]

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

The KCCQ-CSS and the KCCQ-OS (Figure 13) 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.[14] There was a rapid decrease of these differences from weeks 30 through 38, with cessation of the study drug at week 30. For both the KCCQ-CSS and the 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.[14]

Figure 13. Change in KCCQ-OS from baseline to week 38

KCCQ-OS Kansas City Cardiomyopathy Questionnaire – Overall Summary Score.
Note: Mean change from baseline over time in KCCQ-OS score. Error bars are standard error.
Source: Spertus et al. (2021)[14]

Unlike the 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 17), 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.[66]

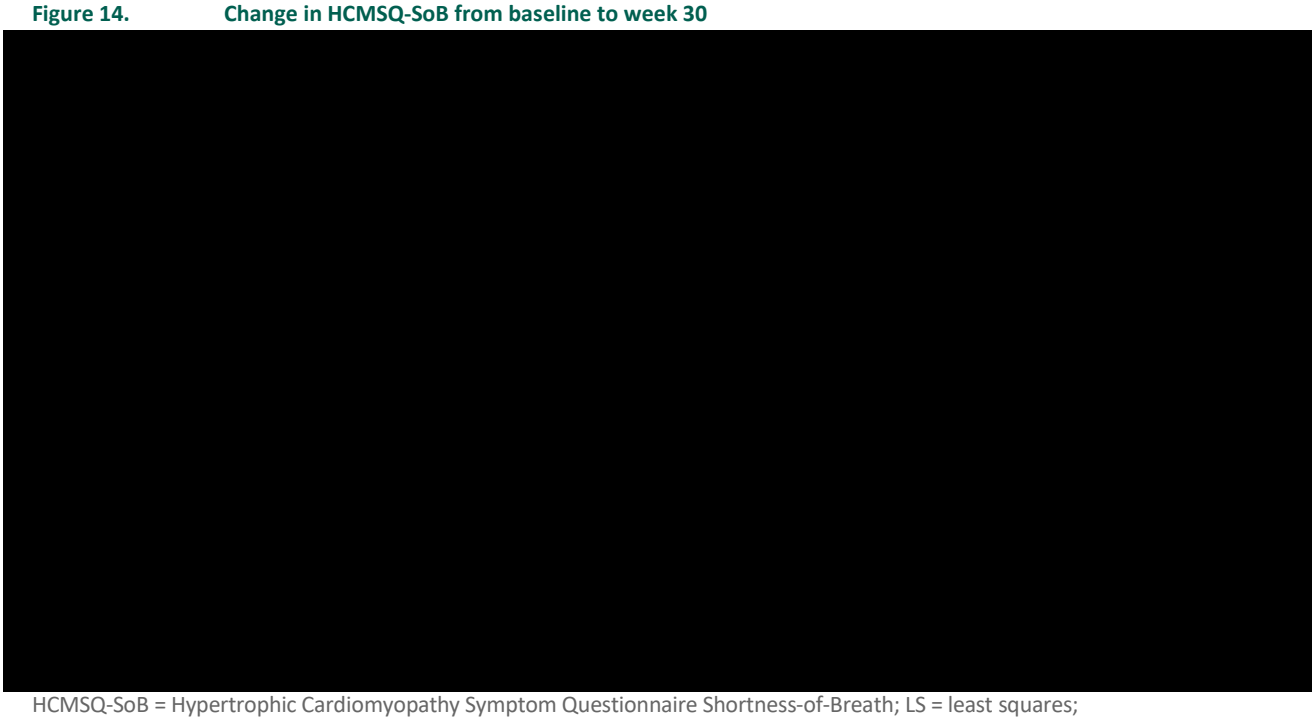
Table 17. EXPLORER-HCM: secondary endpoints, KCCQ subdomain scores

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 analysable 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)[14]

The HCMSQ-SoB favoured 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 14). 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.[67]

Figure 14. Change in HCMSQ-SoB from baseline to week 30



HCMSQ-SoB = Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath; LS = least squares; SE = standard error.

Source: BMS data on file (2021)[67]

Consistent with the 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.[67]

7.2.1.3 EXPLORER-HCM: exploratory efficacy endpoint

Physician-reported outcomes

Compared with placebo, mavacamten demonstrated quick improvements in resting and Valsalva manoeuvre LVOT gradients, which were maintained during the study.[13] 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 18). 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).[13]

Table 18. 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)[13]

Patient-reported outcomes

Improvements in EQ-5D-5L and EQ VAS were also observed with mavacamten compared with placebo.[14,15,68] 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 15). 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%).[15]

Figure 15. Change in EQ-5D-5L and EQ VAS from baseline to week 30

MCT = meaningful change threshold.

Source: Xie et al. (2021)[15]

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).[13] These biomarkers are predictive of long-term outcome in patients with HCM.[13] Prespecified subgroup analyses demonstrated that, regardless of BB use, patients treated with mavacamten had similar improvement in biomarkers (both NT-proBNP and hs-cTnI).[59]

Cardiac structure and function

Echocardiogram parameters of left ventricular structure and function from patients in the EXPLORER-HCM cohort were analysed. 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.[55,56] 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 favourable effect of mavacamten on cardiac remodelling (left ventricular wall thickness, fibrosis) (Figure 16).

Figure 16. EXPLORER-HCM: change in left ventricular mass index from baseline to week 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)[56]

Patients with higher baseline Valsalva manoeuvre LVOT gradients demonstrated greater reductions in left atrial volumes (*P* for interaction = 0.03). No significant interaction was seen between baseline Valsalva manoeuvre LVOT 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%; $P < 0.001$).[56]

7.2.2 MAVA-LTE (EXPLORER-LTE cohort): efficacy results

Patients enrolled in the MAVA-LTE study demonstrated benefit consistent with that achieved in the parent study.[1]6 Of note, the interim findings presented below are for different timepoints because they come from different parent studies. [redacted]

7.2.2.1 MAVA-LTE (EXPLORER-LTE cohort): interim findings

- At weeks 48 and 84, 192 patients (83%) and 196 patients (85%), respectively, were treated with mavacamten ≤ 10 mg.[16]
  - o [redacted]
- Similar to EXPLORER-HCM, rapid and sustained improvements in both resting and Valsalva manoeuvre LVOT gradients were seen with mavacamten starting as early as week 4. At week 84, mean change from baseline (SD) was −32.8 mmHg (30.8) for resting LVOT gradient and −46.4 mmHg (35.8) for Valsalva manoeuvre LVOT gradient.[16]
  - o [redacted]
- Through week 48, improvements in NYHA class were seen such that 67.5% (139/206) improved ≥ 1 NYHA class (60.2% [124/206] improved by 1 NYHA class, and 7.3% [15/206] improved by 2 NYHA classes).[16]
  - o [redacted]

MAVA-LTE (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%]).[61]
  - o In the 31 May 2022 database lock a stabilization in LVEF was observed over time, i.e. no change from the former database lock was observed.[69]
- Improvements in left ventricular filling pressure (lateral E/e' and left atrial volume index) were seen through week 48.[16]
- Decreases in NT-proBNP levels were seen at week 4 and sustained through week 60; the median change from baseline to week 60 was −356 ng/L.[61]

7.2.3 VALOR-HCM: efficacy results

7.2.3.1 VALOR-HCM: primary efficacy endpoint

At week 16, mavacamten showed benefit for the primary endpoint in VALOR-HCM by reducing SRT eligibility across a broad patient population. After 16 weeks of treatment, 10 of 56 patients treated with mavacamten (17.9%) met the composite primary endpoint, continued to meet guideline criteria for SRT, or elected to undergo SRT compared with 43 of 56 patients receiving placebo (76.8%). The difference between the mavacamten and placebo groups was statistically significant (58.9%; 95% CI, 44.0%-73.9%; $P < 0.0001$)(Table 19).[58]

Table 19. VALOR-HCM: primary endpoint – composite of patient decision to proceed with SRT or eligibility for SRT according to the ACC/AHA 2011 guidelines at week 16 (ITT population)

Parameters	Mavacamten (n = 56)	Placebo (n = 56)
Patients meeting the primary endpoint,[a] n (%)	10 (17.9)	43 (76.8)
Patients who decided to proceed with SRT before or at week 16, n (%)	2 (3.6)	2 (3.6)
Patients eligible for SRT based on the guideline criteria[b] at week 16 and who did not decide to proceed with SRT, n (%)	8 (14.3)	39 (69.6)
Patients whose SRT status not evaluable and who did not decide to proceed with SRT, n (%)	0	2 (3.6)
	Diff (placebo vs. mavacamten) Stratified analysis[c]	
Difference in patients meeting the primary endpoint (95% CI)	58.9pp (44.0pp-73.9pp)	
P value	< 0.0001	

ACC = American College of Cardiology; AHA = American Heart Association; CI = confidence interval; HCM = hypertrophic cardiomyopathy; ITT = intention to treat; NYHA = New York Heart Association; PP = % points; SRT = septal reduction therapy.

Note: Proportion difference (placebo – mavacamten) is estimated using the Mantel-Haenszel method.

[a] Meeting the primary endpoint was defined as patient either decided to proceed with SRT or was eligible for SRT per protocol-specified guidelines at week 16. Patients with missing primary endpoint assessments were classified as meeting the primary endpoint (did not improve).

[b] The guideline criteria are based on 2011 ACC/AHA HCM clinical and hemodynamic criteria.

[c] Cochran-Mantel-Haenszel method stratified by type of SRT recommended (myectomy vs. alcohol septal). NYHA class was removed from the stratification because only 1 patient in the class II underwent alcohol septal ablation stratum.

Source: Desai et al. (2022)[58]

7.2.3.2 VALOR-HCM: secondary efficacy endpoints

Hierarchical testing of secondary endpoint results showed statistically significant and clinically meaningful differences (*P* < 0.0001 for all endpoints) favouring mavacamten (Table 20):[58]

- Difference in mean change from baseline in post-exercise peak LVOT gradient at Week 16 for mavacamten vs. placebo was - 37.2 mmHg (95% CI, −48.08 to −26.24; *P* < 0.0001).
- Difference in the number of subjects who improved ≥ 1 NYHA class at Week 16 for mavacamten vs. placebo was 41.07% (95% CI, 24.481-57.662; *P* < 0.0001).
- Difference in the KCCQ-23 CSS from baseline to Week 16 for mavacamten vs. placebo was 9.45 points (95% CI, 4.868-14.041; *P* < 0.0001).
- Difference in geometric mean ratio from baseline to Week 16 for NT-proBNP and cardiac troponin I was 0.33 (95% CI, 0.266-0.421; *P* < 0.0001) and 0.53 (95% CI, 0.406-0.700; *P* < 0.0001), respectively, for mavacamten vs. placebo.

Table 20. VALOR-HCM: Secondary efficacy endpoints - ITT population

Secondary endpoints	Mavacamten N = 55	Placebo N = 53	Mavacamten vs. placebo: difference (95% CI) *P* value
Post-exercise LVOT peak gradient, mmHg, mean (SD) change from BL at W16	-39.1 (36.51)	-1.8 (28.82)	LS mean of treatment difference: -37.2 (−48.08 to −26.24) < 0.0001

Secondary endpoints	Mavacamten N = 55	Placebo N = 53	Mavacamten vs. placebo: difference (95% CI) *P* value
NYHA improved ≥ 1 class, n/N (%)	35 (62.5)	12 (21.4)	Stratified analysis proportion difference: 41.07 (24.481-57.662) < 0.0001
KCCQ-23 CSS, mean (SD) change from BL at W16	10.4 (16.06)	1.8 (12.01)	LS mean of treatment difference: 9.45 (4.868-14.041) < 0.0001
NT-proBNP (ng/L), geometric mean ratio to BL at W16 (95% CI)	0.35 (83.677)	1.13 (57.809)	Model Based Proportion of Geometric Mean Ratio: 0.33 (0.266-0.421) < 0.0001
hs-cardiac troponin I (ng/L), geometric mean ratio to BL at W16 (95% CI)	0.50 (100.992)	1.03 (85.716)	Model Based Proportion of Geometric Mean Ratio: 0.53 (0.406-0.700) < 0.0001

BL = baseline; CI = confidence interval; CSS = clinical summary score; ITT = intention to treat; KCCQ-23 = Kansas City Cardiomyopathy Questionnaire 23-item version; LVOT = left ventricular outflow tract; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SD = standard deviation; W = week.

Source: Desai et al. (2022)[58]

These secondary endpoint results from the VALOR-HCM study are similar to the results for the equivalent endpoints from the EXPLORER-HCM study and confirm and complement the positive and clinically meaningful efficacy results of the EXPLORER-HCM study.

Post-exercise LVOT gradient

A statistically significant difference in post-exercise LVOT gradient favouring the mavacamten arm over the placebo arm was observed (Figure 17).[58] At baseline, the mean peak post-exercise LVOT gradient was 82.5 mmHg (standard deviation [SD]: 35) in the mavacamten arm and 85.2 mmHg (SD, 37) in the placebo arm. At Week 16, the mean peak post-exercise LVOT gradients were 42.0 mmHg (SD, 30) and 83.2 mmHg (SD, 36) in the mavacamten and placebo arms, respectively. A peak gradient above 50 mmHg is one criterion for considering septal reduction therapy. The change from baseline to Week 16 was −39.1 vs. −1.8 mmHg in the mavacamten and placebo arms, respectively, a between-group difference of −37.2 mmHg (95% CI, −48.1 to −26.2; $P < 0.0001$).

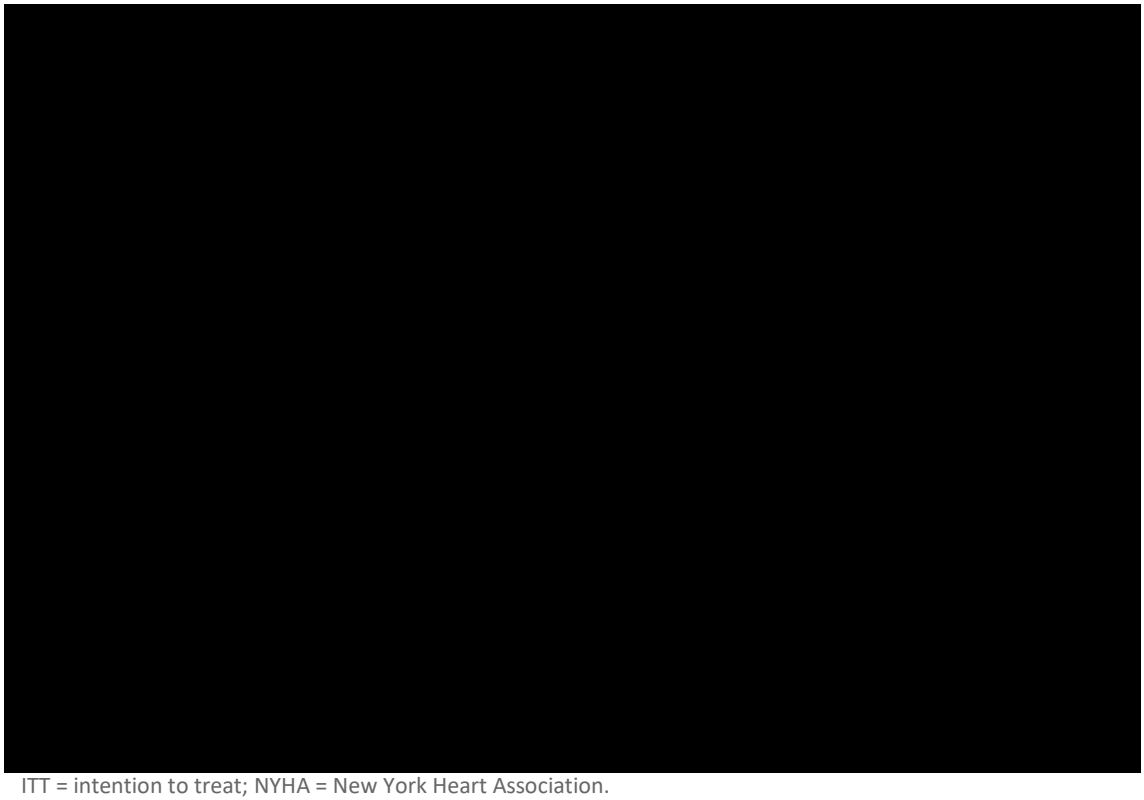
Figure 17. VALOR-HCM: Line graph of LVOT gradient post exercise by treatment group - ITT population

