MAVACAMTEN

RISK MANAGEMENT PLAN

Version Number: 6.1

Data-lock Point for this RMP: 27-Oct-2024

Date of final sign off: 29-Sep-2025

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LIST OF ABBREVIATIONS

Term	Definition
ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
AE(s)	adverse event(s)
AF	Atrial fibrillation
AHA	American Heart Association
ALT	Alanine aminotransferase
AME	Absorption metabolism
APD	Action potential duration
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC(0-∞)	Area under the curve from 0 to infinity
AUC0-24	Area under the curve during 24 hours
BA	Bioavailability
BMS	Bristol-Myers Squibb
BNP	B-type natriuretic peptide
CEAC	Clinical events adjudication committee
CI	Confidence interval
CKD	Chronic kidney disease
Cmax	Maximum serum concentration
CMR	Cardiac magnetic resonance
COVID-19	Coronavirus Disease 2019
CPET	Cardiopulmonary exercise tolerance testing
CSR	Clinical study report
CV	Cardiovascular
CYP	Cytochrome P450
CYP2C9	Cytochrome P-450 2C family isozyme 9
CYP2C19	Cytochrome P-450 2C family isozyme 19
CYP3A4	Cytochrome P-450 3A family isozyme 4
DDI	Drug-drug interaction
ECHO	Echocardiogram
ECI	Events of clinical interest
EEA	European economic area
EEIG	European Economic Interest Grouping

Term	Definition
eGFR	Estimated glomerular filtration rate
EKG	Electrocardiogram
EMA	European Medicines Agency
e-MACE	Expanded MACE
EPAR	European Public Assessment Report
ESC	European Society of Cardiology
EU	European Union
EURD	European Union Reference Date
GFR	Glomerular filtration rate
GVP	Good Pharmacovigilance Practices
HCM	Hypertrophic cardiomyopathy
HCP	Healthcare professional
hERG	Human ether a-go-go-related gene
HF	Heart failure
HOCM	hypertrophic obstructive cardiomyopathy
HV	Healthy volunteer
IBD	International Birth Date
ICD	Implantable cardioverter-defbrillator
IR	Incidence rate
LMP	Last menstrual period
LTE	Long-term extension
LTFU	Long-term follow-up
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow tract
MAA	Marketing Authorisation Application
MACE	Major adverse cardiac events
MAD	Multiple ascending dose
MAVA	Mavacamten
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
mmHg	Millimetre of mercury
MRHD	Maximum recommended human dose
MY	MAD study

Term	Definition
N/A	Not applicable
NCA	National competent authority
nHCM	Nonobstructive hypertrophic cardiomyopathy
NHIS	National Health Interview Survey
NOAEL	No-observed-adverse-effect level
NYHA	New York Heart Association
oHCM	Obstructive hypertrophic cardiomyopathy
OLE	Open-label extension
OTC	Over the counter
PAES	Post-authorisation efficacy study
PASS	Post-authorisation safety study
PBPK	Physiologically based pharmacokinetic(s)
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamic
PI	Patient Information
PK	Pharmacokinetic
pre	Predose
PSF	Pregnancy Surveillance Form
QD	Once daily
QPPV	Qualified Person Responsible for Pharmacovigilance
QRS	the interval between the beginning of the Q wave and the end of S wave in the electrocardiogram
QTc	Rate-corrected QT interval
QTc interval	QT interval corrected for heart rate
QTcF	QT interval with Fridericia correction
RCT	Randomized controlled trial
REMS	Risk Evaluation and Mitigation Strategy
RHD	Recommended human dose
RMP	Risk Management Plan
SAD	Single-ascending dose
SAE	Serious adverse event
SCD	Sudden cardiac death
SD	Standard deviation
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA query

Term	Definition
SRT	Septal reducton therapy
SVI	Stroke volume index
TdP	Torsades de Pointes
UK	United Kingdom
ULN	Upper limit of normal
US	United States

EU RISK MANAGEMENT PLAN (RMP) FOR MAVACAMTEN

RMP version to be assessed as part of this application:

Version Number: 6.1

Data-lock Point for this RMP: 27-Oct-2024

Date of Final Sign-off: 29-Sep-2025

Summary of significant changes in this RMP: Updated description and milestone due date for Study CV027031 in applicable Parts and Annexes of the RMP.

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
Part II Safety Specification		
SI Epidemiology of the indication(s) and target population(s)	NA	V2.0 / 26-Jun-2023
SII Non-clinical part of the safety specification	NA	V2.0 / 26-Jun-2023
SIII Clinical trial exposure	NA	V2.0 / 26-Jun-2023
SIV Populations not studied in clinical trials	NA	V2.0 / 26-Jun-2023
SV Post-authorisation experience	N/A	V5.0 / 04-Sep-2025
SVI Additional EU requirements for the safety specification	NA	V2.0 / 26-Jun-2023
SVII Identified and potential risks	N/A	V5.0 / 04-Sep-2025
SVIII Summary of the safety concerns	NA	V2.0 / 26-Jun-2023
Part III Pharmacovigilance Plan	Updated description and milestone due date of Study CV027031	V6.1 / pending
Part IV Plan for post-authorisation efficacy studies	NA	V2.0 / 26-Jun-2023
Part V Risk Minimisation Measures	N/A	V5.0 / 04-Sep-2025
Part VI Summary of the Risk Management Plan	Updated to reflect the changes in the body of the RMP	V5.0 / 04-Sep-2025
Part VII Annexes		
ANNEX 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	Updated description and milestone due date of Study CV027031	V6.1 / pending

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
ANNEX 3 Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan	Updated reference information for Study CV027031	V6.1 / pending
ANNEX 4 Specific adverse drug reaction follow-up forms	NA	V2.0 / 26-Jun-2023
ANNEX 5 Protocols for proposed and on-going studies in RMP Part IV	NA	V2.0 / 26-Jun-2023
ANNEX 6 Details of proposed additional risk minimisation activities	NA	V2.0 / 26-Jun-2023
ANNEX 7 Other supporting data	NA	V2.0 / 26-Jun-2023
ANNEX 8 Summary of changes to the risk management plan over time	Updated to include V6.1	V6.1 / pending

Other RMP versions under evaluation:

RMP Version Number	Submitted on	Procedure Number
None		

Details of the currently approved RMP:

Version number: 5.0

Approved with procedure: EMA/VR/0000249369

Date of approval: 04-Sep-2025

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QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

1 PART 1: PRODUCT OVERVIEW

Table 1-1: Product Details

Active substance(s) (INN or common name)	Mavacamten, BMS-986427, MYK-461, SAR-439152
Pharmacotherapeutic group(s) (ATC Code)	C01EB24
Marketing Authorisation	Bristol-Myers Squibb Pharma EEIG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	CAMZYOS
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Cardiovascular therapies; small molecules Summary of mode of action: Mavacamten is a selective allosteric inhibitor of cardiac myosin that selectively targets cardiac myosin and reversibly inhibits its binding to actin. Mavacamten binds to and stabilizes the weakly-bound ("off-actin") state of myosin, reversibly inhibiting the binding of myosin to actin and thereby decreasing the power stroke required for contraction. The mechanism of action of mavacamten results in the reduction of sarcomeric contractility. Mavacamten is selective for cardiac versus skeletal forms of myosin and is inactive toward smooth muscle myosin. Important information about its composition: Not applicable
Hyperlink to the Product Information	Refer to current PI
Indication(s) in the EEA	**Current:** CAMZYOS is indicated for the treatment of symptomatic (New York Heart Association, NYHA, class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients (see SmPC section 5.1).
Dosage in the EEA	*CYP2C19 poor metaboliser 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 respone by LVOT gradient with Valsalva manoeuvre 4 and 8 weeks after treatment initiation.

Table 1-1: Product Details

Pharmaceutical form (s) and strength(s)	**Current:** Mavacamten immediate release capsules are supplied in 4 strengths: 2.5, 5, 10, and 15 mg.
Is/will the product be subject to additional monitoring in the EU?	Yes

2 PART II: SAFETY SPECIFICATION

2.1 Epidemiology of the Indication(s) and Target Population(s)

2.1.1 Obstructive Hypertrophic Cardiomyopathy

Table 2.1.1-1: Epidemiologic Characteristics of symptomatic obstructive hypertrophic cardiomyopathy (oHCM)

oHCM	
Incidence	There are limited studies and data on the incidence of oHCM. A study conducted by Husser et al[1] using InGef, with longitudinal data from patients insured in one of approximately 70 German social health insurers reported there was a gradual annual increase of HCM from 75.8/100,000 persons (95% CI: 75.2-76.4) in 2011 to 84.2/100,000 persons (95% CI: 83.5-84.8) in 2015. Using the records linkage system of the Mayo Clinic and of the Rochester Epidemiology Project, which accessed diagnostic data on the entire population of Olmsted County, Minnesota, Codd et al. reported an age and sex adjusted incidence of 2.5 per 100,000 person-years between 1975 and 1984. The incidence of HCM increased from 1.4 per 100,000 in the first 5 years to 3.6 per 100,000 in the last 5 years of study.[2] More recently, Moon et al. used the NHIS claims database, a mandatory universal health insurance service for up to 97% of the entire South Korean population. The incidence rate of HCM steadily increased from 4.15 per 100,000 person-years in 2010 to 5.6 per 100,000 person-years in 2016, which has been attributed to more frequent screening with echocardiography. Irrespective of gender, the incidence rate of HCM reached the highest value in the age category between 70 and 79 years, beyond which the incidence rate began to decrease. The overall incidence of male HCM was 1.72-fold higher than that of female HCM (6.0 vs. 3.5 per 100,000 person-years, $p < 0.001$).[3]
Prevalence	**Prevalence of HCM** HCM is the most common inheritable genetic cardiomyopathy and is known to be an important cause of cardiovascular morbidity and mortality across all ages. Its prevalence in the general population has been previously estimated to be about 1:500 (0.2%).[4,5] However, this prevalence includes individuals with clinically unrecognized HCM in the general population by using aggressive

