Cost-Effectiveness of Mavacamten for the Treatment of Patients With Symptomatic Obstructive Hypertrophic Cardiomyopathy (HCM) in France

Poster number: EE57

Cotté FE[1], Hurst M[2], Akarkoub S[3], Ho M[4], Vernon J[1], Chambry L[3], Vega V[3], Leproust S[3]

[1]Bristol Myers Squibb, Rueil-Malmaison, 92, France, [2]Bristol Myers Squibb, Uxbridge, LON, UK, [3]IQVIA, Courbevoie, 92, France, [4]OPEN Health Group, UK

Introduction

- Hypertrophic cardiomyopathy (HCM) is a chronic and progressive disease characterised by primary left ventricular (LV) hypertrophy, with a large proportion of patients having left ventricular outflow tract obstruction (LVOTO), categorised as obstructive HCM[1]
- In Europe, obstructive HCM therapeutic strategy is based on the use of beta-blockers (BBs) as first-line treatment. Calcium channel blockers (CCBs) are recommended in second-line treatment for patients who are intolerant or have contraindications to BBs[2-4].
- Mavacamten is a first-in-class cardiac myosin ATPase inhibitor that received marketing authorization in Europe in June 2023 for the treatment of symptomatic (NYHA class II-III) obstructive HCM in adult patients, based on EXPLORER-HCM (NCT03470545)[5] and VALOR-HCM (NCT04349072)[6] phase III studies results.
- In EXPLORER-HCM, mavacamten demonstrated superiority over placebo on all secondary endpoints and on the primary composite endpoint, defined either by an improvement ≥ 1.5 ml/kg/min in pVO2 associated with an improvement in at least one NYHA class, or an improvement ≥ 3.0 ml/kg/min in pVO2 without NYHA class worsening), with a positive clinical response achieved at 30-weeks by 36.6% of patients receiving mavacamten compared to 17.2% of patients in the placebo group (CI95% of difference [8.7; 30.1]; p = 0.0005)[5].
- Based on these results, reimbursement in France was granted in October 2023 by the Transparency Committee (TC) in a population estimated to around 18,500 patients[7].
- In parallel, a cost-effectiveness analysis was submitted as part of the pricing and reimbursement process and validated according to the Commission for Economic and Public Health Evaluation (CEESP) requirements[8].

Objective

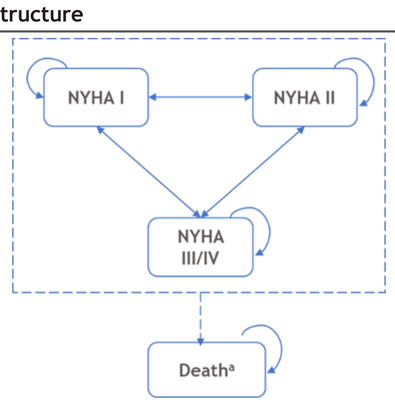
- The objective was to assess the cost-effectiveness of mavacamten in combination with the standard of care (SoC) composed of BBs/CCBs, compared to the SoC alone in symptomatic patients (New-York-Heart-Association [NYHA] class II/III), following French health economic guidelines[9].

Methods

Model overview

- The base-case analysis was conducted from a French healthcare perspective. Given the impact of obstructive HCM symptoms on patients' ability to complete daily activities, a limited societal perspective including productivity loss costs, was evaluated in a scenario analysis.
- A four-state (NHYA I, II and III/IV and death) Markov model structure was developed (**Figure 1**). NYHA III and IV classes were combined given the limited data available for NYHA IV patients in the EXPLORER-HCM trial and the French REMY registry[10].
- Costs and health outcomes were projected and discounted at 2.5% per year over a lifetime horizon (implemented by following the hypothetical cohort of modelled patients until they died or reached the age of 100 years).

Figure 1. Model structure



[a]Death state is accessible from all non-death health states
Abbreviations: NYHA: New York Heart Association

- Two distinctive periods composed the time horizon: a "short-term" period up to 30 weeks, aligned with the longest randomised trial data available comparing mavacamten + SoC vs placebo + SoC alone, and a "long-term" period thereafter.
- Model outcomes included total and incremental costs, quality-adjusted life years (QALYs), life-years (LYs), incremental cost-effectiveness and cost-utility ratios (ICER and ICUR).
- The robustness of results was tested with a deterministic sensitivity analysis (DSA) and a probabilistic sensitivity analysis (PSA).