BL = baseline; ITT = intention to treat; LVOT = left ventricular outflow tract; SD = standard deviation; Wk = week.
Note: Mean (SD) are shown in the plot.
Source: Desai et al. (2022)[58]

NYHA functional classification

At baseline, 104 subjects (52 [92.9%] in each arm) were NYHA class III/IV (marked or severe activity limitations). There was only 1 class IV subject in the VALOR-HCM mavacamten arm. The remainder of the subjects were NYHA class II with a history of exertional syncope or near-syncope. A statistically significant difference in change in NYHA class favouring the mavacamten arm over the placebo arm was observed. No subjects in the mavacamten arm and 1 subject in the placebo arm had worsening of their NYHA class at Week 16 compared with baseline. A statistically significant larger proportion of subjects in the mavacamten group (62.5%) had a NYHA class improvement ≥ 1 compared with subjects in the placebo group (21.4%) (Figure 18). This result is clinically meaningful because functional capacity is a powerful prognostic marker in HCM.[70,71] and an individual reduction in NYHA class of ≥ 1 is a clinically meaningful improvement in a patient's status.[72]

Figure 18. VALOR-HCM: bar chart of NYHA improvement - ITT population



ITT = intention to treat; NYHA = New York Heart Association.
Notes: Category "None" also includes those with change from baseline of NYHA class to be missing or worsened. Subjects who improved by ≥ 2 NYHA classes are included in the bar for those who improved by ≥ 1 NYHA class.
Source: Desai et al. (2022)[58]

KCCQ-23 Clinical Summary Score

A statistically significant difference was observed that favoured the mavacamten arm over the placebo arm. In VALOR-HCM, the mean KCCQ-23 CSS was 68 (SD, 18) points at baseline: 70 points (SD, 16) and 66 (SD, 20) points in the mavacamten and placebo arms, respectively. The change from baseline to Week 16 was +10.4 vs. +1.8 points in the mavacamten and placebo arms, respectively, a between-group difference of +9.45 points (95% CI: +4.9, +14.0 points; $P < 0.0001$).

Substantial differences in proportion of responders were observed at Week 16 across clinically meaningful within-patient change thresholds, demonstrating consistent mavacamten superiority to placebo. The entire distribution of responses for the mavacamten and placebo groups shows clear separation between treatment groups across a range of values indicating that a greater proportion of mavacamten-treated patient demonstrated a clinical benefit (Figure 19).

In summary, mavacamten subjects demonstrated a statistically significant increase (i.e., improvement) in the KCCQ-23 CSS compared with placebo subjects (between-group difference of +9.45 points; $P < 0.0001$). This finding was supported by the responder analyses, which showed marked differences favouring mavacamten in the proportions of patients who achieved various levels of meaningful change thresholds at the individual level.

Figure 19. VALOR-HCM: KCCQ-23 Clinical Summary Score: cumulative distribution of change from baseline to Week 16

KCCQ = Kansas City Cardiomyopathy Questionnaire 23-item version; SD = standard deviation.
Note: Mean (SD) are shown in the plot.
Source: Desai et al. (2022)[58]

NT-proBNP

A statistically significant difference in change in geometric mean ratio from baseline to Week 16 for NT-proBNP favouring the mavacamten arm over the placebo arm was observed (Figure 20). The overall geometric mean NT-proBNP was 629.0 ng/L (% coefficient of variation [CV] 191) at baseline: 735.8 ng/L (%CV: 211) and 537.6 ng/L (%CV: 170) in the mavacamten and placebo arms, respectively. The change from baseline to Week 16 was −971.3 vs. +141.9 ng/L in the mavacamten and placebo arms, respectively, a between-group geometric mean ratio of 0.33 (95% CI, 0.27-0.42; $P < 0.0001$).[58]

These results demonstrate that mavacamten treatment resulted in a reduction in NT-proBNP. Based on the evidence in the literature, elevated NT-proBNP is associated with worse outcomes in HCM. In a large cohort of patients with HCM, NT-proBNP was an independent predictor of morbidity and mortality with levels of ≥ 298 ng/L associated with a nearly 5× lower 3-year survival rate than levels > 98 ng/L to ≤ 298 (hazard ratio: 4.88, $P = 0.006$) and nearly 7× lower than levels ≤ 98 ng/L (hazard ratio: 6.98, $P = 0.003$).[58] Studies in heart failure demonstrated that reductions in NT-proBNP were associated with lower risk of heart failure hospitalisations and cardiovascular death, cardiovascular death alone, recurrent heart failure hospitalisations alone,[73] and significant decreases in left atrium size.[74]

Figure 20. VALOR-HCM: line graph of NT-proBNP by treatment group - ITT population

BL = baseline; ITT = intention to treat; NT-proBNP = N-terminal pro B-type natriuretic peptide; Wk = week.
Note: Median (Q1, Q3) are shown in the plot.
Source: Desai et al. (2022)[58]

Cardiac troponin I

A statistically significant difference in change in geometric mean ratio from baseline to Week 16 for cardiac troponin I favouring the mavacamten arm over the placebo arm was observed. The geometric mean cardiac troponin I was 15.3 ng/L (SD, 171) at baseline: 17.1 ng/L (%CV: 199) and 13.7 ng/L (%CV: 145) in the mavacamten and placebo arms, respectively. The change from baseline to Week 16 was −22.2 vs. −3.1 ng/L in the mavacamten and placebo arms, respectively, a between-group geometric mean ratio of 0.53 (95% CI, 0.41-0.70; $P < 0.0001$).[58]

7.2.4 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 was 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 enrolment. 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.[13]

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.[13]

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.[14,15]

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.

7.3 Safety results

7.3.1 Effect of mavacamten on LVEF

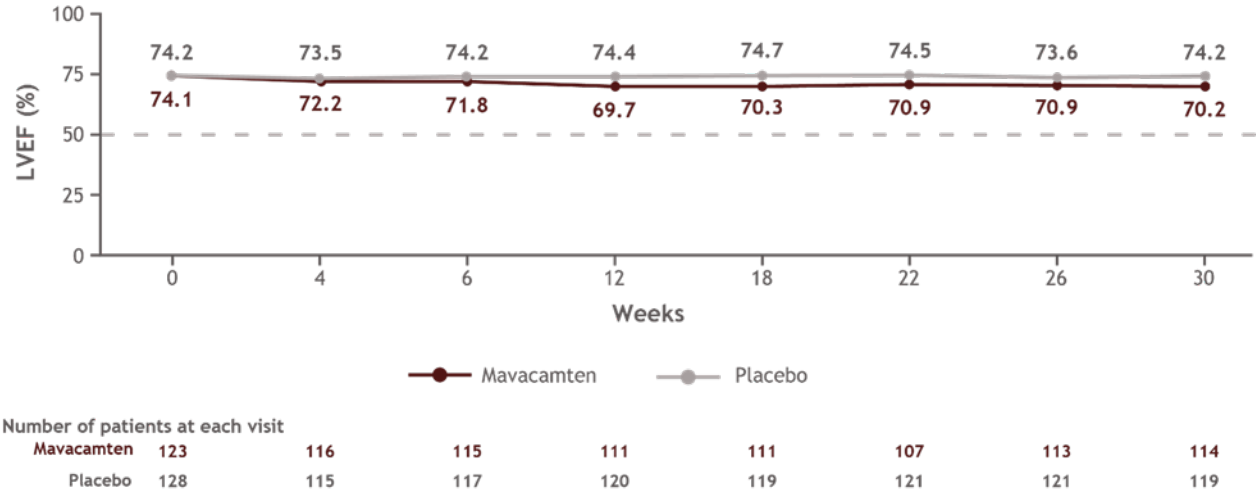
An LVEF ≤ 30% was a prespecified adverse event (AE) of special interest in EXPLORER-HCM; therefore, safety in terms of LVEF is presented here.

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 21).[13] 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 normalised 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%.[13]

More patients taking mavacamten met the primary composite endpoint than placebo irrespective of baseline LVEF < 75% or ≥ 75%[13]:

- 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.[55,75]
- 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 substudy (1 patient for each arm) and both were asymptomatic at time of measure.

Figure 21. 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)[13]

At week 84 of MAVA-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.[16]

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.[58]

7.3.2 Safety: integrated summary of safety

7.3.2.1 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 analysed in integrated populations and by indications for the integrated summary of safety for submission to the EMA. Table 21 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 21. Integrated summary of safety

	Number of patients (%)		
	All-mavacamten combined (n = 314)	Patients with oHCM from EXPLORER-HCM	
		Mavacamten (n = 123)	Placebo (n = 128)
At least 1 AE	291 (92.7)	108 (87.8)	104 (81.3)
Grade 1	102 (32.5)	53 (43.1)	48 (37.5)
Grade 2	141 (44.9)	43 (35.0)	42 (32.8)
Grade 3	42 (13.4)	11 (8.9)	13 (10.2)
Grade 4	3 (1.0)	1 (0.8)	0
Grade 5	3 (1.0)	0	1 (0.8)
Grade ≥ 3	48 (15.3)	12 (9.8)	14 (10.9)
At least 1 SAE	58 (18.5)	14 (11.4)	12 (9.4)
At least 1 drug-related AE	86 (27.4)	19 (15.4)	18 (14.1)
At least 1 AE leading to study discontinuation[a,b]	12 (3.8)	2 (1.6)	1 (0.8)
At least 1 AE leading to permanent treatment discontinuation	17 (5.4)	2 (1.6)	0
At least 1 AE leading to drug interruptions	28 (8.9)	3 (2.4)	6 (4.7)
At least 1 AE leading to death	3 (1.0)	0	1 (0.8)

AE = adverse event; HCM = hypertrophic cardiomyopathy; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Note: Data presented in this table are treatment emergent.

[a] Patients with a TEAE leading to study discontinuation may have had reasons other than "adverse event" entered as reason for study discontinuation under disposition (e.g., death, stopping criteria met, or other).

[b] 3 patients from EXPLORER-LTE with AEs leading to study discontinuation did not permanently discontinue the study per disposition.

Source: BMS data on file (2022)[17]

7.3.2.2 Summary of serious adverse event safety data

Across indications, 18.5% of mavacamten-treated patients in the integrated summary of safety analyses experienced at least 1 serious AE (SAE) (Table 22).

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 22).

Table 22. Integrated analysis: patient incidence of serious adverse events reported by ≥ 2 patients

	Number of patients (%)		
	All-mavacamten combined (n = 314)	Patients with oHCM from EXPLORER-HCM	
		Mavacamten (n = 123)	Placebo (n = 128)
At least 1 SAE	58 (18.5)	14(11.4)	12 (9.4)

	Number of patients (%)		
	All-mavacamten combined (n = 314)	Patients with oHCM from EXPLORER-HCM	
		Mavacamten (n = 123)	Placebo (n = 128)
AF	14 (4.5)	3 (2.4)	5 (3.9)
Cardiac failure	5 (1.6)	1 (0.8)	0
Syncope	3 (1.0)	3 (2.4)	1 (0.8)
Stress cardiomyopathy	2 (0.6)	2 (1.6)	0
Systolic dysfunction	2 (0.6)	1 (0.8)	0
Pneumonia	2 (0.6)	0	0
Ejection fraction decreased	2 (0.6)	0	0
Acute kidney injury	2 (0.6)	0	0
Urinary tract infection	0	0	2 (1.6)

AF = atrial fibrillation; oHCM = obstructive hypertrophic cardiomyopathy; SAE = serious adverse event.
Note: Data presented in this table are treatment emergent.
Source: BMS data on file (2022)[17]

7.3.2.3 Common adverse event data

Table 23 presents a summary of common AEs (for purposes of this section, defined as occurring in ≥ 5% of patients in either treatment arm). Regardless of treatment group or indication, most patients experienced at least 1 AE[17]:

- Patients with oHCM from EXPLORER-HCM: mavacamten arm, 87.8%; placebo arm, 81.3%.
- All-mavacamten combined or integrated pool of all mavacamten-treated patients: 92.7%.

Considering all mavacamten-exposed patients across the integrated analyses (all-mavacamten combined), the most frequently (≥ 5%) reported AE was dizziness (19.7%) and other frequently reported AEs included fatigue (15.6%), nasopharyngitis (15.0%), headache (14.6%), dyspnoea (13.4%), AF (12.1%), hypertension (11.1%), and upper respiratory tract infection (10.2%). Additionally, across the integrated analyses AF was the most commonly reported grade 3 AE.

Table 23. Overview of common adverse reactions (occurring in over 5% of patients in a treatment arm)

	Number of patients (%)					
	All-mavacamten combined (n = 314)		Patients with oHCM from EXPLORER-HCM			
			Mavacamten (n = 123)		Placebo (n = 128)	
Preferred term	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
At least 1 AE	291 (92.7)	48 (15.3)	108 (87.8)	12 (9.8)	104 (81.3)	14 (10.9)
Dizziness	62 (19.7)	1 (0.3)	26 (21.1)	1 (0.8)	17 (13.3)	0
Fatigue	49 (15.6)	1 (0.3)	7 (5.7)	0	7 (5.5)	0
Nasopharyngitis	47 (15.0)	0	15 (12.2)	0	19 (14.8)	0
Headache	46 (14.6)	0	15 (12.2)	0	10 (7.8)	0
Dyspnoea	42 (13.4)	1 (0.3)	18 (14.6)	0	13 (10.2)	0
AF	38 (12.1)	10 (3.2)	10 (8.1)	3 (2.4)	10 (7.8)	4 (3.1)

	Number of patients (%)					
			Patients with oHCM from EXPLORER-HCM			
	All-mavacamten combined (n = 314)		Mavacamten (n = 123)		Placebo (n = 128)	
Preferred term	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Hypertension	35 (11.1)	0	6 (4.9)	0	4 (3.1)	0
Upper respiratory tract infection	32 (10.2)	0	10 (8.1)	0	6 (4.7)	0
Back pain	30 (9.6)	0	10 (8.1)	0	8 (6.3)	0
Palpitations	28 (8.9)	0	7 (5.7)	0	10 (7.8)	0
Cough	24 (7.6)	0	10 (8.1)	0	4 (3.1)	0
Nausea	21 (6.7)	0	4 (3.3)	0	4 (3.1)	0
Oedema peripheral	20 (6.4)	0	6 (4.9)	0	3 (2.3)	0
Pain in extremity	20 (6.4)	0	2 (1.6)	0	3 (2.3)	0
Diarrhoea	19 (6.1)	0	5 (4.1)	0	7 (5.5)	0
Urinary tract infection	19 (6.1)	1 (0.3)	6 (4.9)	0	5 (3.9)	1 (0.8)
Arthralgia	19 (6.1)	0	7 (5.7)	0	2 (1.6)	0
Fall	18 (5.7)	0	5 (4.1)	0	3 (2.3)	0
Constipation	16 (5.1)	0	2 (1.6)	0	2 (1.6)	0
Ventricular tachycardia	16 (5.1)	0	2 (1.6)	0	2 (1.6)	1 (0.8)

AE = adverse event; AF = atrial fibrillation; HCM = hypertrophic cardiomyopathy; oHCM = obstructive hypertrophic cardiomyopathy.

Notes: Data presented in this table are treatment emergent.

Safety population includes all patients who received at least 1 dose of study drug.