Table 2.1.1-1: Epidemiologic Characteristics of symptomatic obstructive hypertrophic cardiomyopathy (oHCM)

oHCM	
	echocardiographic screening; therefore, most of them may not seek medical attention due to the absence of cardiovascular symptoms. Numerous studies have been conducted to estimate the prevalence of HCM in various countries in Europe. Estimates ranged from 4-7 per 10,000 covering various timeframes from 1997 through 2016.[1,6,7,8,9] Husser et al. is the only study to adjust the estimates to the general population. Several additional studies are often cited as HCM prevalence studies. A recent study by Lannou et al.[10] estimated prevalence of HCM in France as 10 per 10,000. However, this study only used inpatient records to identify HCM. Pujades-Rodriguez et al.[7] reported on the proportion of HCM patients identified in inpatient and outpatient settings, and approximately 30% of HCM patients identified did not have a hospitalization for HCM. Therefore, a study of HCM patients identified through inpatient records only, would not be an accurate estimate of disease prevalence. The CARDIA study[5] was the first to examine the prevalence of echocardiographic features of HCM (ie, hypertrophied, nondilated left ventricle and maximal wall thickness ≥15 mm that were not associated with systemic hypertension) in a general population of 4111 men and women.[5] Although this study as well as more recent population genetic studies have shown a prevalence of HCM around 1:500 or even higher, most of the patients whose echocardiograph results met the criteria for HCM were asymptomatic and undiagnosed, which is supported by the observation that a majority of patients are asymptomatic and do not get diagnosed in their lifetime. In contrast, a recent analysis of the US claims database showed a prevalence of clinically established HCM of only approximately 1:3,000 (0.03%). Thus, the number of patients with HCM who are diagnosed are much smaller, suggesting that most patients with HCM experience a normal life span without limiting symptoms or the need for major treatments. **Prevalence of obstructive HCM** Estimates of the proportion of the HCM population with oHCM range from 22% to 70%. Javidonbadi et al. was the only study to report on oHCM specifically: 251 per 1.6 million or 1.6 per 10,000. In this study, only 22% of the HCM patients had oHCM.[6] In summary, taking all mentioned prevalence studies above, and assuming an approximate 70% proportion of patients with HCM have the obstructive phenotype, prevalence of symptomatic oHCM in the adult population is below approximately 5 in 10,000.

Table 2.1.1-1: Epidemiologic Characteristics of symptomatic obstructive hypertrophic cardiomyopathy (oHCM)

oHCM

HCM prevalence in European countries

Study	Country	Timeframe	HCM Prevalence	Prevalence Rate
Javidgonbadi et al. 2019	Sweden (regional)	2002-2013	1142/1.6 million (251/1.6 million for oHCM)	7/10000 (1.6/10000 for oHCM)
Husser et al. 2018	Germany	2011-2015	4000/5.5 million	7/10000
Pujades-Rodriguez et al. 2018	UK	1997-2010	1375/3.3 million	4/10000
Magnusson et al. 2017	Sweden	2006-2016	74/183, 337	4/10000
Adalsteinsdottir et al. 2014	Iceland	1997-2010	180/320, 000	5/10000

Note: Javidonbadi et al. was the only study to report on oHCM specifically, with a prevalence of 251 per 1.6 million or 1.6 in 10,000. None of studies have distinguished between the prevalence of symptomatic and asymptomatic HCM or oHCM.

Demographics of the population: age, gender, racial and/or ethnic origin

Median age at diagnosis of symptomatic oHCM is 47 years. Many studies show an age-related prevalence, with much lower rates in patients diagnosed under the age of 25 years. Prevalence of oHCM has been shown to increase with age; patients with HCM of more advanced age, beyond mid-life, are being increasingly recognized due to heightened index of suspicion for this disease and increased penetration of advanced cardiac imaging into practice.

Husser et al,[1] demonstrated in the German population, the prevalence increased from 7.4 per 100,000 persons (95% CI 5.2–10.1) in 0 to 9 years old to 298.7 per 100,000 persons (95% CI 276.4–322.4) in patients > 80 years. In all age categories, men had a numerically higher prevalence than women with significant differences in patients > 30 years. In the Cardiomyopathy Registry of the EURObservational Research Programme, the mean age of diagnosis was 47 years, with the 25th percentile and 75th percentiles at 33 and 59 years of age, respectively. Thus, using these data, and assuming an approximate 70% proportion of patients with oHCM, prevalence can be estimated as 1 and 21 per 10,000 (0 to 9 year old and > 80 years, respectively), throughout a wide age range.

In pediatric registries, the prevalence of HCM in children is unknown, but population-based studies report an annual incidence of 0.3 to 0.5 per 100,000.[11,12]

Table 2.1.1-1: Epidemiologic Characteristics of symptomatic obstructive hypertrophic cardiomyopathy (oHCM)

oHCM	
	HCM is most frequently transmitted as an autosomal dominant trait, most studies report a small male preponderance (60% men). This finding remains unexplained but might reflect bias in screening strategies as well as genetic and hormonal modifiers.[13] The prevalence of HCM in different racial groups is similar. The HCM phenotype appears comparable between black and white populations. Current management guidelines for oHCM make no distinctions based on racial or ethnic background of patients[14] and there is no evidence that disease-related genetic variants are more prevalent in the black population.[15,16]
Risk factors for the disease	In up to 60% of adolescents and adults with HCM, the disease is an autosomal dominant trait caused by mutations in cardiac sarcomere protein genes.[17,18,19,20,21] Twenty percent of patients with HCM have family history of SCD and 50% with evidence of familial disease.[13] Five to ten percent of adult cases are caused by other genetic disorders including inherited metabolic and neuromuscular diseases, chromosome abnormalities and genetic syndromes[22,23] Some patients have non-genetic disorders that mimic genetic forms of the disease, for example, senile transthyretin-related amyloidosis and AL amyloidosis (immunoglobulin light chain amyloidosis).[24,25]
Main treatment options	The main goals of pharmacological therapy in HCM relate to control of symptoms and improvement of exercise limitation, abolition or reduction of dynamic intraventricular gradients, treatment of LV dysfunction and HF, control of AF and ventricular arrhythmias, and prevention of cardioembolism.[26] The only medicinal products approved in Europe for use in the management of HCM are the β-blockers propranolol and nadolol. However, there are no targeted treatments or disease-modifying agents for HCM currently available. oHCM patients are prescribed a β-blocker as a first-line treatment titrated to the maximally tolerated dose, followed by a non-dihydropyridine calcium-channel blocker or disopyramide. Pharmacotherapies for symptomatic relief include β-blockers, non-dihydropyridine calcium-channel blockers (diltiazem or verapamil), and disopyramide. Surgical interventions are options for those patients with the most severe form of obstructed HCM (ie, symptomatic oHCM) and include alcohol septal ablation and septal myectomy. Non-pharmacologic therapies include septal reduction therapies (surgical myectomy or alcohol septal ablation therapy), which can be effective in reducing obstruction and improving LV outflow, do not address the underlying myocardial disease. ICD, which may be an option used to prevent oHCM-related SCD, is also an invasive procedure, requiring specialized clinic settings, and may not be available to all patients.[4,27]