Model inputs

- Short-term transition probabilities were directly derived from the EXPLORER-HCM trial, mirroring short-term variable cycle lengths for both treatment arms until week 30.
- Afterwards, patients were assumed to retain the NYHA class achieved at the end of week 30. To address the lack of clinical validity of this hypothesis, an additional natural disease progression matrix was applied in the long-term period to both arms to reflect anticipated progression and worsening of disease over time, informed by the French REMY registry[10].
- All grade treatment-related adverse events (AEs) observed in the EXPLORER-HCM trial were applied throughout the entire simulation, with an impact on costs and utilities only for grade 3-4 AEs.
- French value set weighted EQ-5D-5L data derived from the EXPLORER-HCM trial were used to estimate treatment independent utilities by NYHA classes.

Methods *(continued)*

- Only direct costs were considered in the base-case analysis, comprising treatment acquisition, mavacamten treatment and NYHA class-specific monitoring, AE management, subsequent treatment lines, medical transport, and palliative care costs
- Costs associated with productivity loss presented in the limited societal perspective scenario analysis were estimated and valued using the National Health Insurance Database (NHID; *SNDS*)[11]
- Main model inputs are presented in the **Table 1.**

Table 1. Main model inputs

Parameters	Base-case value	Source
Baseline patients characteristics		
Mean age, years	59	EXPLORER-HCM[5]
Proportion of male	59.4%	EXPLORER-HCM[5]
Clinical inputs		
Initial health state distribution		
NYHA I	0%	EXPLORER-HCM[5]
NYHA II	72.9%	EXPLORER-HCM[5]
NYHA III/IV	27.1%	EXPLORER-HCM[5]
Long-term transition: disease natural progression		
NYHA I to NYHA II	1.4%	REMY registry[10]
NYHA I to III	0.5%	REMY registry[10]
NYHA II to III/IV	3.2%	REMY registry[10]
Mortality HRs vs French general population		
NYHA I	1.0	Wang et al.[12]
NYHA II	1.8	Wang et al.[12]
NYHA III/IV	4.9	Wang et al.[12]
NYHA classes-dependent utilities		
NYHA I	0.98	EXPLORER-HCM[5]
NYHA II	0.94	EXPLORER-HCM[5]
NYHA III/IV	0.87	EXPLORER-HCM[5]
Costs inputs		
Mavacamten acquisition cost		
Public list price (28 tab.)	€ 1,383.69	Journal Officiel de la République Francaise[13]
HCRU by NYHA classes		
NYHA I	€ 706 (€ 5,243)*	NHID study[11]
NYHA II	€ 1,878 (€ 10,166)*	NHID study[11]
NYHA III/IV	€ 6,924 (€ 16,175)*	NHID study[11]

Abbreviations: NYHA: New York Heart Association, Public list price: price without accounting for any confidential discounts
*Including indirect costs due to productivity loss (population ≤65 years old) estimated using human-capital method

Results

Base-case analysis

- Over a lifetime horizon, mavacamten + SoC resulted in an incremental QALY gain of 1.52 and an incremental LY gain of 1.35. This differential primarily stems from a higher proportion of patients in NYHA class I in the mavacamten arm, reflecting mavacamten's effectiveness data from the EXPLORER-HCM trial and accumulation of higher utilities and lower mortality rates. In total, patients accumulated an additional 4.33 LYs and 4.21 QALYs compared to the SoC within the NYHA I class.
- Total healthcare costs for mavacamten + SoC compared with the SoC alone were estimated to be €172,060 and €49,409, respectively, resulting in an incremental cost of €122,651. Additional incremental costs was driven primarily by treatment acquisition costs (€133,042) offset by NYHA class monitoring (€10,966), subsequent treatments (€551) and palliative care savings (€117).
- Detailed health and costs results are presented in the **Table 2.**