Source: BMS data on file (2022)[17]

7.3.2.4 Integrated summary of safety analyses: deaths

In the mavacamten integrated analyses, 3 deaths occurred during EXPLORER-LTE (3 of 314 [1%]). Of these deaths, 1 was due to bacterial endocarditis, 1 was due to cardiac arrest, and 1 was due to acute myocardial infarction. All 3 deaths were considered unrelated to study treatment by the investigator.[17]

One death occurred in a patient in the placebo arm of EXPLORER-HCM. The death was reported as a fatal (grade 5) SAE of sudden death and was considered causally related to study treatment by the treatment-blinded investigator.[17]

In addition to the deaths in the integrated analyses discussed above, 1 patient treated with mavacamten died in the clinical pharmacology hepatic impairment study. The patient was in the moderate hepatic impairment group and had a medical history of headaches, hypertension, hepatic enzymes increased due to alcohol abuse, hepatosplenomegaly, and ascites. A fatal SAE of ischaemic stroke occurred 40 days after a single dose of mavacamten. For this patient, the mavacamten plasma concentration 35 days after dosing (5 days before the SAE) was 0.332 ng/mL.[17]

7.3.3 Safety: VALOR-HCM

7.3.3.1 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. Long-term safety is summarised based on the total time that patients have received mavacamten. Table 24 summarises 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 24).

Table 24. VALOR-HCM: safety summary

	Number of patients (%)		
	Double-blind [a]		Long-term follow-up [b]
	Mavacamten (n = 56)	Placebo (n = 55)	Overall mavacamten (n = 108)
At least 1 AE leading to death	0	0	1 (0.9)
At least 1 on-treatment SAE	3 (5.4)	1 (1.8)	9 (8.3)
At least 1 study drug–related AE	9 (16.1)	9 (16.4)	17 (15.7)
At least 1 AE leading to study discontinuation	0	0	1 (0.9)
At least 1 AE leading to permanent treatment discontinuation	0	0	2 (1.9)
At least 1 AE leading to drug interruptions	4 (7.1)	1 (1.8)	5 (4.6)

AE = adverse event; SAE = serious adverse event.

[a] Double-blind data were collected from day 1 of mavacamten treatment until week 16.

[b] Long-term follow-up data were collected from day 1 of mavacamten treatment until end of treatment for the mavacamten treatment group and from week 16 until end of treatment for the group that transitioned from placebo to mavacamten.

Source: BMS data on file (2022)[17]

7.3.3.2 VALOR-HCM: summary of serious adverse event 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 25).

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), 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 25).

Table 25. VALOR-HCM: serious adverse event safety summary

	Number of patients (%)		
	Double-blind		Long-term follow-up
	Mavacamten (n = 56)	Placebo (n = 55)	Overall mavacamten (n = 108)
Patients with ≥ 1 study drug–related AE	9 (16.1)	9 (16.4)	17 (15.7)
Patients with ≥ 1 treatment SAE	3 (5.4)	1 (1.8)	9 (8.3)
Cardiac disorders			
Moderate	2 (3.6)	0	3 (2.8)
Severe			1 (0.9)
AF			
Moderate	2 (3.6)	0	2 (1.9)
Severe			1 (0.9)
Congestive heart failure			
Moderate			1 (0.9)
Gastrointestinal disorders			
Severe			2 (1.9)
Large intestine perforation			
Severe			1 (0.9)
Pneumatosis intestinalis			
Severe			1 (0.9)
Gastroesophageal reflux disease			
Severe			1 (0.9)
General disorders and administration site conditions			
Fatal			1 (0.9)
Sudden cardiac death			
Fatal			1 (0.9)
Infections and infestations			
Severe	1 (1.8)	0	1 (0.9)
COVID-19			
Severe	1 (1.8)	0	1 (0.9)
Clostridium difficile infection			
Severe			1 (0.9)
Injury, poisoning, and procedural complications			
Moderate	0	1 (1.8)	1 (0.9)
Fall			
Moderate			1 (0.9)
Alcohol poisoning			
Moderate	0	1 (1.8)	
Renal and urinary disorders			
Moderate			1 (0.9)

	Number of patients (%)		
	Double-blind		Long-term follow-up
	Mavacamten (n = 56)	Placebo (n = 55)	Overall mavacamten (n = 108)
Nephrolithiasis			
Moderate			1 (0.9)
Respiratory, thoracic, and mediastinal disorders			2 (1.9)
Moderate			1 (0.9)
Life-threatening			1 (0.9)
Acute respiratory failure			
Life-threatening			1 (0.9)
Pulmonary embolism			
Moderate			1 (0.9)
Vascular disorders			
Moderate			1 (0.9)
Peripheral venous disease			
Moderate			1 (0.9)

AE = adverse event; AF = atrial fibrillation; LTE = long-term extension; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Note: At each level of patient summarisation, a patient is counted once for the most severe event if the patient reported ≥ 1 event. If the severity of an AE is missing, the AE is reported as "severe." *On-treatment AE* is defined as an AE that started or worsened from the first dose date of the double-blind period up to the first dose of the LTE period or the last dose of the double-blind period if the patient did not start the LTE. During the LTE period, AE summary includes TEAEs that occurred since the first dose of mavacamten treatment for both groups. TEAE is defined as an AE that occurred or worsened since the first dose date of mavacamten to the last dose date + 56 days.

Source: BMS data on file (2022)[17]

7.3.3.3 VALOR-HCM: common adverse event 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 26 presents on-treatment AEs that occurred in ≥ 5% of patients.

Table 26. VALOR-HCM: overview of common adverse events, double-blind period

	Mavacamten (n = 56)	Placebo (n = 55)
Total number of on-treatment AEs	125	95
Patients with at least 1 on-treatment AE, n (%)	41 (73.2)	34 (61.8)
AF, n (%)	4 (7.1)	0
Nausea, n (%)	4 (7.1)	1 (1.8)
Fatigue, n (%)	5 (8.9)	2 (3.6)
Urinary tract infection, n (%)	3 (5.4)	1 (1.8)
Dizziness, n (%)	4 (7.1)	3 (5.5)
Dyspnoea, n (%)	4 (7.1)	3 (5.5)
Rash, n (%)	4 (7.1)	0

	Mavacamten (n = 56)	Placebo (n = 55)
Hypertension, n (%)	3 (5.4)	2 (3.6)

AE = adverse event; AF = atrial fibrillation; LTE = long-term extension.

Note: At each level of patient summarisation, a patient is counted only once if the patient reported ≥ 1 event.
On-treatment AE is defined as an AE that started or worsened from the first dose date of the double-blind period up to the first dose of the LTE period or the last dose of the double-blind period if patients did not start the LTE.

Source: BMS data on file (2022)[17]

For the long-term follow-up period, 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 27 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 27. VALOR-HCM: overview of common adverse reactions, long-term follow-up period

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]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]			
[redacted]			
[redacted]			

7.3.3.4 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.[17]

7.3.4 Safety conclusion

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). The most commonly reported side effects were dizziness, fatigue, nasopharyngitis, headache, dyspnoea, AF, hypertension, and upper respiratory tract infection.[17]

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%; MAVA-LTE: mean change in LVEF over 84 weeks, −9.0% ± 8.1%; VALOR-HCM: mean change in LVEF, −3.4%).[13,16]

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.[13]

7.4 Comparative analyses of efficacy and safety

The intervention (mavacamten in combination with standard of care) and comparators (placebo in combination with individually optimised 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 Health economic analysis and model

8.1 Health economic analysis

8.1.1 Type of economic evaluation

A cost-utility analysis informed by the EXPLORER-HCM clinical trial was conducted. Outcomes were expressed as incremental costs per quality-adjusted life-year (QALY) gained as recommended by the methods guide of the DMC.[76] Cost-effectiveness results were also reported as incremental costs per life-year (LY) gained.

8.1.2 Perspective

This economic model represents the perspective of Denmark, with a limited societal perspective. All relevant costs associated with treatment and illness were included (i.e., costs related to disease management, testing, medications, monitoring, AE management, patient time, and transportation).[76]

8.1.3 Time horizon and discounting

The DMC guidelines recommend that the time horizon for estimating clinical effectiveness and cost-effectiveness should be sufficiently long to cover the period when the main health effects and costs arise.[76] Due to the chronic nature of oHCM, a lifetime horizon was used in the model to capture all relevant differences in costs and utilities in health states between the treatments being compared.[77]

Furthermore, both costs and effects/benefits were discounted at 3.5% annually until year 35 of the time horizon and then at 2.5% annually from year 36, in line with the DMC guidelines.[76] Varying discount rates (i.e., 0.0% and 3.5% discount, and 2.5% on costs and health effects throughout the time horizon) were tested in scenario analyses.

8.1.4 Cycle length and half-cycle correction

During the first 30 weeks of the model, variable cycle lengths were used in line with clinical assessment timepoints from EXPLORER-HCM (i.e., weeks 4, 8, 10, 14, 16, 18, 22, 26, 30). This allowed for the transition rates observed in the trial to be directly applied in the model.

After week 30, a cycle length of 28 days (i.e., 4 weeks) was used in the model to align with the anticipated dosage of mavacamten (i.e., 28-day cycles, each pack with 28 capsules; 1 capsule per day).

In addition, a half-cycle correction was included to adjust for the fact that transitions in reality can occur any time during a cycle, not only at the start or end of a cycle.

8.2 Model

The model was constructed to estimate the health economic value of mavacamten by calculating the costs and health outcomes (i.e., LYs and QALYs) associated with mavacamten + BB/CCB treatment 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 the 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.[78-80]

8.2.1 Core model of health-state transitions

Initially, a model based on the primary composite endpoint of EXPLORER-HCM (i.e., NYHA class and pVO_2) was explored; however, the inclusion of pVO_2 was not feasible because:

- There was a lack of clear cut-off points for changes in pVO_2 if it is included within each NYHA class and for differentiating patients within each class.
- In EXPLORER-HCM, pVO_2 was collected only at trial initiation and week 30, resulting in a lack of granular data on changes in pVO_2.

In addition, a feasibility assessment was conducted to explore the possibility of linking surrogate endpoints, such as NYHA class or pVO_2, to long-term endpoints such as mortality. This assessment concluded that such an analysis would be possible only for linking NYHA class and mortality because insufficient data were available for linking pVO_2 with mortality. Hence, health states for this model were defined based only on patients' NYHA class (Figure 22). 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.[1] An NYHA class–based model is a well-established framework that has been used in technology appraisals for various treatments for heart disease (e.g., National Institute for Health and Care Excellence [NICE] TA314, implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure; and TA696, tafamidis for treating transthyretin amyloidosis with cardiomyopathy)[79,80] and in published economic evaluations.[78] In Denmark, the NYHA class–based model has been used in the evaluation of tafamidis by Medicinrådet (document r. 151826).[81]

An 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.[78]

In addition, NYHA class correlates well with patient utility and mortality and is commonplace within published literature both within heart failure and cardiomyopathies.[82] Where data were collected, this model is informed by clinical trial data for mavacamten, with published literature used to supplement where 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 is likely to be a conservative approach, considering these events may lead to a higher utilisation of healthcare services.

As shown in Figure 22, the simplified model structure 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 anticipated 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 NYHA III. However, the number of patients moving to NYHA class IV was small, irrespective of the treatment arm.

At each cycle/assessment period, patients can transition to any other NYHA health state or stay in the same health state based on the probability of experiencing improvement or worsening of NYHA class; this is driven by

transitional probabilities (TPs) implemented in the model. Furthermore, all patients are considered at risk of death in each model cycle.

8.2.2 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.

Table 28. Treatment posology

Treatment	Dosing schedule	Reference
Mavacamten	2.5/5/10/15 mg per day Administered as an oral capsule	EXPLORER-HCM[13]; Camzyos SmPC (2021)[51]
Metoprolol (BB)	50 mg twice a day Administered as a prolonged release tablet	Metoprolol tartarate SmPC (2022)[83]
Verapamil (CCB)	120 mg 3 times a day Administered as an oral tablet	Verapamil SmPC (2022)[84]

BB = beta-blocker; CCB = calcium channel blocker; SmPC = summary of product characteristics.

During the first 30 weeks (i.e., the 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. Section 8.4.3 presents a detailed description of the various reasons for discontinuation or escalation from initial therapy, as well as the inputs.

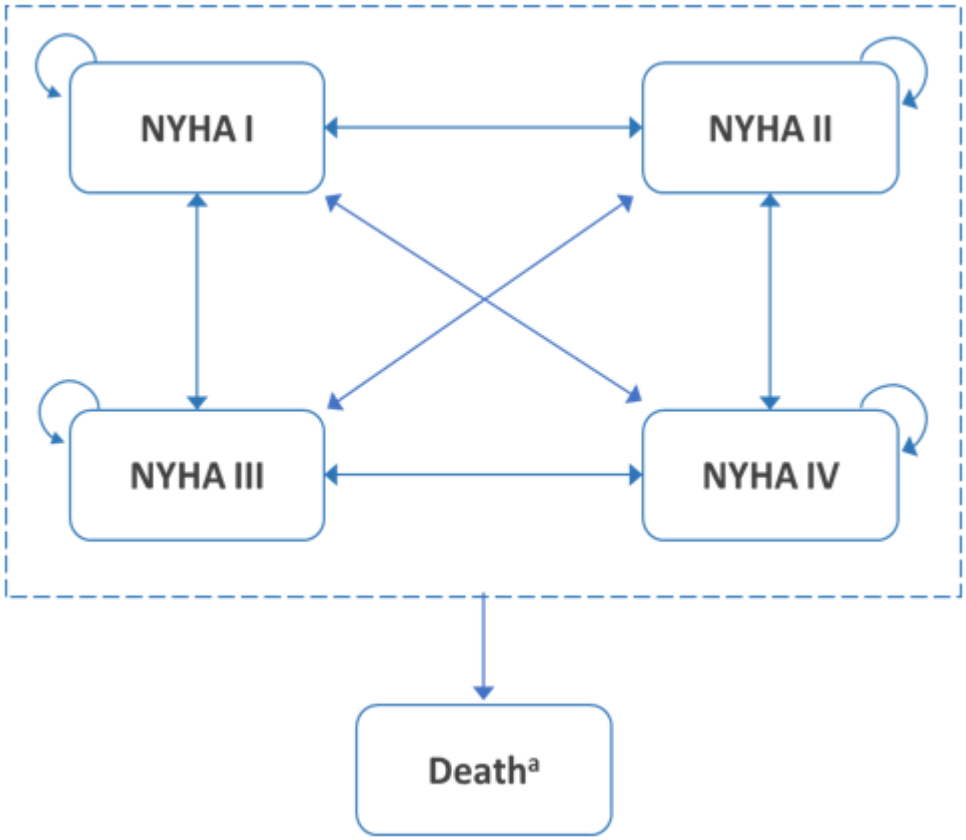
Details of each treatment pathway for patients in the intervention and comparator arms are described in subsequent sections and depicted in Figure 23.

8.2.2.1 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[3]) 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, as well as to model an incident transition of NYHA health state as a consequence of the procedure. During the post-SRT state, patients reverted back 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.

Figure 22. Simplified model schematic



NYHA = New York Heart Association.