Table 2.1.1-1: Epidemiologic Characteristics of symptomatic obstructive hypertrophic cardiomyopathy (oHCM)

oHCM	
	Studies identified from the literature review were generally supportive of the view that pharmacological interventions only provide variable symptomatic relief to patients with HCM. No medical or surgical therapies have been shown to have a disease-modifying effect. Medical device implants (eg, ICD) have contributed to a decrease in mortality based on their treatment of malignant arrhythmias, which can lead to sudden death.
Mortality and morbidity (natural history)	Patients with HCM are often symptomatic with shortness of breath (on exertion or at rest), fatigue, chest pain and reduced exercise tolerance[28] that impacts their daily lives. Among referral-based cohorts of patients with HCM, 30% to 40% will experience adverse events, including: 1) sudden death events; 2) progressive limiting symptoms because of left ventricular outflow tract obstruction or diastolic dysfunction; 3) HF symptoms associated with systolic dysfunction; and 4) AF with risk of thromboembolic stroke.[29] Studies reporting relatively long-term HCM patient outcomes have demonstrated that for patients at risk for, or who develop one of these, disease-related complications, the application of contemporary cardiovascular therapies and interventions has lowered HCM mortality rates to 0.5%/year.[30,31] One of the major treatment initiatives responsible for lowering mortality has been the evolution of SCD risk stratification strategies based on a number of major noninvasive risk markers, which can identify adult patients with HCM at greatest risk for sudden death who are then candidates for ICD placement. The decrease in sudden death rates in HCM appears now to have shifted focus to HF as the predominant cause of disease-related morbidity and mortality and, therefore, greatest unmet treatment need in adults. Data from SHaRe registry reported that the cumulative morbidity in HCM was dominated by complications related to HF and AF. Among patients diagnosed before 40 years of age, the risk of having HF or AF by age 60 year was 47% (95% CI: 42-52) and 62% (95% CI: 56-67), respectively. For context, a 40-year-old in the US general population has a lifetime risk of 20% to 45% for HF and 23% to 26% (women and men, respectively) for AF. SHaRe also demonstrated that regardless of age at diagnosis, the majority of HCM-related complications occurred later in life, peaking between 50 and 70 years of age. Ventricular arrhythmia and sudden death were rare in those diagnsed at > 60 years of age (2% cumulative incidence in SHaRe), all other risks, including AF, HF, and overall mortality, were greatest in this age group.[32] **Mortality** Mortality associated with HCM is variable and can be up to 6% annually across the patient population, but up to 11% per year in patients with end stage HCM.[33,34] The risk of SCD ranges from 0.5% to 2% per year in adults with HCM, and HCM is the most common cause of SCD in adolescents and athletes.[35] The 5-year risk for SCD as predicted by the ESC risk calculator is impacted by age, family history of SCD, history of syncope, and presence of non-sustained ventricular tachycardia as well as by LVOT gradient and structural parameters (eg, left ventricular wall thickness and left atrial size).[4]

Table 2.1.1-1: Epidemiologic Characteristics of symptomatic obstructive hypertrophic cardiomyopathy (oHCM)

oHCM	
	Preventative measures for SCD include exercise restriction, anti-arrhythmic drugs and ICD. Data from a large international cardiomyopathy registry (SHaRE) demonstrate that mortality in patients with HCM is significantly higher than in the general population.[32] While the SHaRe data confirmed that absolute mortality in young patients with HCM is low compared to patients who were 50 years of age or older, it was 4-fold higher than expected for 20- to 29-year-olds without HCM. Prior natural history studies reported sudden cardiac death as the leading cause of mortality in HCM, accounting for ~40% of deaths [36,37] data from SHaRe indicated that 16% of deaths were sudden. Overall mortality in SHaRe was driven by HF and noncardiac death, both of which were more common than lethal arrhythmias, consistent with recent evidence from other cohorts. The reported rates of all-cause mortality and sudden death in a Europe based study was consistent with those reported in US-focused studies. A retrospective study in primarily adult patients with HCM evaluating a single center in Greece (N = 509; mean age: 51.0 years) between 1995 through 2014 reported a 7.1% all-cause mortality rate, 5.5% HCM-related death, 2.8% HF-related death rate, and 2.2% sudden cardiac death rate.[38] The study also reported that AF was associated with higher rates of all-cause (15.1%), HCM-related (12.6%), and HF-related (7.6%) mortality.
Important co-morbidities	The key complications or comorbidities associated with HCM are AF, stroke, and HF. Variability in the reported frequencies of these adverse cardiovascular outcomes, particularly for AF, may be attributable to differences in patient demographics (eg, age) and clinical/disease status (eg, newly diagnosed vs. progressed/severe patients who have experienced a hospitalization event). For HF, differences in the definition and classification methodologies may also have been a contributing factor.[39,40] Reported rates of AF ranged from 4% (newly diagnosed patients) to 33% (hospitalized patients). Reported rates of stroke ranged from 4% (multinational registry study of patients who received care at an HCM specialty center) to 9.2% (hospitalized patients with HCM and AF). The rate of HF related events ranged from 15% (multinational registry in pregnant women) to 43% (natural history study in patients at a specialty center). A systematic literature review of studies published between 1996 through 2016 that described the prevalence of HF among children and adolescents identified one study reporting a 13.5% prevalence rate for congestive HF in pediatric patients with HCM.[41] A recent analysis of data from the Cardiomyopathy Registry of the EURObservational Research Program (N = 3,208; 1,739 with HCM, 1,260 with DCM, rest with other cardiomyopathies) based on adult patients enrolled from 2012 through 2016 reported that the majority of patients with HCM have NYHA Class II/III HF, with Class II being most common for each condition (Class II: 49.9% for HCM; Class III: 16.1% for HCM).[13] Among patients with HCM (median age at enrollment: 55.0 years), 26.6% had a history of AF, 7.7% had sustained ventricular tachycardia, 2.8% had resuscitated ventricular

Table 2.1.1-1: Epidemiologic Characteristics of symptomatic obstructive hypertrophic cardiomyopathy (oHCM)

oHCM	
	fibrillation/cardiac arrest, 3.4% had stroke, and 9.5% had atrioventricular block. Reported rates of AF and stroke in HCM were comparable to those reported in US-based studies. Pujades-Rodriguez et al. identified all HCM patients in a UK-based, linked data system covering 3 million lives and matched them to non HCM patients. The study demonstrated that patients with HCM had a significantly higher risk of ventricular arrhythmia, cardiac arrest or sudden cardiac death, heart failure, AF, myocardial infarction, and cardiac revascularization.[7] Two recent US-based retrospective studies reported on predictors of death, which included being female, NYHA Class III/IV HF, burned out HCM (defined as having EF $\leq$ 50%), and having AF, coronary artery disease, hypertension, or stroke.[42] Although HCM tends to be more common in males, female patients tend to have more severe symptoms and be at higher risk of adverse outcomes including death.[43] Recent studies have also shown that patients with HCM with pathogenic/likely pathogenic mutations in sarcomeric genes may be at higher risk for adverse cardiovascular outcomes, such as death, HF, and arrhythmias. Pathogenic mutations in MYH7 may confer a particularly severe phenotype even when compared to pathogenic mutations in other sarcomeric genes.

2.2 Nonclinical Part of the Safety Specification

The key safety findings and their relevance to human usage are provided in Table 2.2-1.

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings	Relevance to human usage
Toxicity	
Cardiac toxicity	All cardiac toxicities in non-clinical studies, including echocardiographic findings, reduction in systolic performance, cardiac dilation, cardiac inflammation, death, and metaplasia, as well as increased heart weights in rats and QTc prolongation in dogs, were considered secondary to exaggerated mavacamten pharmacology. Toxicities (eg, edema and/or congestion) observed in other tissues, including lung, liver, pancreas, and pleural cavity, were secondary to decreased cardiac function. Plasma exposures (AUC) at the no effect doses for adverse effects in rats and dogs were less than those in humans at the RHD.
Reproductive toxicity	A study evaluating the effects of mavacamten on mating performance, fertility, and early embryonic development in male and female rats showed no effects on these parameters at doses up to 1.2 mg/kg/day. Plasma exposure (AUC) of mavacamten at the highest dose tested was less than in humans at RHD. In a pre/postnatal development study, mavacamten was administered orally to pregnant rats (0, 0.3, 0.75, and 1.5 mg/kg/day) from gestation Day 6 to lactation/postpartum Day 20. No adverse effects were observed in the dams or

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings	Relevance to human usage
Toxicity	
	offspring exposed daily from before birth (in utero) through lactation. The dosage of 1.5 mg/kg/day (the highest dosage level tested) was considered to be the NOAEL for F0 maternal systemic toxicity, F1 neonatal/developmental toxicity, F1 parental systemic toxicity, F1 reproductive toxicity, and F2 embryonic toxicity when mavacamten was administered orally (by gavage) to Crl:CD(SD) rats. The maternal exposure at the NOAEL was inferred from the rat developmental toxicity study dosed at the same level and was less than the RHD.
Developmental toxicity	When mavacamten was administered orally to pregnant rats (0.0, 0.3, 0.75, or 1.5 mg/kg/day) during the period of organogenesis, post implantation loss, decreased mean foetal body weight, and foetal malformations (visceral and skeletal) were increased in the high dose group. Visceral malformations (heart malformation in fetuses, including one total situs inversus) and increased incidences of skeletal malformations (mainly fused sternebrae) were observed. Plasma exposure (AUC) at the no effect dose for embryo-foetal development in rats is less than those in humans at the RHD. When mavacamten was administered orally to pregnant rabbits (0.0, 0.6, 1.2, or 2.0 mg/kg/day) during the period of organogenesis, foetal malformations (visceral and skeletal) were increased at doses of 1.2 mg/kg/day and higher. Visceral findings consisted of great vessels malformations (dilatation of pulmonary trunk and/or aortic arch) noted in 4 fetuses from 4 litters at 2 mg/kg/day. Skeletal malformations consisted of higher incidences of fused sternebrae (38 fetuses from 10 litters) at 2 mg/kg/day. Plasma exposure (AUC) at the no effect dose for embryo-foetal development in rabbits is less than those in humans at the RHD. Based on the developmental findings in rats and rabbits, strict use of effective contraceptive methods were required of study participants; pregnancy or plans to become pregnant were an exclusion criteria for the mavacamten clinical trials.
Nephrotoxicity	No nephrotoxicity was observed.
Hepatotoxicity	Hepatotoxicity observed in preclinical dog or rat studies was secondary to decreased cardiac function and passive venous congestion and necrosis in the centrilobular region because of venous hypertension. No direct hepatotoxicity was observed in any rat or dog study.
Genotoxicity	Mavacamten was not found to be genotoxic in reverse mutation bacterial test (Ames test), human in vitro lymphocyte clastogenicity, or rat in vivo micronucleus assays.
Carcinogenicity	Mavacamten was not carcinogenic in a 6-month rasH2 transgenic mouse study at doses of up to 2.0 mg/kg/day in males and 3.0 mg/kg/day in females or in a 2-year rat carcinogenicity study at doses up to 0.6 mg/kg/day in male and female rats. Exposures at the high doses in mice and rats were up to 3-fold or 0.2-fold, respectively, compared to the RHD.
General Safety Pharmacology	
Cardiovascular	In a 39-week toxicology study in dogs, there was prolongation of the QTc interval.
Nervous system	No central nervous system adverse effects were noted in preclinical studies.
Other systems	No adverse effects were noted other than those related to the heart in preclinical studies.