Table 2. Detailed base-case analysis health and costs outcomes

	Mavacamten + SoC	SoC alone	Increment
Efficacy outcomes (discounted)			
Total LY	**15.82**	**14.47**	**1.35**
NYHA I	7.51	3.18	4.33
NYHA II	6.03	7.35	-1.32
NYHA III/IV	2.28	3.95	-1.67
Total QALY	**14.90**	**13.38**	**1.52**
NYHA I	7.30	3.09	4.21
NYHA II	5.64	6.88	-1.24
NYHA III/IV	1.97	3.42	-1.45
AE QALY loss	-0.02	-0.01	-0.01
Costs outcomes (discounted)			
Total lifetime costs	**€ 172,060**	**€ 49,409**	**€ 122,651**
Acquisition	€ 134,582	€ 1,540	€ 133,042
Treatment specific monitoring	€ 1,143	€ -	€ 1,143
NYHA classes monitoring	€ 32,440	€ 43,407	- € 10,966
AE management	€ 863	€ 714	€ 148
Subsequent treatment	€ 800	€ 1,351	- € 551
Palliative care	€ 2,174	€ 2,290	- € 117

Abbreviations: AE: Adverse Event; LY: Life Year; NYHA: New York Heart Association; QALY: Quality Adjusted Life Year

- Consequently, the discounted ICUR was €80,799 and the ICER was €91,063 (**Table 3**).

Table 3. Deterministic base-case analysis results

Strategies	Costs	LYs	QALYs	ICER (€/LY)	ICUR (€/QALY)
SoC alone	49 409 €	14.47	13.38	-	-
Mavacamten + SoC	172 060 €	15.82	14.90	**91 063€**	**80 799€**

Abbreviations: SoC: Standard Of Care; LY: Life Year; QALY: Quality Adjusted Life Year; ICER: Incremental Cost-Effectiveness Ratio; ICUR: Incremental Cost-Utility Ratio

Sensitivity analysis

- When performing the DSA, adjusting variables by -/+10%, the greatest impact observed on the ICUR was adjusting the mortality HR for NYHA III/IV *versus* NYHA I from 4.94 to 4.04 and 5.97 respectively, with an impact <10% on the ICUR (**Figure 2**).
- The mean ICUR obtained from the PSA was almost identical to the base-case deterministic one (€80,777 vs €80,799), highlighting the low uncertainty associated with the analysis (**Figure 3**).
- The cost-effectiveness acceptability curve demonstrates that mavacamten + SoC would be cost-effective in 80% of cases at a willingness-to-pay threshold of €93,750 per QALY (**Figure 4**).

Broader perspective scenario analysis

- An additional scenario was explored looking at the impact of absenteeism in the model, based on productivity loss costs estimated using the NHID[11], yielding a reduction in the deterministic ICUR from €80,799 to €77,290.