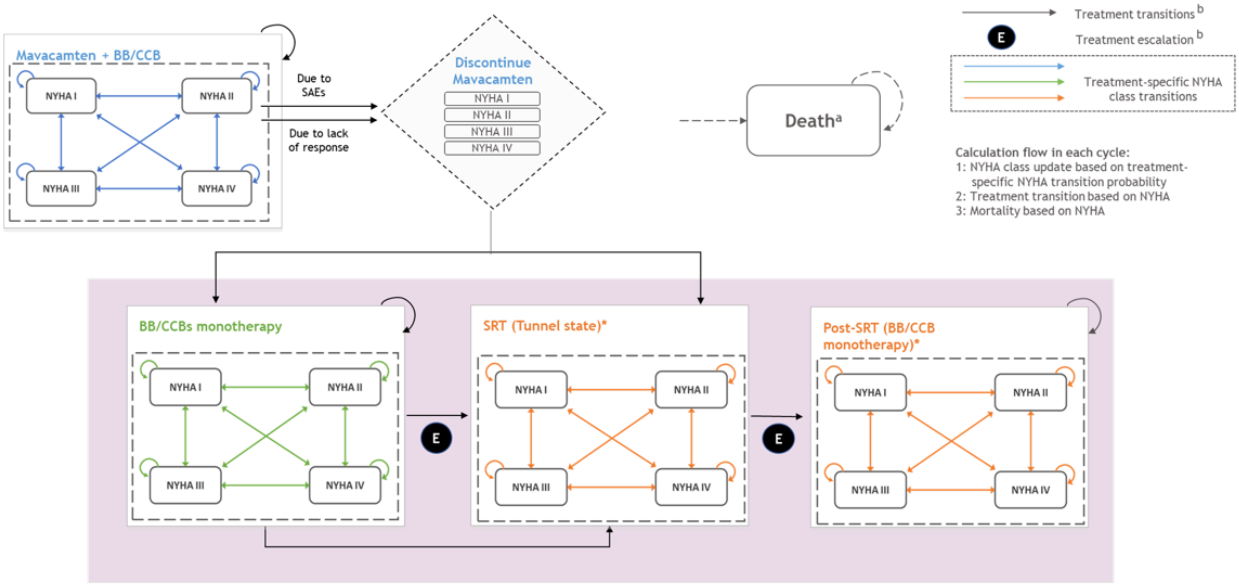
[a] Death state is accessible from all non-Death health states.

8.2.2.2 Treatment pathways in the intervention arm

In the intervention arm, patients received mavacamten in combination with BB/CCB monotherapy, reflecting the treatment regimen of the EXPLORER-HCM trial'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 SAEs or lack of response (discussed further in Section 8.4.3). 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 (as detailed in Section 8.4.3.3) (Figure 23).

Figure 23. Schematic of NYHA health states and subsequent treatment options



BB = beta-blocker; CCB = calcium channel blocker; MAVA = mavacamten; 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.

8.3 Relationship between the data for relative efficacy, parameters used in the model, and relevance for Danish clinical practice

8.3.1 Presentation of input data used in the model and how data were obtained

Table 29 presents the data sources of model 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 29. Summary of 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
Baseline characteristics	Sex, mean age, and percentage of patients in each NYHA class	Presented in Table 30	EXPLORER-HCM; Olivotto et al. (2020)[13]
Clinical inputs			
Short-term TPs	Based on EXPLORER-HCM (for both intervention and BB/CCB monotherapy arm)	Presented in Section 8.4.1.1	EXPLORER-HCM; Olivotto et al. (2020)[13]
Long-term TPs	Retain NYHA class (for both intervention and BB/CCB monotherapy arm)	Presented in Section 8.4.1.5	Assumption, supported by EXPLORER-LTE and BMS data on file (2021)[85]

Name of estimates[a]	Results from study or indirect treatment comparison	Input value used in the model	How is the input value obtained/estimated
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 8.4.3.1	EXPLORER-HCM; Olivotto et al. (2020)[13]
	Post-trial period: annual rate of discontinuation due to SAEs after week 30	Presented in Section 8.4.3.1	Assumption based on EXPLORER-HCM and Olivotto et al. (2020)[13]
Due to lack of response	Discontinue if no NYHA class improvement from baseline at end-of-trial period	Presented in Section 8.4.3.2	EXPLORER-HCM; Olivotto et al. (2020)[13]
Treatment distribution of patients who discontinued mavacamten	All patients revert to pre-existing treatment with BB/CCB monotherapy	Presented in Section 8.4.3	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 37	BMS data on file (2022)[46]
Efficacy of subsequent treatments	SRT + BB/CCB	Presented in Table 38	BMS data on file (2022)[46]
	After SRT (BB/CCB monotherapy)	Presented in Section 8.4.5	Assumption
Other clinical inputs			
Natural disease progression	Disease progression rates by NYHA	Presented in Section 8.4.2	Maron et al. (2016)[86]; Maron (2018)[25]
AE incidence rates	Mavacamten + BB/CCB	Presented in Section 8.4.6	EXPLORER-HCM; Olivotto et al. (2020)[13]
	BB/CCB monotherapy	Presented in Section 8.4.6	EXPLORER-HCM; Olivotto et al. (2020)[13]
	SRT + BB/CCB	Presented in Section 8.4.6	Assumption, same as BB/CCB monotherapy arm in EXPLORER-HCM
Mortality inputs	All-cause mortality (age adjusted)	Presented in Section 8.4.7	Statistics Denmark (2021)[87]
	Mortality by NYHA, based on Market Clarity	Presented in Section 8.4.7	Wang et al. (2023)[32]
	Surgical mortality due to SRT (incident)	Presented in Section 8.4.7	Bytyci et al. (2020)[11]
Utility inputs			
Health-state utilities (by NYHA class)	Regardless of treatment arm	Presented in Table 44	BMS data on file (2021)[88]
	Included age-adjusted utilities	Presented in Section 8.5.1	Medicinrådet (2021)[89]

AE = adverse event; BB = beta-blocker; CCB = calcium channel blocker; NYHA = New York Heart Association; SRT = septal reduction therapy; TP = transitional probability.

[a] Some of these estimates will be presented in other tables in the document.

8.3.2 Relationship among clinical documentation, data used in the model, and Danish clinical practice

8.3.2.1 Patient population

The relevant population for this economic analysis was assumed to be the same as the ITT population of EXPLORER-HCM.[13] Section 7.1.1.1 presents key inclusion criteria.

The baseline characteristics of patients in EXPLORER-HCM (Table 30) are expected to reflect those of patients in Danish clinical practice (see Section 5.1.2).

- 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.
- The proportion of patients taking background monotherapy of BB/CCB was used to estimate the drug cost for BB/CCB monotherapy.

Table 30. Patient characteristics in EXPLORER-HCM used in the model

Patient population: important baseline characteristics	Value	Reference
Age (years), mean	59	EXPLORER-HCM[13]
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)[13]

8.3.2.2 Intervention

The intervention as expected in Danish clinical practice (as defined in Section 5.3.1) is mavacamten + BB/CCB. The posology, dose, and position of mavacamten as described in the SmPC (see Section 5.3 and Table 6) match those used in the cost-utility analysis and anticipated for use in Denmark.

8.3.2.3 Comparators

The comparator in the current Danish clinical practice is placebo + BB/CCB monotherapy. This is represented by placebo in EXPLORER-HCM because background therapy (BB/CCB) was allowed in both arms (see Section 5.2.2).

Follow-up resource and cost use for patients who continue with BB/CCB monotherapy as the comparator is included in the cost-utility model and aligns with the anticipated use in Denmark.

8.3.2.4 Relative efficacy outcomes

Estimates of relative efficacy are included in the cost-utility analysis and are expected to align with Danish clinical practice (see Section 7).

8.3.2.5 Adverse reaction outcomes

Estimates of adverse reaction outcomes are included in the cost-utility analysis and are expected to align with Danish clinical practice (see Section 7).

8.4 Clinical data

8.4.1 Transitional probabilities (TPs)

The model differentiates between 2 periods: short-term and long-term. The short-term period uses trial-based TPs. Section 8.4.1.3 describes short-term TPs, and Section 8.4.1.4 describes the rationale behind the choice of short-term TPs in the base case of the model. The long-term period relies solely on extrapolations of trial-based TPs. Long-term TPs are described in detail in Section 8.4.1.5.

8.4.1.1 Short-term transitional probabilities

For the mavacamten + BB/CCB arm, short-term was defined as the first 30 weeks (i.e., the EXPLORER-HCM trial period). For the BB/CCB monotherapy arm, short-term in the base case of the model was defined as the period until the baseline assessment in EXPLORER-LTE. Section 8.4.1.4 presents further details on the rationale for this approach.

8.4.1.2 Handling missing data

Patients in EXPLORER-HCM occasionally missed the scheduled assessments and their NYHA class was not observed at those assessment points. To compute the 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 a 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 31 summarises the number of patients at risk of HCM, with observed and imputed NYHA class at each assessment point, by treatment arm. The slight reduction in the number of patients at risk during the first 38 weeks reflects discontinuations from EXPLORER-HCM. There were fewer patients in the BB/CCB monotherapy arm observed at the start of the LTE because 9 patients from the BB/CCB monotherapy arm in EXPLORER-HCM were not subsequently observed in EXPLORER-LTE (see notes to Table 31).

Table 31. **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	[redacted]					
Week 4						
Week 6						
Week 8						
Week 12						
Week 14						
Week 18						
Week 22						
Week 26						
Week 30						
Week 38[b]						
Start of EXPLORER-LTE (week 46)[c]						

BB = beta-blocker; CCB = 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. Moreover, 9 patients who were in the BB/CCB monotherapy arm in EXPLORER-HCM were not subsequently observed in the long-term extension.

[a] Imputations done in the clinical study report.

[b] In EXPLORER-HCM, patients within the intervention arm discontinued mavacamten (due to the washout and post-study period) at week 30; as such, assessments after week 30 are not included.

[c] The average number of days between the week 38 assessment of EXPLORER-HCM and the baseline assessment for EXPLORER-LTE was 59.7 (standard deviation, 56.1; range, 3-262 days); this is referred to as *week 46*.

8.4.1.3 Short-term transitional probabilities per treatment arm

Mavacamten + BB/CCB arm

Patients in the mavacamten + BB/CCB arm of EXPLORER-HCM did not receive mavacamten between week 30 and the baseline assessment of EXPLORER-LTE. 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 randomisation. Thus, in the CEM, TPs for this group were computed only from the trial data for the period until week 30 (see Table 32). Section 8.4.1.4 provides further information on the rationale for not including EXPLORER-LTE data in the short-term TP estimation for the base case. Section 8.4.1.3 describes the TPs used in the model for the mavacamten + BB/CCB arm after week 30.

BB/CCB monotherapy arm

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).[61] 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 32 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 32. Transitional probabilities across various NYHA classes

Week	To / From	Mavacamten + BB/CCB, %				BB/CCB monotherapy, %			
		NYHA I	NYHA II	NYHA III	NYHA IV	NYHA I	NYHA II	NYHA III	NYHA IV
Baseline to week 4	NYHA I[a]	[redacted]							
	NYHA II	[redacted]							
	NYHA III	[redacted]							
	NYHA IV[a]	[redacted]							
Weeks 4-6	NYHA I	[redacted]							
	NYHA II	[redacted]							
	NYHA III	[redacted]							
	NYHA IV	[redacted]							
Weeks 6-8	NYHA I	[redacted]							
	NYHA II	[redacted]							
	NYHA III	[redacted]							
	NYHA IV	[redacted]							
Weeks 8-12	NYHA I	[redacted]							
	NYHA II	[redacted]							
	NYHA III	[redacted]							
	NYHA IV	[redacted]							
Weeks 12-14	NYHA I	[redacted]							
	NYHA II	[redacted]							
	NYHA III	[redacted]							
	NYHA IV	[redacted]							
Weeks 14-18	NYHA I	[redacted]							
	NYHA II	[redacted]							
	NYHA III	[redacted]							
	NYHA IV	[redacted]							
Weeks 18-22	NYHA I	[redacted]							
	NYHA II	[redacted]							
	NYHA III	[redacted]							
	NYHA IV	[redacted]							
Weeks 22-26	NYHA I	[redacted]							
	NYHA II	[redacted]							
	NYHA III	[redacted]							
	NYHA IV	[redacted]							

Week	To / From	Mavacamten + BB/CCB, %				BB/CCB monotherapy, %			
		NYHA I	NYHA II	NYHA III	NYHA IV	NYHA I	NYHA II	NYHA III	NYHA IV
Weeks 26-30	NYHA I	[redacted]							
	NYHA II								
	NYHA III								
	NYHA IV								
Weeks 30-38[b]	NYHA I								
	NYHA II								
	NYHA III								
	NYHA IV								
Weeks 38-46[b,c]	NYHA I								
	NYHA II								
	NYHA III								
	NYHA IV								

BB = beta-blocker; CCB = calcium channel blocker; NA = not applicable; NYHA = New York Heart Association; TP = transitional 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). NA 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.

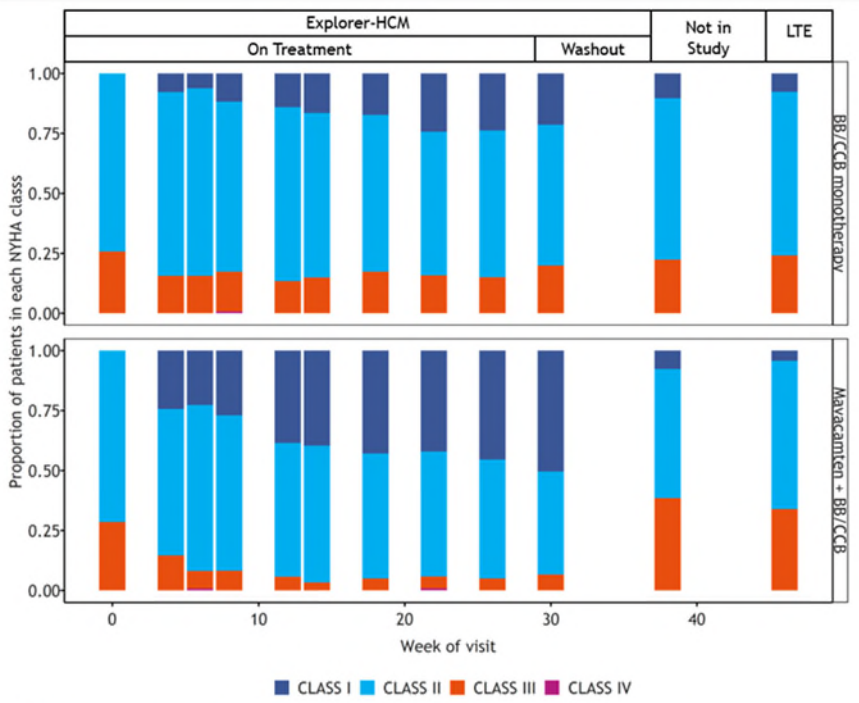
[b] TPs for weeks 30-38 and weeks 38-46 were reported for 8 weeks. These estimates were converted to 4 weeks to be used in the model (i.e., to adjust as per the cycle length).

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

8.4.1.4 Rationale for the choice of short-term transitional probabilities in the base case

To explain the rationale for the short-term TPs used for the base case of the model, Figure 24 shows the evolution of the NYHA class distribution throughout EXPLORER-HCM and the baseline assessment of EXPLORER-LTE, separated by treatment arm.

Figure 24. **Evolution of NYHA class distribution in EXPLORER-HCM and baseline assessment of EXPLORER-LTE by treatment-arm allocation in EXPLORER-HCM**



Number of patients ar risk per treatment arm allocation in EXPLORER-HCM

	Baseline	Week 4	Week 6	Week 8	Week 12	Week 14	Week 16	Week 22	Week 26	Week 30	Week 38	Week 46
BB/CCB monotherapy	128	128	128	127	127	127	127	127	126	126	125	116
Mavacamten + BB/CCB	123	123	123	122	122	121	121	121	121	121	117	115

BB = beta-blocker; CCB = 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 are 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.

Rationale for the use of transitional probabilities to week 46 for the BB/CCB monotherapy arm

As seen in the top panel of Figure 24, the NYHA distribution among patients in the BB/CCB monotherapy arm of EXPLORER-HCM shows a slightly favourable improvement until approximately week 22 of the trial, even though most of these patients were already receiving BB/CCB before the trial and their treatment did not change upon joining the trial (only 20 patients [8%] were not receiving BB/CCB before the trial: 4 in the mavacamten + BB/CCB arm and 16 in the BB/CCB monotherapy arm).[85] This can also be seen in Figure 25, which presents NYHA class as a continuous variable (e.g., NYHA I = 1, NYHA II = 2, NYHA III = 3, NYHA IV = 4) and plots the average NYHA class at each assessment timepoint separately for mavacamten + BB/CCB and BB/CCB monotherapy.