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings	Relevance to human usage
Toxicity	
Mechanisms for drug interactions	Metabolism by CYP2C19 is the predominant mechanism of clearance of mavacamten; CYP3A4 and CYP2C9 are also involved in mavacamten metabolism. CYP2C19 accounts for 74% of mavacamten metabolism, CYP3A4 for 18%, and CYP2C9 for 7.6%. Mavacamten Effect on CYP3A4: In vitro data suggests that mavacamten may be an inducer of CYP3A4. Mavacamten Effect on Other CYP 450 Isoenzymes: Mavacamten does not appear to be an inhibitor of CYP 450 isoenzymes and is neither a substrate nor an inhibitor of major drug efflux or uptake transporters.

2.2.1 Conclusions on Nonclinical Data

Table 2.2.1-1: Nonclinical Safety Concerns

Important Identified Risks	Heart failure due to systolic dysfunction
Important Potential Risks	Teratogenicity, QTc prolongation
Missing Information	Use during lactation

2.3 Clinical Trial Exposure

The initial mavacamten clinical development program comprised of multiple completed Phase 1 studies, 3 phase 2 studies, 1 pivotal phase 3 study, and 2 ongoing open-label extension studies. An overview of the mavacamten clinical program is summarized in Table 2.3-1 of this RMP which supports the safe and effective use of mavacamten. During assessment of the MAA, the CSR of a second Phase 3 study MYK461017 (VALOR-HCM) in adults with symptomatic oHCM who were eligible for SRT was submitted but since the results are not integrated in the analyses, the study is not included in Table 2.3-1.

Table 2.3-1: Mavacamten Clinical Studies Supporting Exposure and Safety Analyses in the RMP

Study Number/ Indication	Study Title	Number of mavacamten Treated Subjects[a]
MYK-461-001/ PK in HCM (SAD)	Phase 1; Safety, Tolerability, Preliminary Pharmacokinetics and Pharmacodynamics of Single Ascending Oral Doses of MYK-461 in Patient Volunteers with Hypertrophic Cardiomyopathy and Healthy Volunteers: A First in Human Study	15
MYK-461-002/ PK in HV (SAD)	Phase 1; Safety, Tolerability, Preliminary Pharmacokinetics and Pharmacodynamics of Single Ascending Oral Doses of MYK-461 In Healthy Volunteers	36
MYK-461-003/ PK in HV (MAD)	Phase 1; Multiple Ascending Dose in Healthy Volunteers	50
MYK-461-009/ Verapamil DDI (CYP3A4 Induction)	Phase 1; An Open-label Drug Interaction Study to Assess the Effects of Verapamil on MYK-461 Pharmacokinetics in Healthy Subjects	25
MYK-461-010/ Oral Contraceptives DDI (CYP3A4)	Phase 1; An Open label Pharmacokinetic Drug Drug Interaction Study Between MYK-461 and Estrogen and Progestin based Hormonal Contraception in Healthy Women	13
MYK-461-011/ Japanese Ethnobridging	Phase 1; Open-label Study of the Pharmacokinetics of MYK-461 in Healthy Japanese and Caucasian Subjects	28
MYK-461-012/ CYP2C19 Metabolizer Status	Phase 1; An Open-label Study of the Pharmacokinetics of Single-Dose Mavacamten in Healthy Adults Who Are	16

Table 2.3-1: Mavacamten Clinical Studies Supporting Exposure and Safety Analyses in the RMP

Study Number/ Indication	Study Title	Number of mavacamten Treated Subjects[a]
	Normal or Poor CYP2C19 Metabolizers Based on Genotype	
MYK-461-013/ AME in HV	Phase 1; An Open-label, Single Dose, Mass-Balance Study to Assess the Absorption, Metabolism, and Excretion of [14C]-Mavacamten in Healthy Males	6
MYK-461-014/ Relative BA and Food Effect in HV	Phase 1; The Relative Bioavailability of the Intended Commercial Capsule Formulation vs. the Initial Capsule Formulation of Mavacamten and the Effect of Food on Its Pharmacokinetics	24
MYK-461-015/ Hepatic Impairment	Phase 1; A Phase 1, Open-Label, Non-Randomized, Single-Dose Study to Investigate the Pharmacokinetics, Safety, and Tolerability of Mavacamten in Participants with Varying Degrees of Hepatic Impairment Compared to Participants with Normal Hepatic Function	27
MYK-461-016/ Midazolam DDI (CYP3A4 Induction)	Phase 1; The Effect of Mavacamten on the Pharmacokinetics of the CYP3A4 Substrate, Midazolam, in Healthy Participants	13
MYK-461-018/ Omprazole DDI (CYP2C19 Inhibition)	Phase 1; An Open-label Drug Interaction Study to Assess the Effect of the Proton Pump Inhibitor Omeprazole, a CYP2C19 Inhibitor, on Mavacamten (MYK-461) Pharmacokinetics in Healthy Participants	28
MYK-461-004 (PIONEER-HCM)/ oHCM	Phase 2; Open-label Pilot Study to Evaluate Efficacy, Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of MYK-461 in Subjects With Symptomatic Hypertrophic Cardiomyopathy and Left Ventricular Outflow Tract Obstruction	21
MYK-461-006 (MAVERICK-HCM)/ nHCM	Phase 2; A Randomized, Double-blind, Placebo-controlled, Concentration-guided, Exploratory Study of Mavacameten in Patients With Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy (nHCM) and Preserved Left Ventricular Ejection Fraction	39
MYK-461-008 (PIONEER-OLE)/ oHCM[b]	Phase 2; An Open-Label Extension Study of Mavacamten (MYK-461) in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy Previously Enrolled in Study MYK-461-004 (PIONEER)	13
MYK-461-007 (MAVA-LTE)/ oHCM and nHCM[c]	Phase 2/3; A Long-term Safety Extension Study of Mavacamten (MYK 461) in Adults with Hypertrophic Cardiomyopathy Who Have Completed the MAVERICK-HCM (MYK-461-006) or EXPLORER-HCM (MYK 461 005) Trials	EXPLORER-LTE Cohort (oHCM): 231 MAVERICK-LTE Cohort (nHCM): 44
MYK-461-005 (EXPLORER-HCM)/ oHCM	Phase 3; A Randomized, Double blind, Placebo controlled Clinical Study to Evaluate Mavacamten (MYK-461) in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy	123

[a] Source: /myk461/hcm/rmp/rmp2022/version1/prog/t_exp_2.sas v9.4 12APR2022:17:27

[b] As MYK-461-008 is an open-label extension study with patients who were previously enrolled in MYK-461-004, there are no unique subjects in MYK-461-008.

[c] As MYK-461-007 is a long-term safety extension study with patients who completed either MYK-461-005 or MYK-461-006, there are no unique subjects in MYK-461-007.

Clinical exposure for oHCM populations and all indications are presented below in Table 2.3-2 through Table 2.3-8. Clinical exposure for nHCM and healthy volunteers is presented in Appendix 2.

Table 2.3-2: Duration of Exposure - All Cumulative Exposure

Duration of Exposure	Participants	Person Years
<= 1 month	283	5.6
>1 to 3 months	16	3.3
>3 to 6 months	11	3.6
>6 to 12 months	29	23.3
>12 to 18 months	58	70.9
>18 to 24 months	86	149.6
>24 to 30 months	74	165.2
> 30 months	38	111.7
Total	595	533.1

Studies included: MYK-461-001, MYK-461-002, MYK-461-003, MYK-461-004, MYK-461-005, MYK-461-006, MYK-461-007, MYK-461-008, MYK-461-009, MYK-461-010, MYK-461-011, MYK-461-012, MYK-461-013, MYK-461-014, MYK-461-015, MYK-461-016, MYK-461-018.

Duration of exposure for a subject in a single study is defined as last dose - first dose + 1, excluding the period of treatment interruptions due to COVID-19 pandemic which affected a subset of patients in 007 study.

For subjects that received mavacamten in more than one study, the total duration of exposure from all studies is presented.