Figure 2. Impact of individual parameters on the ICUR as determined by the DSAs

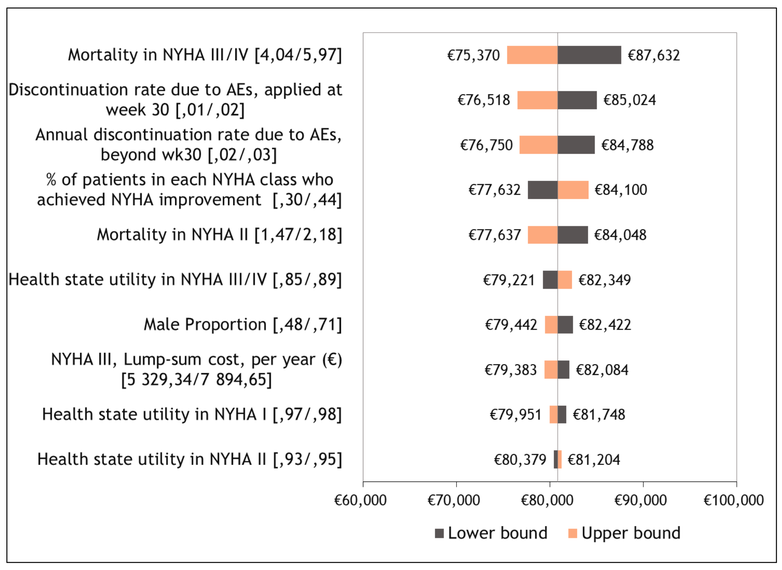


Figure 3. Scatter plot from the PSA

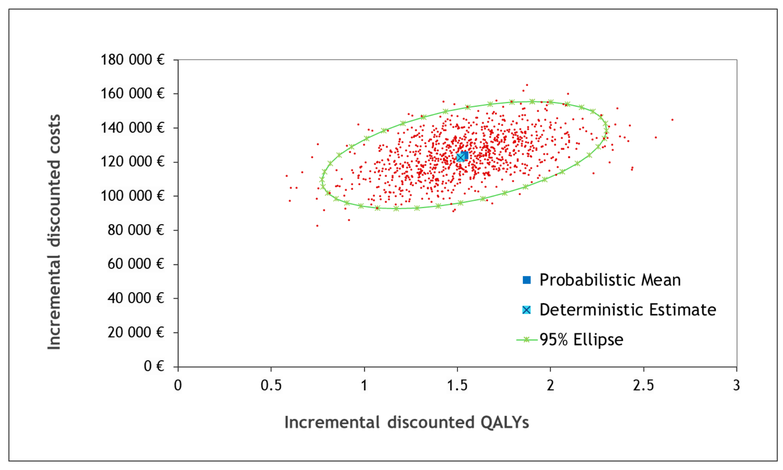
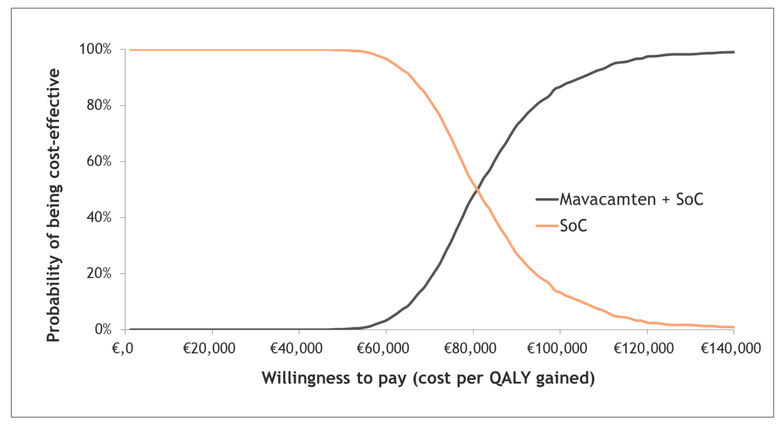


Figure 4. Cost-effectiveness acceptability curve



Limits

- Where data were scarce, model assumptions were kept conservative particularly regarding mavacamten long-term efficacy extrapolation, although the readout of study extension data (i.e., EXPLORER-LTE) has shown a stabilization in NYHA class beyond week 30[13].
- EXPLORER-HCM did not collect mortality and morbidity endpoints and as such causal association of real-world outcomes and NYHA class was assumed.
- Economic models are a simplified assessment of potential longer-term outcomes and as such this might not correctly reflect actual practice.
- Data primarily based on clinical trials. Impact in real world clinical practice is still to be determined, with various studies seeking to assess this.

Conclusion

- This cost-effectiveness analysis conducted over a life-time horizon and within a French healthcare perspective demonstrated that the addition of mavacamten to SoC is cost-effective compared to SoC alone in France, on a public list price basis.
- The results are considered robust given the limited uncertainty provided in the sensitivity and scenario analyses and the positive methodological assessment by the CEESP.
- The introduction of mavacamten has a notable impact on the reduction of NYHA-based HCRU and productivity loss costs, showing an indirect economically benefit but also addressing unmet needs for patients.

Abbreviations: AE, adverse event; CEESP, Commission for Economic and Public Health Evaluation; DSA: deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; ICUR, increment cost-utility ratio; LY, life-years; NHID, National Health Insurance Database, NYHA, New York Heart Association; obstructive HCM, obstructive hypertrophic cardiomyopathy; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life years; SoC, standard of care; TC, Transparency Committee

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Acknowledgments

- The authors thank Philippine Poignant, Rémi Monnier, Victor Vega and Arthur Juban for their contribution to this economic modeling.

Presented at ISPOR Europe 2024; November 17-20, 2024; Barcelona, Spain

Email: francois-emery.cotte@bms.com