Figure 25. Mean NYHA class at each assessment timepoint by treatment arm

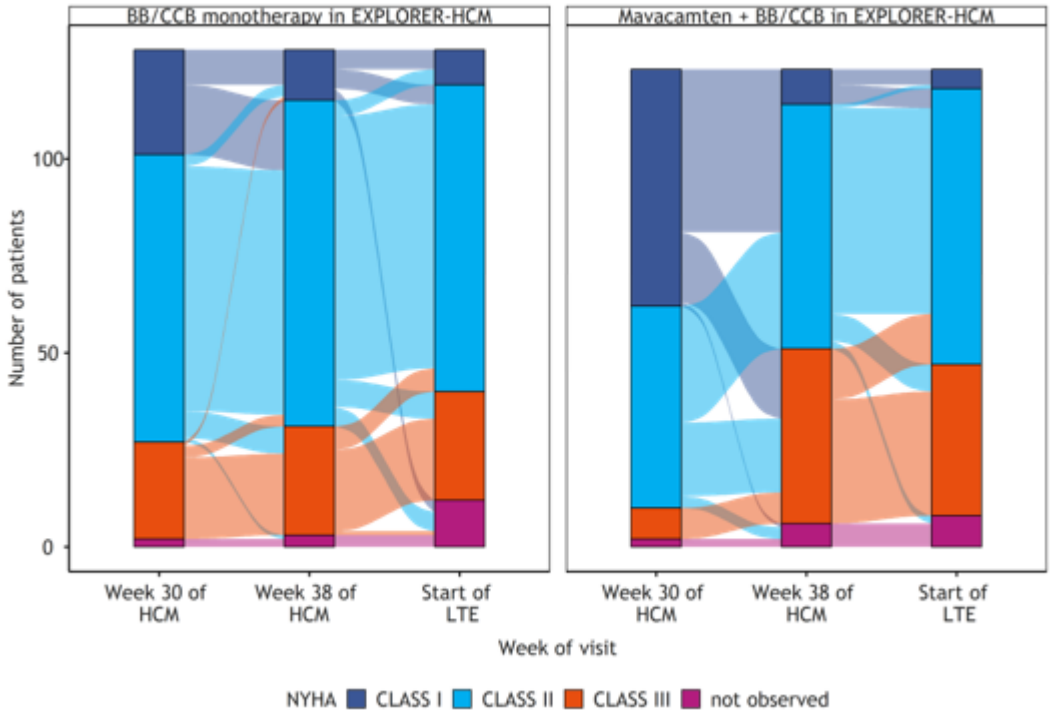
BB = beta-blocker; CCB = calcium channel blocker

Of note, the top panel of Figure 24shows that the placebo effect weakened after week 22, even though patients were still receiving background therapy (BB/CCB) during this period. This is also visible in Figure 25, in which mean NYHA class in the BB/CCB monotherapy arm stabilises between weeks 22 and 26 and then increases until the week 46 assessment (i.e., start of EXPLORER-LTE). Patients within the BB/CCB monotherapy arm did not receive placebo after week 30 (but still received background therapy); however, patients were still blinded to their original randomisation and were still part of the trial or about to commence the LTE study. Thus, all available data were used to inform the TPs for the BB/CCB monotherapy arm by computing the period between weeks 30 and 38 and between weeks 38 and 46 (i.e., the start of MAVA-LTE) of EXPLORER-HCM.

Rationale for not incorporating EXPLORER-LTE data for the short-term transitional probabilities for the mavacamten + BB/CCB arm in the base case

Patients who were initially randomly assigned to mavacamten + BB/CCB discontinued mavacamten after week 30 for an average of 16 weeks. This off-treatment period resulted in a deterioration of NYHA class (Figure 26). The deterioration occurred mostly between weeks 30 and 38 (i.e., end of study) of EXPLORER-HCM, but some further deterioration was also observed between week 38 of EXPLORER-HCM and baseline of EXPLORER-LTE. At the start of EXPLORER-LTE, the distribution of patients across the NYHA classes was similar to that of the initial baseline distribution in EXPLORER-HCM, regardless of treatment allocation. Therefore, it is difficult to use the TPs from baseline for mavacamten-experienced patients returning to treatment within EXPLORER-LTE.

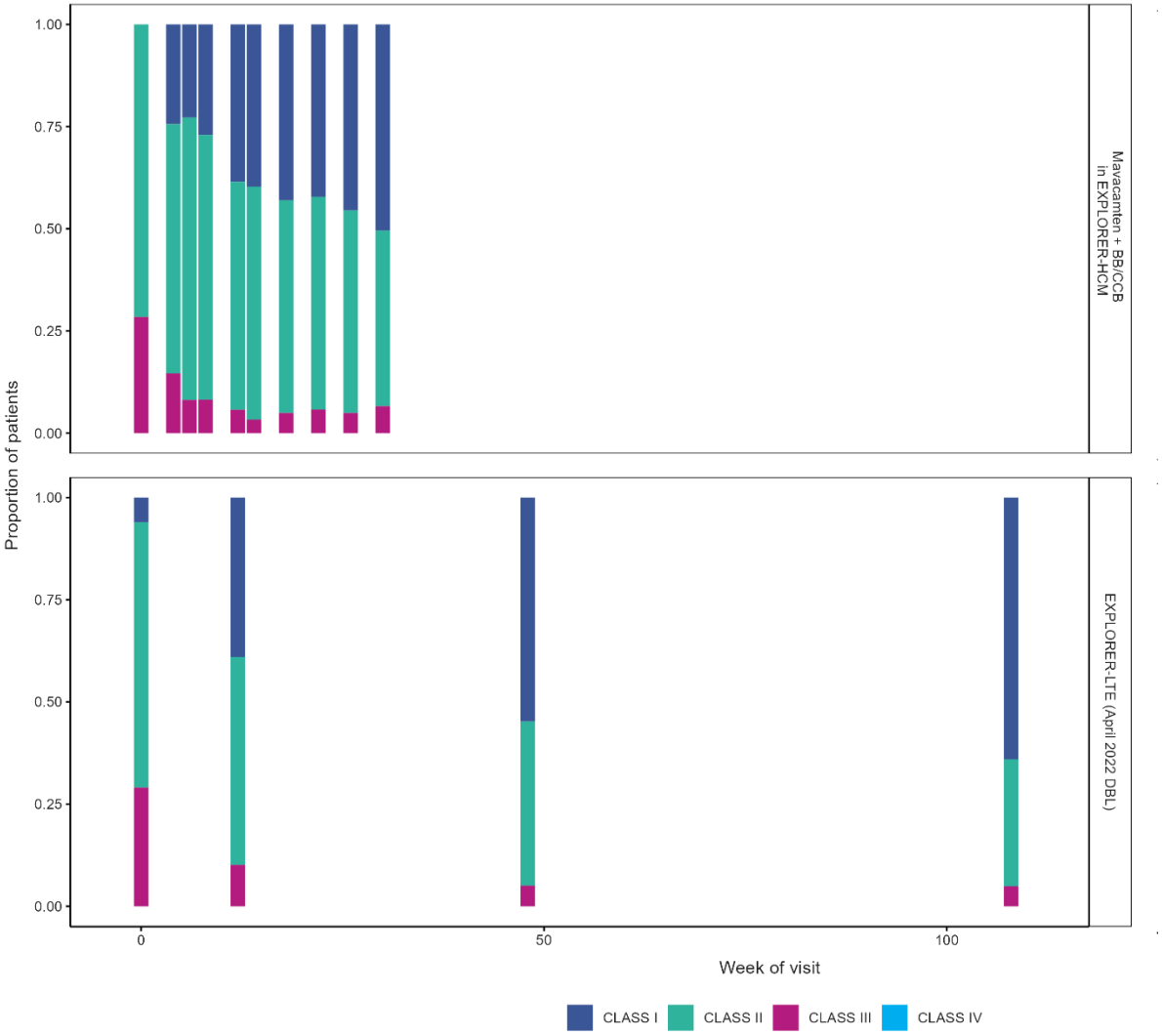
Figure 26. NYHA composition at weeks 30 and 38 of EXPLORER-HCM and at baseline of EXPLORER-LTE by treatment-arm allocation in EXPLORER-HCM



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

The TPs of patients in EXPLORER-LTE who had been on BB/CCB monotherapy during EXPLORER-HCM (and hence could be considered as patients newly starting treatment with mavacamten) could be used to further inform the short-term TPs for the mavacamten + BB/CCB arm. However, the frequency of NYHA assessment timepoints was different between EXPLORER-LTE and EXPLORER-HCM. As a result, the TPs from EXPLORER-LTE pertain to different timepoints and are computed over different periods. Still EXPLORER-LTE can be used to validate the TPs observed in the mavacamten + BB/CCB arm of EXPLORER-HCM and the long-term assumptions for mavacamten. Figure 27 plots the evolution of the proportion of patients in each NYHA class for the mavacamten + BB/CCB arm throughout EXPLORER-HCM and EXPLORER-LTE (regardless of treatment-arm allocation in EXPLORER-HCM). Figure 27 shows a similar proportion of patients across these 2 groups, suggesting a similar treatment benefit from mavacamten in the 2 trials. In addition, Figure 27 shows that this treatment benefit was sustained throughout the course of the MAVA-LTE study. However, only 101patients in EXPLORER-LTE had an assessment at week 108, so there is some uncertainty underlying the findings for that timepoint. In EXPLORER-LTE, there were 231 patients at baseline, 196 patients at week 12, and 219 patients at week 48 (some patients missed their assessment at week 12).

Figure 27. **Evolution of NYHA class distribution of the mavacamten + BB/CCB arms in EXPLORER-HCM (30 weeks) and EXPLORER-LTE throughout MAVA-LTE**



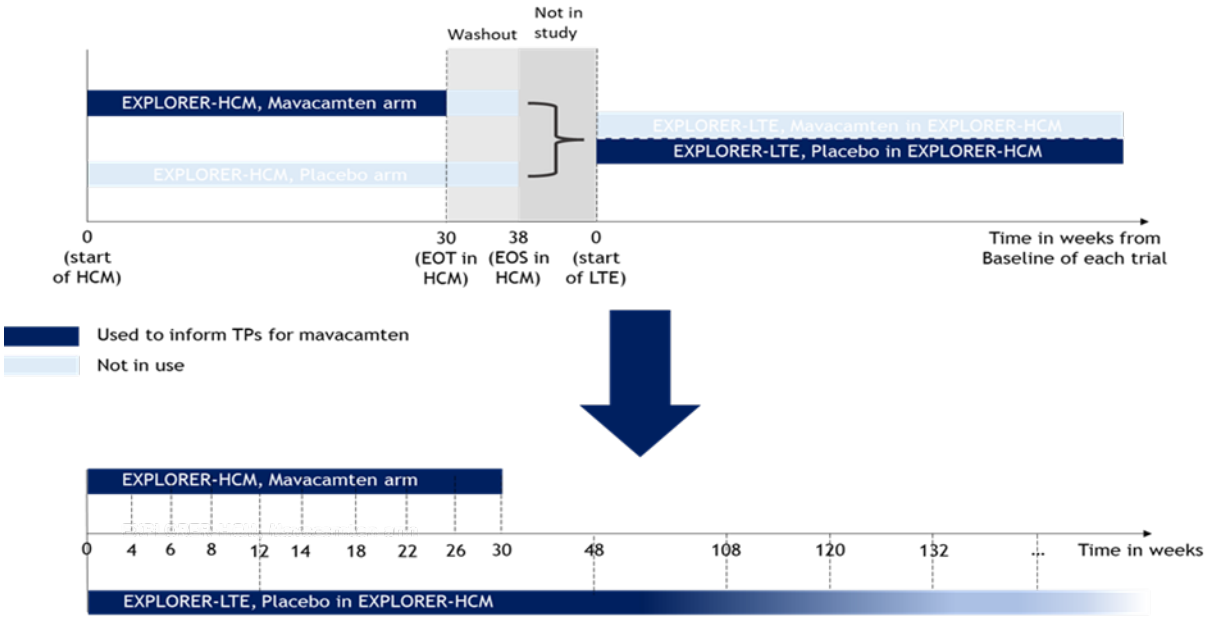
BB = beta-blocker; CCB = calcium channel blocker; NYHA = New York Heart Association.

Scenario using EXPLORER LTE data in estimation of the short-term transitional probabilities for the mavacamten + BB/CCB arm

To explorer the impact of using the LTE data directly in the modelling of TPs an alternative scenario was constructed. In the scenario short term TPs for mavacamten + BB/CCB were informed by a combination of data from the EXPLORER-HCM trial and the EXPLORER-LTE cohort (May 2022 database lock), hereby referred to as the augmented mavacamten arm. The cost-effectiveness result based on the augmented mavacamten arm is presented as a scenario. In the scenario short-term TPs was defined as the first 108 weeks for the mavacamten arm. There were no changes to the TPs of the mavacamten + BB/CCB arm in the scenario.

The augmented mavacamten arm consists of pooling observations from the EXPLORER-LTE cohort for patients who were initially randomised to placebo in the EXPLORER-HCM trial and observations pertaining exclusively to the first 30 weeks of EXPLORER-HCM for patients who were initially randomised to the mavacamten arm (without considering their subsequent EXPLORER-LTE observations), as illustrated in Figure 28.

Figure 28. Overview of Augmented Mavacamten Arm dataset



The assessments pertaining to patients in the EXPLORER-LTE are considered relative to the baseline assessment in the LTE study, whereas the assessments of patients in the EXPLORER-HCM cohort are considered relative to the baseline assessment in the EXPLORER-HCM trial. Thus, it is as if the EXPLORER-HCM trial and the EXPLORER-LTE cohort had started at the same time and ran in parallel, though with different assessment timepoints. The underlying idea for combining the two datasets in this way is that patients who were in the placebo arm of EXPLORER-HCM can be considered a new mavacamten patient upon starting the EXPLORER-LTE. The main advantage of the augmented mavacamten arm is the increased sample size and thus lower uncertainty associated with the estimates.

For computing the TPs from the augmented mavacamten arm, the only EXPLORER-HCM data used pertains to weeks 0 and 12. This is because these are the only assessments that coincide with EXPLORER-LTE assessments. So augmented mavacamten arm TPs between week 0 and week 12 informed by both the mavacamten arm from EXPLORER-HCM and the EXPLORER-LTE patients who were on placebo in EXPLORER-HCM. From week 12 onwards, the augmented mavacamten arm TPs are solely informed by the EXPLORER-LTE patients who were on placebo in EXPLORER-HCM.

Note that patients from the EXPLORER-LTE who were initially randomised to the mavacamten arm of the EXPLORER-HCM trial are not included in this augmented dataset. Since if their EXPLORER-HCM observations are included, there would be statistical correlations between the assessments of the same patients in the two trials that could introduce bias in the estimations. Thus, this combined dataset focused only on patients who were mavacamten-naïve patients at time of initiation.

Table 33 presents the number of patients at risk in the augmented mavacamten arm, with observed and imputed NYHA class at each assessment timepoint. It also presents these figures separately for the two datasets that make up the augmented mavacamten arm, to be explicit about the constraints associated with each dataset. The decline in the number of patients at risk after week 12 reflects two distinct factors. First, while baseline and week 12 are also informed by the mavacamten arm in EXPLORER-HCM, the other timepoints are solely informed by EXPLORER-LTE patients who were on placebo in EXPLORER-HCM. Second, not all patients in EXPLORER-LTE have reached the later assessment timepoints. Of the 116 patients being

newly initiated on mavacamten in the EXPLORER-LTE cohort, 113 (97%) were observed at week 12, whereas there were 107 (92%) observed at week 48 and 45 (39%) observed at week 108.