Data extraction: Final study data were used for this analysis except for the following ongoing studies MYK-461-007 (28OCT2021), MYK-461-008 (12OCT2021), if included. Data cutoff: 31AUG2021.

Source: /myk461/hcm/rmp/rmp2022/version1/prog/t_exp_1.sas v9.4 12APR2022:17:27

Table 2.3-3: Duration of Exposure - oHCM

Duration of Exposure	Participants	Person Years
<= 1 month	2	0.1
>1 to 3 months	11	2.2
>3 to 6 months	3	1.2
>6 to 12 months	26	20.9
>12 to 18 months	57	69.5
>18 to 24 months	84	145.7
>24 to 30 months	50	110.1
> 30 months	27	80.9
Total	260	430.7

Studies included: MYK-461-004, MYK-461-005, MYK-461-007 and MYK-461-008.

Duration of exposure for a subject in a single study is defined as last dose - first dose + 1, excluding the period of treatment interruptions due to COVID-19 pandemic which affected a subset of patients in 007 study.

For subjects that received mavacamten in more than one study, the total duration of exposure from all studies is presented.

Data extraction: Final study data were used for this analysis except for the following ongoing studies MYK-461-007 (28OCT2021), MYK-461-008 (12OCT2021), if included. Data cutoff: 31AUG2021.

Source: /myk461/hcm/rmp/rmp2022/version1/prog/t_exp_1.sas v9.4 12APR2022:17:27

Table 2.3-4: Clinical Exposure by Age Group and Gender - All Cumulative Exposure

	Participants			Person Years		
Age Group	Male	Female	Total	Male	Female	Total
<18	0	0	0	0.0	0.0	0.0
18 to 44	152	75	227	37.7	36.3	74.0
45 to 64	148	98	246	177.7	105.5	283.1
65 to 74	50	50	100	69.6	73.8	143.4
75 to 84	7	15	22	10.2	22.4	32.7
85 and over	0	0	0	0.0	0.0	0.0
Total	357	238	595	295.2	238.0	533.1

Studies included: MYK-461-001, MYK-461-002, MYK-461-003, MYK-461-004, MYK-461-005, MYK-461-006, MYK-461-007, MYK-461-008, MYK-461-009, MYK-461-010, MYK-461-011, MYK-461-012, MYK-461-013, MYK-461-014, MYK-461-015, MYK-461-016, MYK-461-018.

Duration of exposure for a subject in a single study is defined as last dose - first dose + 1, excluding the period of treatment interruptions due to COVID-19 pandemic which affected a subset of patients in 007 study.

For subjects that received mavacamten in more than one study, the total duration of exposure from all studies is presented.

Data extraction: Final study data were used for this analysis except for the following ongoing studies MYK-461-007 (28OCT2021), MYK-461-008 (12OCT2021), if included. Data cutoff: 31AUG2021.

Source: /myk461/hcm/rmp/rmp2022/version1/prog/t_exp_3.sas v9.4 12APR2022:17:27

Table 2.3-5: Clinical Exposure by Age Group and Gender- oHCM

	Participants			Person Years		
Age Group	Male	Female	Total	Male	Female	Total
<18	0	0	0	0.0	0.0	0.0
18 to 44	18	11	29	26.4	17.3	43.7
45 to 64	94	41	135	157.2	73.6	230.8
65 to 74	38	38	76	65.9	60.0	125.9
75 to 84	6	14	20	8.2	22.1	30.3
85 and over	0	0	0	0.0	0.0	0.0
Total	156	104	260	257.7	173.0	430.7

Studies included: MYK-461-004, MYK-461-005, MYK-461-007 and MYK-461-008.

Duration of exposure for a subject in a single study is defined as last dose - first dose + 1, excluding the period of treatment interruptions due to COVID-19 pandemic which affected a subset of patients in 007 study.

For subjects that received mavacamten in more than one study, the total duration of exposure from all studies is presented.

Data extraction: Final study data were used for this analysis except for the following ongoing studies MYK-461-007 (28OCT2021), MYK-461-008 (12OCT2021), if included. Data cutoff: 31AUG2021.

Source: /myk461/hcm/rmp/rmp2022/version1/prog/t_exp_3.sas v9.4 12APR2022:17:27

Table 2.3-6: Clinical Exposure by Dose - oHCM

Dose of Exposure	Participants	Person Years
2 mg	10	0.1
2.5 mg	119	108.2
5 mg	254	147.4
10 mg	150	114.8
15 mg	64	52.9
20 mg	3	<0.1
Total	NA	423.5

Studies included: MYK-461-004, MYK-461-005, MYK-461-007 and MYK-461-008.

A subject may have received more than one dose level of mavacamten and be counted in more than one dose level.

The time during dose interruption is not included in this analysis.

Data extraction: Final study data were used for this analysis except for the following ongoing studies MYK-461-007 (28OCT2021), MYK-461-008 (12OCT2021), if included. Data cutoff: 31AUG2021.

Source: /myk461/hcm/rmp/rmp2022/version1/prog/t_exp_4.sas v9.4 12APR2022:17:27

Table 2.3-7: Clinical Exposure by Ethnic or Racial Origin - All Cumulative Exposure

Ethnic Origin	Participants	Person Years
White	464	484.7
Black or African American	42	18.2
American Indian or Alaska Native	1	1.6
Asian	66	7.0
Native Hawaiian or Other Pacific Islander	1	<0.1
Multiple	3	<0.1
Other	3	<0.1
Unknown/Missing	15	21.4
Total	595	533.1

Studies included: MYK-461-001, MYK-461-002, MYK-461-003, MYK-461-004, MYK-461-005, MYK-461-006, MYK-461-007, MYK-461-008, MYK-461-009, MYK-461-010, MYK-461-011, MYK-461-012, MYK-461-013, MYK-461-014, MYK-461-015, MYK-461-016, MYK-461-018.

Duration of exposure for a subject in a single study is defined as last dose - first dose + 1, excluding the period of treatment interruptions due to COVID-19 pandemic which affected a subset of patients in 007 study.

For subjects that received mavacamten in more than one study, the total duration of exposure from all studies is presented.

Data extraction: Final study data were used for this analysis except for the following ongoing studies MYK-461-007 (28OCT2021), MYK-461-008 (12OCT2021), if included. Data cutoff: 31AUG2021.

Source: /myk461/hcm/rmp/rmp2022/version1/prog/t_exp_5.sas v9.4 12APR2022:17:27

Table 2.3-8: Clinical Exposure by Ethnic or Racial Origin - oHCM

Ethnic Origin	Participants	Person Years
White	238	395.7
Black or African American	7	12.8
American Indian or Alaska Native	1	1.6
Asian	5	6.0
Unknown/Missing	9	14.5
Total	260	430.7

Studies included: MYK-461-004, MYK-461-005, MYK-461-007 and MYK-461-008.

Duration of exposure for a subject in a single study is defined as last dose - first dose + 1, excluding the period of treatment interruptions due to COVID-19 pandemic which affected a subset of patients in 007 study.

For subjects that received mavacamten in more than one study, the total duration of exposure from all studies is presented.

Data extraction: Final study data were used for this analysis except for the following ongoing studies MYK-461-007 (28OCT2021), MYK-461-008 (12OCT2021), if included. Data cutoff: 31AUG2021.

Source: /myk461/hcm/rmp/rmp2022/version1/prog/t_exp_5.sas v9.4 12APR2022:17:27

2.4 Populations Not Studied in Clinical Trials

2.4.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
LVEF (at rest) during screening < 55%	The observed on target- effect of mavacamten is a decrease in cardiac contractility, measured as a decrease in LVEF. Based on PK/PD modeling that was used for dose selection in MYK-461-005 (EXPLORER-HCM), a decrease in LVEF of 5-10% was anticipated; therefore, patients with an LVEF at the lower end of normal were excluded. Also, LVEF < 50% was used as a criterion for temporary discontinuation.	No	This is outside the proposed patient population for mavacamten as subjects must have LVEF ≥ 55% at treatment intiation.
NYHA Class IV	Patients with NYHA Class IV either have or are at risk of LV systolic dysfunction, may be considered candidates for SRT, and would be unable to adequately perform CPET. Patients with NYHA Class IV were excluded from the pivotal study, MYK-461-005.	Yes	Not Applicable
Female subjects who are pregnant or considering becoming pregnant	Mavacamten has shown teratogenic potential in preclinical reproductive toxicity studies at exposures lower than the MRHD in 2 species (rats and rabbits). The risk of mavacamten exposure in human pregnancy is unknown.	No	Mavacamten is suspected to cause fetotoxicity and is contraindicated during pregnancy. Embryo-foetal toxicity is included as an Important Potential Risk.
Female subjects who are lactating	There is no information on the excretion of mavacamten or its metabolites in animal milk.	Yes	Not applicable
Overlapping clinical disorders (known infiltrative or storage disorder causing cardiac hypertrophy that mimics oHCM,	Patients with HCM have a primary cardiac muscle abnormality characterized by enhanced myocardial contractility, largely, but not all due to sarcomere gene mutations. Infiltrative and storage diseases of the heart are diseases due to other	No	This is outside the proposed patient population for mavacamten.