Table 33. Patients at Risk, With Observed and Imputed NYHA Class at Each Assessment Timepoint of the Augmented Mavacamten Arm

Timepoint	Augmented mavacamten arm			EXPLORER-HCM (mavacamten arm)			EXPLORER-LTE (placebo in EXPLORER-HCM)		
	At risk	Observed	Imputed	At risk	Observed	Imputed	At risk	Observed	Imputed
Week 0	[redacted]								
Week 12									
Week 48									
Week 108									

The short-term TPs based on the augmented mavacamten arm are presented in Table 34. These were obtained after applying the last observed carried forward imputation procedure described above. The TPs were converted into TPs over a 4-week period to be incorporated in the model. Furthermore, to align the frequency of assessment timepoints in the EXPLORER-LTE cohort with the 4-weekly cycles in the CEM, the assessment timepoints at week 48 and week 108 are relabelled as week 46 and 106, respectively as there are no cycles in the CEM starting at weeks 48 and 108.

Table 34. Observed Short-Term Transition Probabilities for the Augmented Mavacamten Arm

	From \ To	Mavacamten + BB/CCB, %			
		NYHA I	NYHA II	NYHA III	NYHA IV
Baseline to Week 12	NYHA I	[redacted]			
	NYHA II				
	NYHA III				
	NYHA IV*				
Week 12 to 46	NYHA I				
	NYHA II				
	NYHA III				
	NYHA IV*				
Week 46 to 106	NYHA I				
	NYHA II				
	NYHA III				
	NYHA IV*				

*NA represents a timepoint within the trial in which no patients were assessed to be within the defined NYHA IV class.

Note: Transition probabilities reported in the above table for Baseline to Week 12, Week 12 to Week 46, and Week 46 to Week 106 were observed at assessment timepoints and prior to any transformations applied. These transition probabilities were subsequently converted into 4-weeks to be used in the model (i.e., to adjust as per the cycle length).

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

The approach with the augmented mavacamten arm is limited by not using all the available data from the EXPLORER-HCM and the lower number of observations in the later timepoints of the EXPLORER-LTE. For these reasons the augmented mavacamten arm is not used in the base case.

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

Note: Only 13 patients are observed at week 108 in the data cut used for the analysis.

8.4.1.5 Long-term transitional probabilities

Patients in the mavacamten + BB/CCB arm 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 hereafter. Patients in the BB/CCB monotherapy arm retained the NYHA class attained at the end of week 46 (the baseline assessment of MAVA-LTE).

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 stabilisation of the NYHA class distribution observed towards the later periods of EXPLORER-HCM for mavacamten patients (see Figure 24). A similar pattern was observed in the EXPLORER-LTE cohort of the MAVA-LTE study (see bottom panel of Figure 27).

8.4.2 Natural disease progression

This model considered the 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 as a result of the natural progression of the disease.[86,90]

There is a relative paucity of evidence to be able to quantify the rate of disease progression for patients with oHCM. A targeted literature review identified Liu et al. (2017)[91], a systematic review and meta-analysis of survival and prognostic factors in hypertrophic cardiomyopathy which included studies up to September 2015. However, the inclusion criteria included all patients with HCM, rather than just the obstructive sub-type, therefore further assessment of suitability was required.

Nineteen studies were included inLiu et al. (2017)[91], representing 12,146 patients with HCM. Of these 19 studies, 15 included a NYHA class III/IV outcome. The majority reported the proportion of patients in NYHA class III/IV at baseline, with only some reporting the proportion of patients in NYHA class III/IV also at the end of follow-up.[91] However, of those studies that reported NYHA class III/IV at baseline, this was in a subset of patients specific to a different outcome (i.e. those who had a mortality event). Other issues included the lack of data relating to the obstructive sub-type and generalisability to the target population as well as the variability in follow-up. Therefore, none of the studies identified by Liu et al. (2017)[91]. were deemed appropriate to inform this model scenario.

Additional targeted searches were undertaken (key terms included obstructive/obstruction, HCM and disease progression), which identified Maron et al. (2016)[86], a study published after the search period of Liu et al. (2017)[91](September 2015). This study was considered suitable to inform the modelling based on the following conditions: (1) reported patients with obstructive HCM or obstructive HCM as a pre-defined subgroup; (2) reported NYHA class at baseline and over time; (3) was rate adjusted to allow for a yearly rate to be obtained or calculated.

Maron et al. (2016)[86] quantified this effect, with 3.2% and 7.4% of patients progressing from class I or II to class III or IV per year for the provocable and rest obstruction subgroups, respectively.[86] 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 NYHA class above. The mechanism of action of mavacamten may have a positive impact on underlying natural disease progression. As a consequence, patients treated with mavacamten would have a slower disease progression relative to patients treated with standard of care. To quantify the relative impact of mavacamten, EXPLORER-HCM was used to inform the relative reduction in disease progression.[13] After the first 30 weeks in EXPLORER-HCM, 68.75% of patients on placebo and 34.96% of those on mavacamten saw no NYHA class improvement; a relative difference of 50.85% (mavacamten vs. placebo arm) resulted in an annual disease progression rate (i.e., proportion of patients who worsen by 1 NYHA class) of 2.31% for patients on mavacamten + BB/CCB.[13] Table 36 provides inputs used to model natural disease progression in the base case.

Table 36. Annual disease progression rates

NYHA class	Mavacamten + BB/CCB	BB/CCB monotherapy	SRT + BB/CCB
I to II	2.31%	4.55%	4.55%
II to III	2.31%	4.55%	4.55%
III to IV	2.31%	4.55%	4.55%
Reference	Maron et al. (2016)[86] and EXPLORER-HCM[13]	Maron et al. (2016)[86]	Maron et al. (2016)[86]

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

8.4.3 Discontinuation or escalation from mavacamten

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. Additionally, like patients in the BB/CCB monotherapy arm, patients 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).

8.4.3.1 Discontinuation of mavacamten due to adverse events

End-of-trial period (week 30)

It was assumed that no patients in the intervention arm discontinued mavacamten during 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 1.6% due to SAEs within 30 weeks (see Table 21). 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).[13]

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 2.8% based on the 30-week trial-based estimate of 1.6%) and applied evenly regardless of NYHA class because implementation at the conclusion of the trial period was explored.[13]

8.4.3.2 Discontinuation of mavacamten due to lack of response

End-of-trial period (week 30)

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.[51] It is possible that some patients will experience a beneficial effect of mavacamten to a lesser degree than what will result in a full NYHA class improvement. Some patients might continue treatment despite not experiencing a NYHA class improvement. Thus, in a scenario analysis, 50% of the patients discontinuing at week 30 instead were assumed to stay on treatment. Because the modelling of effect was based on NYHA class, these assumed effects were not captured by the model; hence, the scenario yielded a conservative incremental cost-utility ratio (ICUR).

8.4.3.3 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 at a later timepoint.

8.4.4 Treatment escalation from BB/CCB monotherapy

In the model, patients receiving BB/CCB monotherapy could escalate to treatment with SRT, which was modelled based on the ESC guidelines.[3]

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 37) was permitted to escalate from BB/CCB monotherapy to SRT + BB/CCB at each cycle.

The proportion of patients undergoing various SRT procedures (i.e., myectomy, alcohol ablation therapy) over lifetime (by NYHA class, [redacted] was collected via an expert elicitation study.[46]

These lifetime SRT rates were converted to annual rates by using NYHA class–specific life expectancy from the model ([redacted]

Table 37. 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] %	[redacted]	[redacted]	[redacted]	[redacted]	Expert elicitation study[46]

BB = beta-blocker; CCB = calcium channel blocker; NYHA = New York Heart Association; UK = United Kingdom.

[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.

8.4.5 Efficacy of SRT + BB/CCB

Efficacy estimates used in the base-case analysis were collected via the expert elicitation study.[46] In addition, a scenario with efficacy estimates reported by a Ukraine-based study—Knyshov et al. (2013)[92]—was explored. In this study, 42 patients received either myectomy or alcohol septal ablation 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.[46]

Treatment with SRT was modelled as an event. Patients treated with SRT had incident TPs applied (Table 38) and were moved to a post-SRT state after 1 cycle.

Table 38. Transitional probabilities for patients receiving SRT + BB/CCB

Option	To / From	Transitional probabilities, %			
		NYHA I	NYHA II	NYHA III	NYHA IV
Expert elicitation study[46]	NYHA I	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA II	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA III	[redacted]	[redacted]	[redacted]	[redacted]
	NYHA IV	[redacted]	[redacted]	[redacted]	[redacted]
Scenario					
Knyshov et al. (2013)[92]	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 = beta-blocker; CCB = calcium channel blocker; NYHA = New York Heart Association; SRT = septal reduction therapy.

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.[93,94] In addition, the evidence collected as part of the expert elicitation study also confirmed that up to 20% of patients who received SRT may require a re-intervention (both planned and unplanned).[46] This has been tested by conducting 2 scenario analyses by increasing the SRT procedure cost by both the lower (4.4%) and upper (20%) bounds of the reported re-intervention rates to explore the impact of additional re-intervention costs.

8.4.6 Adverse events

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 the mavacamten + BB/CCB treatment. In all cases, the 30-week probability was converted to a 4-week incidence rate. Adverse events defined as not related to treatment as 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 39 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. Inputs related to disutilities and costs associated with AEs are discussed further in Sections 8.5.1 and 8.6.4, respectively.

Table 39. Treatment-related adverse events and incidence rates

Adverse event	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 ischaemic 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[13]		EXPLORER-HCM[13]		Assumption, same as BB/CCB monotherapy

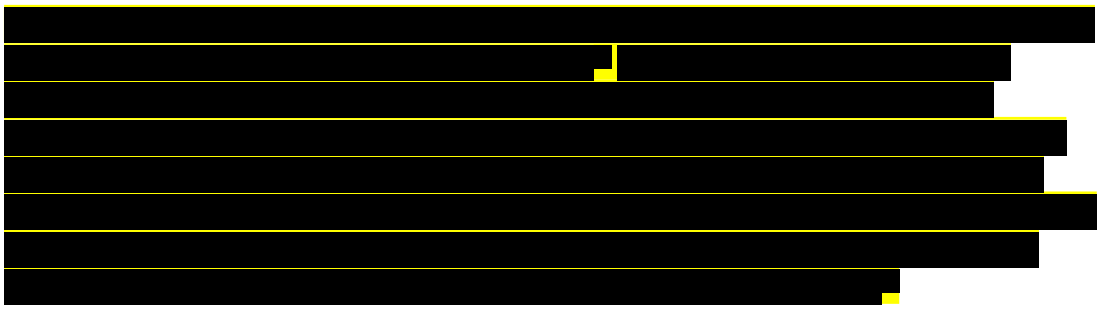
BB = beta-blocker; CCB = calcium channel blocker; SRT = septal reduction therapy.
Note: Intervention arm: n = 123; comparator arm: n = 128.

8.4.7 Mortality

General population and all-cause mortality rates were obtained from the latest (i.e., 2021) national life tables from Statbank Denmark.[87] 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 (RRs) 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:

- A study by Wang et al.[32] 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 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 patient population was white.[32]
- 

In the base case, HRs from the Wang et al.[32] study was used due to the higher number of included patients and the ability to separate mortality data for NYHA class III and IV patients.[32] Scenario analyses included use of HRs from the study using SHaRe data. Only a composite HR for NYHA class III-IV was available; thus, the same was applied to both class III and IV patients. Table 40 provides the HRs by NYHA class.

Table 40. Hazard ratios for each NYHA class compared with NYHA I

NYHA class	HR (95% CI) from Wang et al. (base case)[32]	HR (95% CI) from SHaRe analysis[33] (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.

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 published systemic literature review and meta-analysis by Bytyci et al. (2020)[11] reported a short-term mortality risk of 1.12% and 1.27% in patients receiving alcohol ablation therapy and myectomy, respectively,[11] with a weighted average of 1.20% 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.

8.5 Documentation of health-related quality of life

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

8.5.1 Health-state utility values 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 are included in the health-state utility where related to the level of NYHA class.

The SLR identified 12 studies that investigated HRQOL and utilities in patients with oHCM. However, no publications reporting study utilities by NYHA class which were needed for the health economic model were identified (except one reporting EXPLORER-HCM utilities using US value set[15]) (see Appendix H). 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.

8.5.1.1 EXPLORER-HCM: EQ-5D-5L

The EQ-5D-5L data collected within EXPLORER-HCM were analysed 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 timepoints, 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)[95] was applied to the EQ-5D-5L data collected in EXPLORER-HCM to derive utility values.

A comprehensive analysis was conducted on the reasons for and impact of these missing data. 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 unfavourable outcomes for mavacamten and favourable outcomes for placebo, the estimated treatment effects on PROs remained statistically significant. Additionally, Table 41 shows that response rates for the EQ-5D at each assessment point were similar across treatment arms. Table 42 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 43 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 41. **Response rates to the EQ-5D by assessment timepoint and treatment arm**

	Mavacamten			Placebo		
Visit	N	Observed	%	N	Observed	%
[redacted]						

[redacted]

Table 42. **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]

Table 43. Mean EQ-5D scores throughout the EXPLORER-HCM trial 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]					

[redacted]

Table 44 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 class 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 class III patients are used for NYHA class 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 be an underrepresentation of the real utility values for NYHA class IV patients, which will potentially favour the BB/CCB monotherapy arm because of the lower NYHA class profile of that cohort.[80] However, the proportion of patients in NYHA class IV is likely to be small, so this assumption is expected to have a limited impact on model outcomes.

It should be noted that NYHA class I mean utility is higher than the population norm (0.95 vs. 0.90, respectively).[97] 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 class 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.

Table 44. Danish health-state utility values

Health state	Utility value	95% CI	Reference
NYHA I	[redacted]	[redacted]	EXPLORER-HCM trial analysis

Health state	Utility value	95% CI	Reference
NYHA II	[redacted]	[redacted]	BMS data on file (2021)[88] (Denmark specific)
NYHA III	[redacted]	[redacted]	
NYHA IV	[redacted]	[redacted]	Assumed to be the same as NYHA class III

NYHA = New York Heart Association.

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. In addition, 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 DMC.[89]

8.6 Resource use and 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 utilisation (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 2023 Danish krone (DKK).

8.6.1 Treatment acquisition costs

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 45), whereas costs and presentation of metoprolol and verapamil were extracted from the Lægemiddelstyrelsen medicinpriser (www.medicinpriser.dk; accessed on 5 February 2023)[98]. Costs associated with SRT (i.e., alcohol ablation therapy and myectomy) were collected from Sundhedsdatastyrelsen diagnosis resource group (DRG).[99]

8.6.1.1 Mavacamten

Mavacamten will be marketed as a pack of 28 capsules with an expected pharmacy purchase price of 9,981 DKK per pack [redacted] 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 and generic drug entry is not always relevant for HTAs because treatment durations are often shorter than the time to patent expiry.[100] This is, however, not the case for mavacamten. In the base case, [redacted] of patients are anticipated to still receive mavacamten after [redacted], which will be after the expected generic entry (compound patent expiry [redacted]). Given that generic drugs are priced much lower than the corresponding brand-name before generic entry,[101,102] a large part of the modelled acquisition cost of mavacamten will be highly overestimated if generic drug entry is not taken into consideration. The inclusion of generic drug entry in HTAs is advocated in scientific literature because failure to incorporate these will yield biased estimates of the incremental cost-effectiveness ratio (ICER).[100,103-105] In the present HTA, it would lead to mavacamten appearing less cost-effective than it actually is. In general, not including future price reductions gives a disadvantage to first-in-class drugs that often will be compared with off-patent drugs that will not experience significant price reductions over time. Ultimately, omission of including generic drug entry does not reflect future cost as realistically as possible.[100]

To avoid modelling a biased and unrealistic ICER, the price impact of generic drug entry on mavacamten was included. Patent expiry is expected on [redacted], which is approximately [redacted] years after the assessment at the Danish Medicines Council. Generic drug uptake in Denmark is, in general, fast and results in significant lower prices.[102] This same pattern is anticipated with mavacamten given it is a manufactured molecule.[104] The specific price impact of generic entry varies. A Danish analysis of primary sector drugs suggested the price impact to be 95%.[106] For a hospital drug–related estimate, Amgros Leverandørportalen was leveraged to estimate the average price impact of generic entry in Denmark for a range of recently expired hospital drug patents ([redacted]) and found an average reduction of [redacted] in tender price compared with the brand-name list price (PPP) in the year of patent expiry.