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
such as Fabry disease, amyloidosis, or Noonan syndrome with LV hypertrophy)	etiologies, including metabolic storage disorders, characterized by either extracellular infiltration of the myocyte or intramyocardial deposits, and have other specific treatments. Mavacamten has not been studied in patients with phenocopy diseases that mimic oHCM (such as Fabry disease, amyloidosis, and Noonan syndrome with LV hypertrophy), nor is the mechanism of action targeted at these diseases. Patients with infiltrative or storage diseases of the heart may present with clinical syndromes that phenotypically mimic oHCM and may demonstrate LV hypertrophy on echocardiogram. However, these patients are not expected to benefit from treatment with mavacamten as the underlying pathophysiology of these diseases differs from HCM and, in some cases, other therapies exist (eg, Fabry and amyloidosis).		
History of syncope, history of sustained ventricular tachyarrhythmia with exercise, history of resuscitated cardiac arrest or appropriate ICD discharge for life threatening ventricular arrhythmias within 6 months of treatment initiation	Maximal stress testing as a study requirement may increase the risk of arrhythmias in patients who are already at high risk for the development of syncope and/or serious, life-threatening cardiac arrhythmia. Symptom-limited cardiac exercise stress testing was a primary endpoint in MYK-461-005. These patients were excluded from the MYK-461-005 to minimise risk during exercise, as there is higher chance for the patients with medical history of syncope or ventricular tachycardia to experience these events with exercise.	No	There is no reason to expect the safety of mavacamten to be different in these patients as there is no evidence that mavacamten is pro-arrhythmic.
Current treatment (within 14 days prior to	Disopyramide is a negative inotrope. Disopyramide is not a proven therapy for oHCM. It was	Yes	Not applicable

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Screening) or planned treatment during the study with disopyramide	decided to exclude disopyramide from the pivotal study pending further understanding of the safety profile of mavacamten in the indicated treatment population. Treatment with disopyramide is in ongoing clinical study MYK-461-017.		
Current or planned treatment with a combination of β-blockers and verapamil or a combination of β-blockers and either diltiazem or verapamil	Combination therapy with a β-blocker and either diltiazem or verapamil may be associated with greater effects on heart rate, blood pressure, and inotropy than either drug alone. Mavacamten is also a negative inotrope. Therapy with a β-blocker or either diltiazem or verapamil as monotherapy was allowed in Study MYK-461-005 if the subject was on a stable dose of one of these agents and no dose adjustment was anticipated during the course of the study. However, combination therapy was not allowed in Study MYK-461-005 pending a better understanding of the safety profile of mavacamten in oHCM. Treatment with β-blockers in combination with non-dihydropyridine calcium-channel blockers (verapamil and diltiazem) is in ongoing clinical study MYK-461-017.	Yes	Not applicable
Baseline QT interval with Fridericia correction (QTcF) >500 ms assessed by ECG	Subjects with baseline QT interval with QTcF > 500 ms assessed by ECG were not allowed in Study MYK-461-005 or other HCM clinical trials pending a better understanding of the safety profile of mavacamten	No	There has been no evidence in the clinical studies of prolongation of the QTcF.
Documented obstructive coronary artery disease (> 70% stenosis in one or more epicardial coronary arteries) or history of	Subjects with obstructive coronary artery disease or history of myocardial infarction could have difficulty performing CPET, and could pose the risk of cardiac adverse events occurring. Subjects were allowed to participate in Study	No	Though there is no evidence for increased incidence of ischemic events during mavacamten treatment, data from patients who experience detrimental CV effects will be collected via multiple additional

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
myocardial infarction	MYK-461-005 if they had stent placement prior to the study.		pharmacovigilance activities.
Severe renal impairment; the body size–adjusted eGFR is < 30 mL/min/1.73 m2	Following a single 25 mg dose of 14C labeled mavacamten, 85% of the total radioactivity was recovered in urine. Only 2% was in the form of parent drug. Therefore, subjects with mild and moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m2) were included in Study MYK-461-005. Patients with severe renal impairment have not been studied during the mavacamten clinical program.	No	This patient population is addressed in the SmPC. The anticipated safety profile does not differ in this population. Mavacamten is not significally renally excreted.
Hepatic impairment; alanine aminotransferase or aspartate aminotransferase > 3 × the upper limit of the laboratory reference range	At the time Study MYK-461-005 was designed, mavacamten had not yet been studied in patients with hepatic impairment. Patients with severe hepatic impairment (Child-Pugh class C) were excluded from the study to ensure their safety.	No	This patient population is addressed in the SmPC. The anticipated safety profile does not differ in this population. Any exposure increase due to hepatic impairment will be managed by dosing titration and echocardiographic monitoring.
Concomitant use with potent or mild CYP2C19 inhibitors (eg, omeprazole or esomeprazole), or strong CYP3A4 inhibitors (eg, fluconazole)	Based on study results, patients on these medications (potent or mild CYP2C19 inhibitors; and potentially strong CYP3A4 inhibitors especially in CYP2C19 poor metabolizers) may experience DDIs; therefore, they were excluded during clinical trials.	No	SmPC will provide a warning on the concomitant use of mavacamten with CYP2C19 inhibitors and CYP3A4 inhibitors and is considered to be an important potential risk (adverse events due to overexposure to mavacamten resulting from interaction with CYP2C19 inhibitors in ultrarapid and intermediate CYP2C19 metabolizers and moderate or strong CYP3A4 inhibitors in poor and normal CYP2C19 metabolizers). Starting, stopping, or adjusting doses of these medicines while on mavacamten may require

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
			dose adjustment of mavacamten due to increased exposures.
Current treatment (within 14 days prior to Screening) St. John's wort	St. John's wort is a commonly used herbal CYP3A4/2C19 inducer. Patients taking St. John's wort may experience lower mavacamten concentrations/efficacy; therefore, this concomitant compound was excluded during clinical trials. Lower mavacamten exposure could potentially impact efficacy, and there is a potential of rebound and toxicity if St John's wort is stopped.	No	SmPC provides information on the metabolism of mavacamten primarily through CYP2C19 and CYP3A4 enzymes. Prescribers will assess for drug-drug interactions with medicines affecting CYP2C19 and CYP3A4 activity.
Persistent or permanent AF not on anticoagulation and/or not adequately rate controlled	Patients with AF not being treated with anticoagulation therapy may experience thromboembolic complications, independent of mavacamten administration. According to good clinical practice, these subjects should be treated with anticoagulation therapy for stroke prevention.	No	Cardiologists who will prescribe mavacamten are well versed in the standard of care management of patients with permanent or persistent AF and there is no reason to expect an increase in thromboembolic events based on the pharmacology of mavacamten. Patients with persistent or permanent AF who are anticoagulated and adequately rate-controlled were allowed in Study MYK-461-005.
Paroxysmal/intermittent AF with AF present by ECG at the time of Screening	Patients with documented paroxysmal/intermittent AF could have difficulty performing CPET and could pose the risk of cardiac adverse events occurring. AF can also interfere with accurate reading of CPET, echocardiogram, and cardiovascular magnetic resonance.	No	There is no anticipated difference in the safety profile of mavacamten in patients with paroxysmal/intermittent atrial fibrillation.

2.4.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The initial clinical development programme is unlikely to detect certain types of adverse reactions such as those that are rare or caused by long latency, cumulative effects and limited prolonged mavacamten exposure (> 18 months). Continuing clinical development and safety monitoring will support the identification of new adverse reactions related to mavacamten. Consequently, long-term safety including detrimental CV effects is considered missing information.

2.4.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	No clinical studies conducted
Breastfeeding women	No clinical studies conducted
Patients with relevant comorbidities:	
Patients with hepatic impairment	Patients with ALT or AST ≥ 3 x ULN were excluded from the pivotal clinical study. Exposure in subjects with hepatic impairment:[a] • Mild: 8 subjects (< 0.1 person years) • Moderate: 8 subjects (< 0.1 person years) • Severe: 0 subjects (0.0 person years)
Patients with renal impairment	Patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2) were excluded from clinical studies. Exposure in subjects with renal impairment:[b] • CKD Stage I: 435 subjects (351.8 person years) • CKD Stage II: 134 subjects (149.3 person years) • CKD Stage IIIa: 18 subjects (20.1 person years) • CKD Stage IIIb: 4 subjects (7.1 person years) • CKD Stage IV and above: 0 subjects (0.0 person years) • Missing: 4 subjects (4.9 person years)
Patients with cardiovascular impairment	Not Applicable
Immunocompromised patients	No clinical studies conducted
Patients with a disease severity different from inclusion criteria in clinical trials.	No clinical studies conducted
Population with relevant different ethnic origin	Patients of all ethnicities and races were included in the clinical development program.
Subpopulations carrying relevant genetic polymorphisms	
CYP2C19 poor metabolizers	Exposure in subjects with CYP2C19 phenotype:[c]