In the base case, the price of mavacamten is reduced by [redacted] after [redacted] Using [redacted] could be considered conservative given the price cap agreement that historically has meant a lower list price at patent expiry. Table 45 depicts the presentation and cost details for mavacamten. It is recognised that there is uncertainty regarding both time of generic entry and price impact, hence a scenario analysis with a 2-year delay to generic entry and analyses with ± 10% price impact were conducted. A scenario analysis presenting results without reduced cost due to generic drug entry was also conducted.

Table 45. Input of mavacamten acquisition costs

Treatment	Form/administration route	Dose per unit	Pack size	Price (per pack/ procedure) (DKK)	Reference
Mavacamten ≤ year 11	Oral capsule	2.5/5/10/15 mg	28	9,981 (price: 130,200 PPPY)	BMS
Mavacamten > year 11	Oral capsule	2.5/5/10/15 mg	28	[redacted]	[redacted] lower than list price based on average generic entry price impact (Amgros Indkøbscentral)

PPPY = per patient per year.

8.6.1.2 Standard of care and subsequent treatments

For metoprolol and verapamil cost per dose was multiplied by the number of doses per cycle to estimate the cost per cycle. In addition, the impact of genotype testing (i.e., cytochrome P450 [CYP] test) costs, were included as a one-off cost (985 DKK, sourced from Gentest-Filadelfia[107]) in the model and assumed that all

patients treated with mavacamten were tested for genotype. Table 46 depicts the presentation and cost details for the standard of care treatments.

Table 46. Input related to acquisition costs of comparators and subsequent treatments

Treatment	Form/administration route	Dose per unit	Pack size	Price (per pack or per procedure) (DKK)	Reference
Metoprolol	Oral tablets	50 mg	100	407	Lægemiddelstyrelsen Medicinpriser
Verapamil	Oral tablets	120 mg	250	78	
Alcohol septal ablation therapy	Surgical procedure	One-time procedure in model	NA	84,140	Sundhedsdatastyrelsen, DRG; 05MP52
Myectomy			NA	79,636	Sundhedsdatastyrelsen, DRG; 05MP13
One-off CYP test	NA	NA	NA	985	Gentest-Filadelfia[107]

CYP = cytochrome P450; DRG = diagnosis resource group; NA = not applicable.

The market share of alcohol septal ablation therapy and myectomy were obtained based on expert elicitation study responses (Table 47).[46]

Table 47. Market share of various septal reduction therapies

Treatment	Proportion of patients (%)	Reference
Alcohol septal ablation therapy	48.95	Expert elicitation study[46]
Myectomy	51.05	

8.6.2 Healthcare resource utilisation

Data on consumed healthcare resources were collected from an expert elicitation study.[46] 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 DRG tariffs of CV-related visits.

Table 48 presents the resources used in the model along with unit costs. Unit cost associated with each resource was collected from Sundhedsdatastyrelsen, DRG-takster 2023.[99]

Table 48. Frequencies of resources used and their unit costs

Resources	Resources by NYHA class per year				Unit cost (DKK)	Reference
	I	II	III	IV		
Secondary care						
Day case admissions	0.39	0.59	2.06	3.50	1,141	DRG 2023: 05MA98 (MDC05 1-dagsgruppe, pat. mindst 7 år)
Outpatient (CV related) visits	0.69	0.88	2.13	3.25	1,975	DRG 2023: 05PR04 (Kardiologisk undersøgelse, udvidet)
Outpatient (non–CV related) visits	0.31	0.63	0.00	0.00	1,141	DRG 2023: 05MA98 (MDC05 1-dagsgruppe, pat. mindst 7 år)
Inpatient (elective) ≤ 1 days	0.00	0.04	0.60	1.01	2,089	DRG 2023: 05MA08 (Andre hjertesygdomme)

Resources	Resources by NYHA class per year				Unit cost (DKK)	Reference
	I	II	III	IV		
Inpatient (elective) > 1 day	0.00	0.00	0.60	4.04	2,240	DRG 2023: lang-ligger-takst 2,240 DKK per dag efter dag 1
Inpatient (emergency) ≤ 1 day	0.00	0.14	1.73	2.24	2,089	DRG 2023: 05MA08 (Andre hjertesygdomme)
Inpatient (emergency) > 1 day	0.00	0.00	6.92	15.68	2,240	DRG 2023: lang-ligger-takst 2,240 DKK per dag efter dag 1
Tests/procedures						
Cardiac MRI procedures	0.10	0.13	0.34	0.29	2,103	DRG 2023: 30PR03 (MRI scan, uncomplicated)
Total cost						
Cost per cycle (DKK)	182	288	2,221	4,752		
Cost per annum (DKK)	2,370	3,759	28,975	61,984		

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

Sources: Resource frequency: expert elicitation; costs: Sundhedsdatastyrelsen, DRG-takster 2023[108]

8.6.3 Treatment monitoring 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. 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 anticipated SmPC,[51] 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. In the event that 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 49 presents the additional monitoring requirements required while receiving mavacamten, by NYHA class, based on the underlying base-case assumption of HCRU as discussed in Section 8.6.2. 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 49. 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]	BMS data on file (2022)[46]; Camzyos SmPC (2021)[51]; DRG 2023: 05PR05 (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 6 for all NYHA classes, as described above (e.g., the total number of CV visits for NYHA I class is a sum of 54.31 and 0.69, which equals 6).

8.6.4 Adverse event management costs

To ascertain AE management costs, resources used to manage AEs were identified with associated costs based on Sundhedsdatastyrelsen, DRG-takster 2023.[99] In the model, AE management costs were estimated as the sum product of the AE incidence (see Table 39) and the associated costs of each AE. Table 50 presents the management costs associated with each AE.

Table 50. Adverse event management costs

Adverse event	Management cost (DKK)	Reference
Syncope	17,735	05MA07 (cardiac arrhythmia and syncope)
Transient ischaemic attack	21,810	01MA13 (transient insufficient blood supply to brain and occlusion of precerebral arteries)
Cardiac failure congestive	35,525	05MA04 (heart failure and shock)
Viral gastroenteritis	7,530	06MA11 (malabsorption and inflammation of the oesophagus, stomach, and intestines, patients 18 years +)
Urinary tract infection	28,523	11MA07 (infection in the kidneys and urinary tract, patients 16 years +)

Source: Sundhedsdatastyrelsen, DRG - takster 2023[99]

8.6.5 Patient costs related to time and transportation

Along with the before-mentioned cost components, transportation and time spent by patient because of the treatment were also included in current analysis. Table 51 presents the inputs required to estimate costs associated with time spent and transportation. 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 51. Inputs related to patient time and transport

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)	181.00	Medicinrådet, Værdisætning af enhedsomkostninger[108]
Transportation cost per hospital visit	140.00	

8.7 Results

8.7.1 Base-case overview

In addition to the base-case analysis, several scenario analyses were conducted to estimate the impact of key model assumptions on model outputs. These scenarios have been described in detail in Section 8. Table 52 summarises the options and values used for the base-case model versus scenario analyses for which a scenario analysis was undertaken.

Table 52. Model settings: base-case model versus scenario analyses

No.	Parameter	Base case	Scenario
1	Discounting	Annually 3.5% for both costs and outcomes until year 35, followed by 2.5% from year 36	A. 0% for both costs and effects B. 3.5% for both costs and effects C. 2.5% for both costs and effects
Other scenarios			
2	Response-based discontinuation at week 30	Discontinue if no NYHA class improvement from baseline	A. Only 50% of patients discontinue when NYHA class worsens
3	Efficacy of SRT + BB/CCB (incident TPs)	Expert elicitation study estimates, excluding interventionalist[109]	A. Knyshov et al. (2013)[92]
4	Mortality	Wang et al.[32]	A. SHaRe[33]
5	Impact of SRT re-intervention rate	Exclude	A. 4.4% increase in SRT procedure cost[94] B. 20% increase in SRT procedure cost[93,110]
6	Impact of generic entry	Include generic entry	A. Exclude generic entry
7	Impact of generic entry timing	[redacted]	A. [redacted]
8	Impact of % price impact of generic entry	[redacted]	[redacted] B. [redacted]
9	Short-term transition probabilities for the mavacamten arm	30 weeks based on EXPLORER-HCM data	A. Augmented mavacamten arm. 108 weeks based on EXPLORER-HCM and EXPLORER-LTE data

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

8.7.2 Sensitivity analyses

Sensitivity analyses (both deterministic [DSA] and probabilistic [PSA]) were conducted in line with recommendations outlined in the economic evaluation section of the DMC guidelines.[76] For these analyses, each model parameter was assigned an appropriate uncertainty distribution. The uncertainty around the central estimate was set according to distributional information provided in the original source. When distributional information was not available, the standard error was typically assumed to be 20%, although this setting is user adjustable.

For event probabilities and utility values, a beta distribution was used to restrict draws to the 0 to 1 range. For costs and resource use estimates, a gamma distribution was used to restrict draws to the 0 to positive infinity range to prevent values smaller than 0. For distributional parameters that sum to 1, a Dirichlet distribution was used to ensure these parameters always sum to 1 regardless of how they varied around the point estimates. Some inputs required custom implementation into the sensitivity analyses; these are presented below.

Not all parameters are included in the DSA or PSA. Model settings such as time horizon and discount rates are fixed and, as such, are not included. Instead, uncertainty around the discount rates is explored in scenario analyses.

Transition matrices were added to the sensitivity analyses using a Dirichlet distribution. The TPs for each row of a transition matrix were jointly modelled to sum to 1. The standard errors of the distribution were calculated using the TP and the sample size at the assessment period.

Utilities associated with NYHA classes as states of the model were included in the sensitivity analyses using their Cholesky decomposition to reflect covariance of the states in the PSA. The treatment-specific utility values associated with NYHA classes for mavacamten + BB/CCB with BB/CCB monotherapy were jointly modelled by using a single Cholesky matrix. Similarly, the utility values—regardless of treatment arm—were jointly modelled.

Healthcare resource utilisation inputs were not varied in sensitivity analyses because these inputs were collected via an expert elicitation study; thus, no sample variability was available. However, HCRU inputs were implemented in the PSA as a special case. Specifically, the HCRU for NYHA class I is modelled as a baseline, using the gamma distribution. Increase in HCRU as a result of transitioning to a higher NYHA class is calculated by adding normally distributed increments to this baseline. The mean of the increments is positive to ensure that the resource utilisation for each NYHA class is on average higher than the resource use for a lower NYHA class.

8.7.2.1 Deterministic sensitivity analysis

Deterministic sensitivity analyses were conducted to identify which model parameters had the greatest influence on results. Deterministic sensitivity analyses are conducted by varying one parameter at a time and assessing the subsequent impact on incremental costs, incremental QALYs, and incremental costs per QALY gained. Each parameter has been allocated a “lower” and “upper” value that corresponds to the lower and upper bounds of the 95% CI. When the 95% CI was not available, the standard error was assumed to be equal to 10% of the point estimate to generate the lower and upper bound. By adjusting each parameter independently, the sensitivity of the model parameter could be estimated.

Results are presented as tornado diagrams demonstrating the parameters for which the associated uncertainty has the greatest impact on the relevant model outcomes.

8.7.2.2 Probabilistic sensitivity analysis

The PSA involves drawing values for each parameter from its individual uncertainty distribution. The distribution is selected to reflect the known bounds for the parameter (e.g., a beta distribution has been used for parameters bounded between 0 and 1). Contrary to the DSA, PSAs are simultaneously performed for all selected parameters, with the subsequent incremental results recorded. This constitutes 1 “simulation.” In total, 1,000 simulations were performed, providing a distribution of incremental results and, consequently, an estimate of the overall uncertainty surrounding the cost-effectiveness results. In addition, a seed was specified to allow reproducibility of the results. The results are presented using scatter plots on the cost-effectiveness plane, and the probability that mavacamten + BB/CCB is cost-effective at different levels of willingness to pay (WTP) per QALY gained is presented using a cost-effectiveness acceptability curve.

8.7.3 Base-case results

8.7.3.1 Incremental results

Table 53 shows the incremental results for the comparison between mavacamten + BB/CCB and BB/CCB monotherapy. Mavacamten + BB/CCB is costlier than BB/CCB monotherapy but is also more efficacious, yielding an ICUR of 277,829.12 DKK.

Table 53. Incremental results

Treatment arm	Total costs (DKK)	Total LYs	Total QALYs	Δ Costs (DKK)	Δ LYs	Δ QALYs	ICER (incremental DKK/LYs)	ICUR (incremental DKK/QALYs)
Intervention	919,189.47	13.58	12.25					
Comparator	408,318.49	11.96	10.41	510,870.99	**1.63**	1.84	**313,590.86**	**277,829.12**

ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio (incremental cost per QALY); LY = life-year; QALY = quality-adjusted life-year.

8.7.3.2 Disaggregated costs

Table 54 shows the breakdown of per-patient costs (discounted) for both arms over the lifetime horizon. Total per-patient costs are estimated to be 919,189.47 DKK for the mavacamten + BB/CCB arm and 408,318.49 DKK for the BB/CCB monotherapy arm. Mavacamten treatment acquisition cost was the main cost driver in the mavacamten + BB/CCB arm. The largest cost category for the BB/CCB monotherapy arm was patient time costs, resulting in 44% of total costs. This is because these patients spent more time, on average, in a worse NYHA class compared with patients in the mavacamten + BB/CCB arm and may have accrued more inpatient time in hospital.

Table 54. Breakdown of costs

Outcome	Intervention (DKK)	Comparator (DKK)	Incremental Results (DKK)
Total costs	**919,189.47**	**408,318.49**	**510,870.99**
Treatment acquisition cost	**698,315.95**	**34,905.92**	**663,410.03**
Mavacamten + BB/CCBs	678,330.62	0.00	678,330.62
BB/CCBs monotherapy	17,487.75	29,738.76	-12,251.01
BB/CCBs + SRT	1,951.58	3,981.55	-2,029.96
Post-SRT	546.00	1,185.62	-639.62
Drug monitoring cost	**8,334.81**	**0.00**	**8,334.81**
NYHA I	4,332.86	0.00	4,332.86
NYHA II	3,720.72	0.00	3,720.72
NYHA III	275.32	0.00	275.32
NYHA IV	5.90	0.00	5.90
One-off CYP test cost	**985.00**	**0.00**	**985.00**
Healthcare resource utilisation	**96,373.90**	**159,028.50**	**-62,654.61**
NYHA I	14,648.43	2,516.04	12,132.39
NYHA II	21,028.19	26,480.13	-5,451.94

Outcome	Intervention (DKK)	Comparator (DKK)	Incremental Results (DKK)
NYHA III	45,094.94	95,240.33	-50,145.38
NYHA IV	15,602.33	34,792.00	-19,189.67
AE cost	16,541.91	22,678.47	-6,136.57
Patient time costs	**90,962.68**	**180,468.31**	**-89,505.63**
Transportation costs	**7,675.23**	**11,237.28**	**-3,562.05**

AE = adverse event; BB = beta-blocker; CCB = calcium channel blocker; CYP = cytochrome P450; NYHA = New York Heart Association; SRT = septal reduction therapy.