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
	• Rapid/Ultra: 146 subjects (129.3 person years) • Normal: 255 subjects (211.0 person years) • Intermediate: 117 subjects (127.1 person years) • Poor: 17 subjects (8.2 person years) • Not Poor: 4 subjects (7.3 person years) • Missing: 56 subjects (50.2 person years)
Other	
• Elderly Patients	Exposure in elderly subjects (All Indications):[d] • 65 to 74 years: 100 subjects (143.4 person years) • 75 to 84 years: 22 subjects (32.7 person years) • 85 years and over: 0 subjects (0.0 person years) Exposure in elderly subjects (oHCM):[e] • 65 to 74 years: 76 subjects (125.9 person years) • 75 to 84 years: 20 subjects (30.3 person years) • 85 years and over: 0 subjects (0.0 person years)
• Pediatric patients < 18 years	No clinical studies conducted

[a] Only data from hepatic impairment Study MYK-461-015 is presented.
Source: /myk461/hcm/adhoc/rmp_request_eu/version1/prog/t_exp_6_1.sas v9.4 04FEB2021:16:27

[b] Studies included: MYK-461-001, MYK-461-002, MYK-461-003, MYK-461-004, MYK-461-005, MYK-461-006, MYK-461-007, MYK-461-008, MYK-461-009, MYK-461-010, MYK-461-011, MYK-461-012, MYK-461-013, MYK-461-014, MYK-461-015, MYK-461-016, MYK-461-018.
CKD Stage determined based on baseline eGFR derived using the Cockcroft-Gault formula.
Source: /myk461/hcm/rmp/rmp2022/version1/prog/t_exp_6_2.sas v9.4 12APR2022:17:28

[c] Studies included: MYK-461-001, MYK-461-002, MYK-461-003, MYK-461-004, MYK-461-005, MYK-461-006, MYK-461-007, MYK-461-008, MYK-461-009, MYK-461-010, MYK-461-011, MYK-461-012, MYK-461-013, MYK-461-014, MYK-461-015, MYK-461-016, MYK-461-018.
CYP2C19 metabolizer status is presented.
Source: /myk461/hcm/rmp/rmp2022/version1/prog/t_exp_6_4.sas v9.4 12APR2022:17:28

[d] Studies included: MYK-461-001, MYK-461-002, MYK-461-003, MYK-461-004, MYK-461-005, MYK-461-006, MYK-461-007, MYK-461-008, MYK-461-009, MYK-461-010, MYK-461-011, MYK-461-012, MYK-461-013, MYK-461-014, MYK-461-015, MYK-461-016, MYK-461-018.
Source: /myk461/hcm/rmp/rmp2022/version1/prog/t_exp_3.sas v9.4 12APR2022:17:27

[e] Studies included: MYK-461-004, MYK-461-005, MYK-461-007 and MYK-461-008.
Source: /myk461/hcm/rmp/rmp2022/version1/prog/t_exp_3.sas v9.4 12APR2022:17:27
Duration of exposure for a subject in a single study is defined as last dose - first dose + 1, excluding the period of treatment interruptions due to COVID-19 pandemic which affected a subset of patients in 007 study.

2.5 Post-Authorisation Experience

Mavacamten was first approved on 28-Apr-2022 in the US for the treatment of adults with symptomatic NYHA class II-III oHCM to improve functional capacity and symptoms. The EU granted marketing authorisation on 26-Jun-2023 and as of 27-Oct-2024, mavacamten has received marketing authorisation approval in 51 countries.

2.5.1 Post-Authorisation Exposure

2.5.1.1 Method Used to Calculate Exposure

In the US, mavacamten is marketed under a special restricted distribution program called Risk Evaluation and Mitigation Strategy (REMS) and is dispensed through contract pharmacies. The mavacamten REMS program provides the exact number of patients exposed in the US. For countries outside of the US, there is no readily available information on the number of patients treated with marketed mavacamten. However, an estimate of the number of treated patients can be derived from available sales figures. Vendors provide sales figures to the Company for mavacamten on a quarterly basis that are generally available 3 months after the close of a calendar quarter. Although these data represent the bulk of the Company's worldwide sales of mavacamten, they are only an estimation of the total quantity of product sold based on the total amount of product distributed in all countries worldwide. The sales data only capture an estimated 80% to 85% of the true total worldwide sales data.

2.5.1.2 Exposure

The cumulative post-marketing patient exposure to mavacamten is available to 27-Oct-2024. The combined cumulative exposure globally includes estimates from sales data outside of the US and patient exposure in the US REMS program was estimated to be 12,043 patients or 13,018 patient-years exposure.

2.6 Additional EU Requirements for the Safety Specification

2.6.1 Potential for Misuse for Illegal Purposes

No evidence exists from the available data that mavacamten treatment results in dependence, could be misused for illegal purposes, enhancing performance, or facilitating assault. No specific nonclinical or clinical studies have been performed on the effects of the potential for mavacamten for misuse for illegal purposes, enhancing performance, causing dependence, or facilitating assault.

2.7 Identified and Potential Risks

2.7.1 Identification of Safety Concerns in the Initial RMP Submission

Safety concerns identified in the initial submission of the RMP are summarized in Table 2.7.1-1.

Table 2.7.1-1: Safety Concerns in the Initial RMP

Important identified risks	None
Important potential risks	Heart failure due to systolic dysfunction Adverse events due to overexposure to mavacamten resulting from interaction with CYP2C19 inhibitors in ultrarapid and intermediate CYP2C19 metabolizers and moderate or strong CYP3A4 inhibitors in poor and normal CYP2C19 metabolizers Embryo-foetal toxicity
Missing information	Patients with Class IV NYHA Patients being treated with disopyramide Patients being treated with a combination of β-blockers and non-dihydropyridine calcium-channel blockers (verapamil/diltiazem) Long-term safety, including detrimental CV effects Use during lactation Safety in CYP2C19 poor metabolizers

2.7.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason(s) for not including a risk as identified or potential in the list of safety concerns in the RMP is/are provided in Table 2.7.1.1-1:

Table 2.7.1.1-1: Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)	None
Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated	None
Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorised)	Dizziness, syncope, dyspnoea
Known risks that do not impact the risk-benefit profile	None
Other reasons for considering the risks not important	None

2.7.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
Important identified risks	None
Important potential risks	
Heart failure due to systolic dysfunction	Heart failure due to systolic dysfunction represents an exaggerated ontarget effect (excessive decrease in myocardial contractility) of mavacamten that has been seen alone or in combination with intercurrent illnesses (eg, uncontrolled atrial fibrillation, serious infection, stress cardiomyopathy). Heart failure due to systolic dysfunction has been reversible in the clinical program upon temporary or permanent dose discontinuation. The available clinical data in Study MYK-461-005 are insufficient to conclude a causal association for heart failure although a contributory role of mavacamten cannot be ruled out. Excessive and/or sustained reduction in ejection fraction can be life-threatening.
Adverse events due to overxposure to mavacamten resulting from interaction with CYP2C19 inhibitors in ultrarapid and intermediate CYP2C19 metabolizers and moderate or strong CYP3A4 inhibitors in poor and normal CYP2C19 metabolizers	Mavacamten exposures (AUC) increase by about 2-fold when it is taken with moderate CYP2C19 inhibitors and 3.4-fold with strong CYP2C19 inhibition as demonstrated in poor CYP2C19 healthy volunteer metabolizers. Higher mavacamten concentrations may contribute to new events of heart failure due to systolic dysfunction or make it more difficult to control. Other adverse events may also manifest.
Embryo-foetal toxicity	Mavacamten may cause foetal harm in humans based on animal studies. No clinical data exists on the safety of mavacamten during pregnancy in humans.
Missing Information	
Patients with Class IV NYHA	Subjects with NYHA Class IV were not included in Study MYK-461-005 due to limited experience available with mavacamten at the time the study was conducted. There are limited data in NYHA Class IV patients in Study MYK-461-017 (only 1 patient enrolled).
Patients being treated with disopyramide	Patients on disopyramide were excluded from the pivotal study (MYK-461-005) pending further understanding of the safety profile of mavacamten in the indicated treatment population. There are limited data available from Study MYK-461-017. In Study MYK-461-017, the efficacy and safety results of patients receiving mavacamten and disopyramide were similar to those not receiving disopyramide. There is limited information available on the potential for a PD interaction between mavacamten and other substances that also reduce cardiac contractility.
Patients being treated with a combination of β-blockers and non-dihydropyridine	Therapy with a β-blocker or either diltiazem or verapamil as monotherapy was allowed in Study MYK-461-005 if the subject was on a stable dose of one of these agents, and no dose adjustment was anticipated during the course of the study. However, combination therapy was not allowed in Study MYK-461-005 pending a better understanding of the safety profile of mavacamten in oHCM. There are limited

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
calcium-channel blockers (verapamil/diltiazem)	data on combination therapies in Study MYK-461-017. In Study MYK-461-017, the efficacy and safety results of patients receiving mavacamten in combination with β-blockers and nondihydropyridine calcium-channel blockers were similar to those receiving mavacamten monotherapy.
Long-term safety, including detrimental CV effects	Mavacamten is intended as a chronic therapy for patients with oHCM. In the oHCM clinical development program, 260 oHCM patients were exposed to mavacamten for periods up to 30 months. 57 patients have been exposed to mavacamten for ≥ 12 to 18 months, 84 patients have been exposed for ≥ 18 to 24 months, 50 patients have been exposed for ≥ 24 to 30 months, and 27 patients have been exposed for > 30 months. The development program showed mavacamten to have a positive benefit-risk profile, and the available data show no evidence to suggest that mavacamten causes CV detriment. Long-term safety including detrimental CV effects is considered missing information because long-term data are limited and the current incidence of events is low.
Use during lactation	It is unknown whether mavacamten or its metabolites are excreted in human milk. There is no information on the excretion of mavacamten or its metabolites in animal milk.
Safety in CYP2C19 poor metabolizers	Mavacamten is extensively metabolized, predominantly by CYP2C19 (74%). Mavacamten terminal half-life is increased from 6-9 days in normal metabolizers to 23 days in poor CYP2C19 metabolizers. There are limited data on the safety of mavacamten in CYP2C19 poor metabolizers in clinical studies.