8.7.3.3 Disaggregated effects

Table 55 presents the LYs and QALYs accrued over the model's lifetime horizon (discounted). Overall, the mavacamten + BB/CCB arm accrues more LYs than the BB/CCB monotherapy arm (13.58 vs. 11.96). Due to the higher efficacy of mavacamten + BB/CCB as measured in EXPLORER-HCM, the mavacamten + BB/CCB arm accrued most of its LYs in NYHA class I (6.18), whereas the BB/CCB monotherapy arm accrued most of its LYs in NYHA class II (7.05).

Similarly, the mavacamten + BB/CCB arm accrued more QALYs than the BB/CCB monotherapy arm (12.25 vs. 10.41). Due to the higher efficacy of mavacamten + BB/CCB as measured in EXPLORER-HCM, the mavacamten + BB/CCB arm accrued most of its QALYs in NYHA class I (5.81), whereas the BB/CCB monotherapy arm accrued most of its QALYs in NYHA class II (6.30).

Table 55. Breakdown of life-years and QALYs

Outcome	Intervention	Comparator	Incremental results
Life-years	**13.58**	**11.96**	**1.63**
NYHA I	6.18	1.06	5.12
NYHA II	5.59	7.05	-1.45
NYHA III	1.56	3.29	-1.73
NYHA IV	0.25	0.56	-0.31
QALYs	**12.25**	**10.41**	**1.84**
NYHA I	5.81	1.00	4.81
NYHA II	4.98	6.30	-1.32
NYHA III	1.25	2.66	-1.41
NYHA IV	0.20	0.45	-0.25

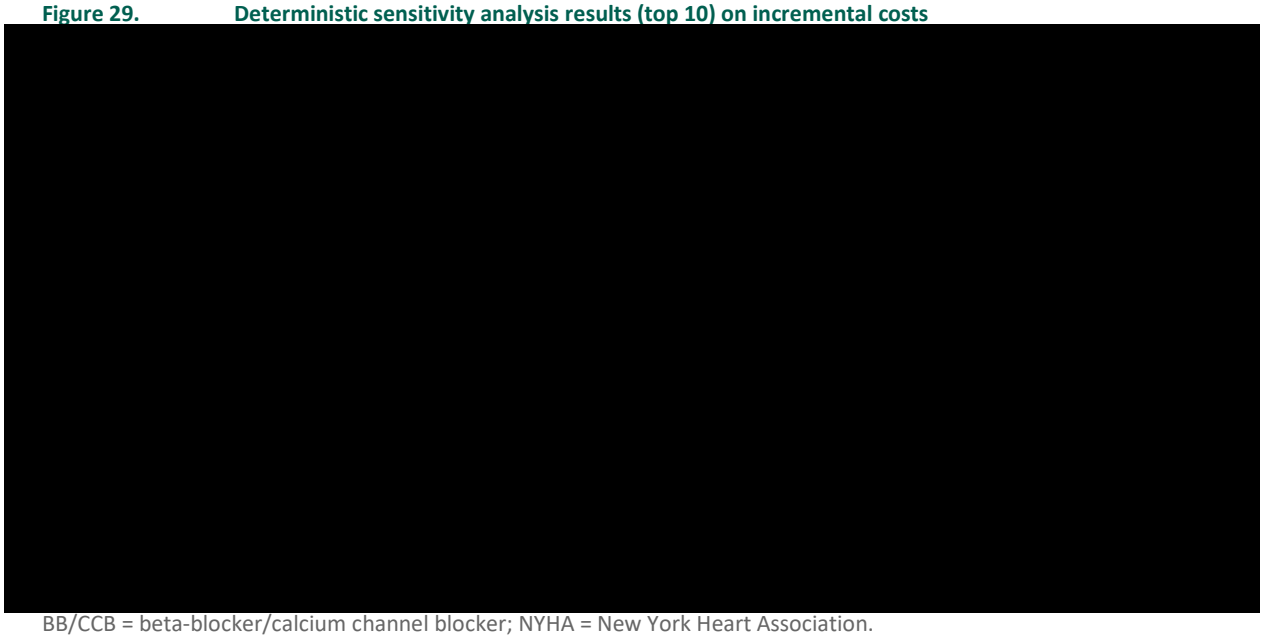
AE = adverse event; NYHA = New York Heart Association; QALY = quality-adjusted life-year.

Note: Disutility due to AE incidence was not included in the model to avoid double counting of AE impact within the underlying utilities observed in the trial.

8.8 Deterministic sensitivity analysis

Figure 29, Figure 30, and Figure 31 present the tornado plots with the top 10 parameters that have the largest impact on incremental costs, incremental QALYs, and ICUR, respectively, for mavacamten + BB/CCB versus BB/CCB monotherapy. The greatest impact on incremental costs is due to the percentage of patients in each NYHA class who achieved NYHA improvement. The greatest driver of incremental QALYs is the mortality rate for patients in NYHA class III, followed by the health-state utility value for NYHA class I and mortality rate for patients in NYHA class II.

Figure 29. Deterministic sensitivity analysis results (top 10) on incremental costs



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

Figure 30. Deterministic sensitivity analysis results (top 10) on incremental QALYs

BB = beta-blocker; CCB = calcium channel blocker; NYHA = New York Heart Association; QALY = quality-adjusted life-year.

Figure 31. Deterministic sensitivity analysis results (top 10) on incremental cost-utility ratios

BB = beta-blocker; CCB = calcium channel blocker; ICUR = incremental cost-utility ratio; NYHA = New York Heart Association.

The ICER per percentage discount of mavacamten is explored in Figure 32. A negative ICER means that mavacamten dominates treatment over BB/CCB monotherapy.

Figure 32. ICER per percentage discount of mavacamten price versus mavacamten list price

8.9 Probabilistic sensitivity analysis

The PSA jointly samples 1,000 simulations from the assigned distribution of each model parameter. The mean total costs and total QALYs obtained from the PSA, together with their 95% CIs, are presented in Table 56, which also allows a comparison between the probabilistic and deterministic results. Overall, the total cost and QALY estimates are comparable across the deterministic and probabilistic analyses. Table 57 presents the incremental results from the PSA. Figure 33 presents the cost-effectiveness plane for the incremental costs

and QALYs obtained in the PSA. Figure 34 presents the cost-effectiveness acceptability frontier, which shows the cost-effectiveness acceptability curves for the treatment alternatives that have the highest probability of being cost-effective at different WTP thresholds.

Figure 33. Cost-effectiveness plane for incremental costs and QALYs

QALY = quality-adjusted life-year; WTP = willingness to pay.

Figure 34. Cost-effectiveness acceptability curve

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

8.10 Scenario analyses

Table 56 shows the results of various scenario analyses conducted for the base case of the CEM. The first set of scenarios assessed the impact of different discount rate combinations. Removing discount rates improves the ICUR for mavacamten + BB/CCB. Assuming that 50% of patients discontinue mavacamten due to lack of response at week 30 increases the ICUR because a proportion of the patients who did not respond at week 30 incur (drug) costs in the mavacamten + BB/CCB arm without benefiting from the treatment in terms of an improvement in NYHA class. Scenarios using efficacy data for BB/CCB monotherapy + SRT from Knyshov et al. (2013)[92] (instead of using data generated from the expert elicitation study) yielded slightly lower ICURs than the base case.

Table 56. Scenario analysis results

		Intervention		Comparator		
No.	Scenario	Total costs (DKK)	Total QALYs	Total costs (DKK)	Total QALYs	ICUR (DKK/QALYs)
-	**Base case**	**919,189.47**	**12.25**	**408,318.49**	**10.41**	**277,829.12**
1	**Discount rates (costs and effects)**					
1A	0% for both costs and effects	[redacted]	17.25	[redacted]	14.05	[redacted]
1B	3.5% for both costs and effects	[redacted]	12.25	[redacted]	10.41	[redacted]
1C	2.5% for both costs and effects	[redacted]	13.40	[redacted]	11.27	[redacted]
2	**Discontinuation of mavacamten due to lack of response/AE response–based discontinuation at week 30**					
2A	50% of patients discontinue when NYHA class worsens	[redacted]	12.32	[redacted]	10.41	[redacted]
3	**Efficacy of SRT + BB/CCB (incident TPs)**					
3A	Knyshov et al. (2013)[92]	[redacted]	12.23	[redacted]	10.37	[redacted]
4	**Mortality**					
4A	SHaRe	[redacted]	12.83	[redacted]	11.39	[redacted]
5	**Impact of SRT re-intervention rate**					
5A	4.4% increase in SRT procedure cost	[redacted]	12.25	[redacted]	10.41	[redacted]
5B	20% increase in SRT procedure cost	[redacted]	12.25	[redacted]	10.41	[redacted]
6	**Impact of generic entry**					
6A	Impact of generic entry excluded	[redacted]	12.25	[redacted]	10.41	[redacted]
7	**Impact of timing of generic entry**					
7A	After 13 years	[redacted]	12.25	[redacted]	10.41	[redacted]
8	**Impact of % price impact of generic entry**					
8A	71%	[redacted]	12.25	[redacted]	10.41	[redacted]
8B	91%	[redacted]	12.25	[redacted]	10.41	[redacted]
9	**Short-term transition probabilities for mavacamten arm**					

No.	Scenario	Intervention		Comparator		ICUR (DKK/QALYs)
		Total costs (DKK)	Total QALYs	Total costs (DKK)	Total QALYs	
9A	108 weeks augmented mavacamten arm (EXPLORER-HCM + EXPLORER-LTE)	[redacted]	11.93	[redacted]	10.41	[redacted]

AE = adverse event; BB, beta-blocker; CCB = calcium channel blocker; ICUR = incremental cost-utility ratio; NYHA = New York Heart Association; QALY = quality-adjusted life-year; SRT = septal reduction therapy; TP = transitional probability.

9 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 the 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 5.1.2 describes the estimation of eligible patients within the 5-year period.

9.1 Market share

BMS has estimated the uptake for mavacamten over a 5-year period if mavacamten is introduced. Table 57 shows the uptake figures used in the budget-impact analysis.

Table 57. Market shares

	Year 1	Year 2	Year 3	Year 4	Year 5
Situation without mavacamten					
Mavacamten + BB/CCB	0%	0%	0%	0%	0%
BB/CCB monotherapy	100%	100%	100%	100%	100%
Situation with mavacamten					
Mavacamten + BB/CCB	38%	72%	100%	100%	100%
BB/CCB monotherapy	62%	28%	0%	0%	0%

BB = beta-blocker; CCB = calcium channel blocker.

Table 58 shows the resulting number of patients based on the uptake shown above and the patient numbers presented in Section 5.1.2.

Table 58. Number of patients based on market share

	Year 1	Year 2	Year 3	Year 4	Year 5
Situation without mavacamten					
Mavacamten + BB/CCB	0	0	0	0	0
BB/CCB monotherapy	244	270	296	322	348
Situation with mavacamten					
Mavacamten + BB/CCB	92	220	296	322	348
BB/CCB monotherapy	152	50	0	0	0

BB = beta-blocker; CCB = calcium channel blocker.

Note: Totals may not sum due to rounding.

9.2 Budget impact

The budget-impact costs are estimated based on the base-case parameters outlined in Table 52, with the exception of healthcare provider perspective and discount rates set to zero. The budget impact is presented in Table 59 to Table 62. The introduction of mavacamten leads to an increase in budgets over all 5 years compared with a situation without mavacamten (Table 62).

Table 59. Average cost per eligible patient by treatment

	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BB/CCB monotherapy	12,358	14,524	15,179	15,701	16,044

BB = beta-blocker; CCB = calcium channel blocker.

Table 60. Expected budget impact if mavacamten is introduced

	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
Mavacamten + BB/CCB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BB/CCB monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BB = beta-blocker; CCB = calcium channel blocker.

Table 61. Expected budget impact if mavacamten is not introduced

	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
Mavacamten + BB/CCB	0	0	0	0	0
BB/CCB monotherapy	3,015,419	3,865,175	4,402,714	4,924,578	5,416,615
Budget impact	3,015,419	3,865,175	4,402,714	4,924,578	5,416,615

BB = beta-blocker; CCB = calcium channel blocker.

Table 62. Base-case budget impact

	Year 1 (DKK)	Year 2 (DKK)	Year 3 (DKK)	Year 4 (DKK)	Year 5 (DKK)
If mavacamten is introduced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
If mavacamten is not introduced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10 Discussion on the submitted documentation

10.1 Interpretations and conclusions of the clinical evidence

The EMA approval of mavacamten is based on the phase 3, placebo-controlled EXPLORER-HCM trial, supported by the phase 2, open-label, proof-of-concept PIONEER-HCM study, as well as the phase 3, placebo-controlled efficacy and safety study VALOR-HCM. Long-term supporting evidence is also presented from EXPLORER-LTE, a long-term, safety extension study of mavacamten in adults with oHCM who have completed MAVERICK-HCM or EXPLORER-HCM. Results from the trials include patients from Denmark and are likely to be generalisable to the anticipated population in Denmark.

10.1.1 Strengths and limitations of the clinical evidence

EXPLORER-HCM is generally considered a high-quality study, based on a quality assessment using the University of York Centre for Reviews and Dissemination criteria for assessment of risk of bias in RCTs. These criteria include questions on randomisation scheme, allocation concealment, balance of prognostic factors, blinding of patients, care providers, outcome assessors, imbalances in dropouts between groups, selective outcome reporting, ITT analysis, and handling of missing data.

Another strength regarding the clinical evidence is that efficacy was evaluated in a head-to-head study evaluating mavacamten + BB/CCB with placebo + BB/CCB, the standard of care in Denmark. Although approval of mavacamten is based on 1 phase 3 study (EXPLORER-HCM), the efficacy and safety were supported by data from 5 studies (VALOR-HCM, PIONEER-HCM, MAVERICK-HCM, EXPLORER-LTE, and PIONEER-OLE).

Obstructive HCM is a rare condition, which results in a small study population. However, the oHCM programme has managed to recruit and follow a sizeable population from multiple centres across the world.

10.2 Interpretation and conclusions of economic evidence

The cost-effectiveness analysis estimated that patients on mavacamten + BB/CCB incur costs of 919,189 DKK and accrue 12.25 QALYs over their lifetime. Comparing these figures with the costs and QALYs for patients on BB/CCB monotherapy yields an ICUR of 277,829 DKK per QALY.

10.2.1 Strengths and limitations of economic evaluation

Although there is some uncertainty underlying these results, extensive scenario analyses were conducted to further investigate the role of model assumptions and data sources in driving the base-case results. The base-case results held across a variety of scenarios.

The lack of randomised data for long-term modelling introduced the need to make several assumptions in the CEM, which introduced uncertainty. However, for all assumptions, the best possible data were used in the base case to inform the model. Whenever possible, the modelling approach was conservative. First, based on published literature, up to 20% of patients who undergo SRT may require a re-intervention.[93,94] Although this is assessed in a scenario analyses, the base case in the model does not include the additional costs of a re-intervention in patients undergoing SRT. Furthermore, the base case also does not include any longer-term disutility or monitoring after SRT. Because SRT is more frequent among patients on BB/CCB monotherapy than for those on mavacamten + BB/CCB, the base case is conservative and may potentially underestimate the costs associated with BB/CCB monotherapy and, in turn, overestimate the ICUR.

The strengths of the model are worth noting. The model uses patient-level, trial-based data to inform both costs and QALYs associated with adding mavacamten to the treatment pathway for patients with oHCM. The model incorporates treatment sequencing according to Dansk Cardiologisk Selskab[19] and ESC and AHA clinical practice guidelines.[1,3] The health states in the model are defined based on NYHA classification, a commonly used tool that has been used in previous technology assessments.[79,80]

Additionally, the model developed in this report makes an important contribution towards filling the evidence gap that existed regarding the HCRU of patients with oHCM. Indeed, there were no available data on HCRU among patients with oHCM by their NYHA class before the development of this model. An expert elicitation study was designed and conducted to collect these data separately by NYHA class so that it could be used to populate the model.[111]

11 List of experts

Not applicable.

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