2.7.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

2.7.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

The important identified and potential risks as well as missing information are listed below.

Important Identified Risks

- None

Important Potential Risks

- Heart failure due to systolic dysfunction
- Adverse events due to overexposure to mavacamten resulting from interaction with CYP2C19 inhibitors in ultrarapid and intermediate CYP2C19 metabolizers and moderate or strong CYP3A4 inhibitors in poor and normal CYP2C19 metabolizers
- Embryo-foetal toxicity

Missing Information

- Patients with Class IV NYHA
- Patients being treated with disopyramide
- Patients being treated with a combination of β-blockers and non-dihydropyridine calcium-channel blockers (verapamil/diltiazem)
- Long-term safety, including detrimental CV effects
- Use during lactation
- Safety in CYP2C19 poor metabolizers

2.7.3.1 Presentation of Important Potential Risks

Table 2.7.3.1-1: Important Potential Risk: Heart failure due to systolic dysfunction

Heart failure due to systolic dysfunction	
Potential mechanisms	Mavacamten is a cardiac myosin inhibitor that reduces myocardial contractility. This mechanism leads to a reduction in LVEF which is expected and generally well tolerated. Systolic dysfunction due to an excessive reduction in LVEF (ie, < 50%) may be asymptomatic or result in heart failure.
Evidence source and strength of evidence	Systolic dysfunction (reversible) has been reported in mavacamten clinical trials. Heart failure due to systolic dysfunction represents a clinical outcome of an exaggerated on-target effect (excessive decrease in myocardial contractility) of mavacamten that has been seen alone or in combination with intercurrent illnesses (eg, uncontrolled atrial fibrillation, serious infection, stress cardiomyopathy) in clinical trials. Systolic dysfunction has been reversible in the clinical program upon dose discontinuation and down-titration. Excessive or prolonged reduction in ejection fraction can be life-threatening. The clinical data are insufficient to conclude a causal association between mavacamten use and heart failure due to systolic dysfunction.
Characterization of risk	In the pivotal RCT EXPLORER, MYK-461-005, the incidence of cardiac failure in the mavacamten treatment arm (2.4%) is overall lower than the incidence of cardiac failure in the placebo treatment arm (3.9%). Therefore, due to a lack of imbalance between these 2 treatment groups (see Table 1), heart failure is not considered as an identified risk. Decreases in LVEF <50% did not consistently correlate with mavacamten concentrations exceeding therapeutic levels. Also, patients with reduced LVEF <50% ranged in symptomatology from being asymptomatic to experiencing heart failure.

Table 1: Incidence of cardiac failiure in Study MYK-461-005

Preferred Term	**Mavacamten (N = 123) n (%)**	**Placebo (N = 128) n (%)**
Cardiac failure	3 (2.4)	3 (2.3)
Cardiac failure acute	0	2 (1.6)
Cardiac failure congestive	0	1 (0.8)
Cardiogenic shock	1 (0.8)	0

Table 2.7.3.1-1: Important Potential Risk: Heart failure due to systolic dysfunction

Heart failure due to systolic dysfunction			
	Overall: Cardiac failure	**3 (2.4)**	**5 (3.9)**

Source: Table 14.3.1.3 Treatment-Emergent Adverse Events by ECI Safety Analysis Population Database cutoff: 01-Jul-2020

Risk factors and risk groups	History of significant ischemic events, history of arrhythmias, and history of systolic dysfunction are identified as prior risk factors for developing systolic dysfunction leading to heart failure. Intercurrent events of stress cardiomyopathy, atrial fibrillation, infection, arrhythmias with rapid ventricular rate, ischemia, and higher mavacamten concentrations may contribute to new events of systolic dysfunction, which may lead to heart failure or make it more difficult to control. Drug-drug interactions with CYP2C19 inhibitors or moderate or strong CYP3A4 inhibitors.
Preventability	Prior to initiating (or during) mavacamten therapy, reducing the risk of arrhythmias in patients who are already at high risk for the development of serious, life-threatening cardiac arrhythmia, adequate rate control of atrial fibrillation, prevention and treatment of underlying infections, and careful, step-wise, dose up titration during the dose adjustment period, are approaches that can be taken to reduce the incidence and/or severity of potential systolic dysfunction. Dose adjustment should be based on HCM symptoms and Valsalva LVOT gradient, and LVEF should be maintained above 50%. LVEF should be assessed 4 weeks after any new dose level. LVEF should be monitored at treatment initiation and 4 weeks following any dose adjustment. Once an individualised maintenance dose is achieved with LVEF ≥ 55%, patients should be assessed every 6 months. If at any visit the patient's LVEF is < 50%, the treatment should be interrupted for 4 weeks and until LVEF returns to ≥ 50%. Consider assessing LVEF for patients with a serious intercurrent illness such as infection or arrythmia (eg, atrial fibrillation or uncontrolled tachyarrhythmia), as well as for signs of HF (eg, increased shortness of breath, leg swelling, etc.).
Impact on the risk-benefit balance of the product	Events that occurred in association with mavacamten plasma concentrations in the highest quartile included SAEs of cardiac failure and systolic dysfunction, and although a modest reduction in LVEF is expected with mavacamten based on the mechanism of action, a contributory role for excessive pharmacodynamic effects of mavacamten at high concentrations is biologically plausible. Decreases in LVEF have not all resulted in heart failure. Systolic dysfunction has been reversible in the clinical program upon temporary discontinuation of mavacamten followed by return to treatment at the same or lower dose. Although heart failure from systolic dysfunction is reversible with treatment interruption, it can be life threatening and can impact the benefit-risk balance of mavacamten.
Public health impact	The public health impact is considered low given the preventability of heart failure due to systolic dysfunction
MedDRA terms	SMQ (narrow) cardiac failure

Table 2.7.3.1-2: Important Potential Risk: Adverse events due to overexposure to mavacamten resulting from interaction with CYP2C19 inhibitors in ultrarapid and intermediate CYP2C19 metabolizers and moderate or strong CYP3A4 inhibitors in poor and normal CYP2C19 metabolizers

Adverse events due to overexposure to mavacamten resulting from interaction with CYP2C19 inhibitors in ultrarapid and intermediate CYP2C19 metabolizers and moderate or strong CYP3A4 inhibitors in poor and normal CYP2C19 metabolizers	
Potential mechanisms	Mavacamten is extensively metabolized primarily through CYP2C19 (74%); CYP3A4 (18%), and CYP2C9 (7.6%). Mavacamten exposures (AUC) increase by about 2-fold when it is taken with moderate CYP2C19 inhibitors. Patients may also be subject to influence by CYP3A4 and CYP2C19 inhibitors, with the extent dependent on the enzyme inhibited and CYP2C19 metabolizer status resulting in elevated plasma concentrations of mavacamten. Poor metabolizers are more strongly influenced by modulators of CYP3A4, while rapid metabolizers and ultrarapid metabolizers are more strongly influenced by modulators of CYP2C19. Higher mavacamten concentrations may contribute to new events of systolic dysfunction which may lead to heart failure.
Evidence source and strength of evidence	PK parameters from in vitro studies, population PK modeling and drug interaction studies in healthy volunteers, demonstrated metabolism largely by CYP2C19 and CYP3A4 and increased mavacamten concentrations in the presence of CYP2C19 and moderate or strong CYP3A4 inhibitors. In the pivotal EXPLORER study, 7 (6%) subjects in the mavacamten group and 2 (2%) subjects in the placebo group experienced reversible reductions in LVEF to < 50% (median 48%: range 35-49%) while on treatment. Among 7 subjects in the mavacamten group with on-treatment LVEF reduction to < 50%, concentration levels were not highly correlated with the changes (eg, 4 of 7 events of LVEF < 50% occurred with mavacamten plasma concentrations < 700 ng/mL, and 3 of 7 occurred with mavacamten concentrations > 700 ng/mL). Therefore, elevation in plasma concentration did not consistently precede changes in LVEF. In all 7 patients treated with mavacamten, LVEF recovered following interruption of mavacamten and none of them were associated with an event of heart failure.
Characterization of risk	• Co-administration of mavacamten with the weak CYP2C19 inhibitor omeprazole (over the-counter 20 mg strength), resulted in a 48% increase in mavacamten AUC(0-∞) with no effect on Cmax.[44] • Co-administration of mavacamten with the moderate CYP3A4 inhibitor verapamil resulted in a 16% and 52% increase in mavacamten AUC(0-∞) and Cmax, respectively. These changes were not considered clinically significant.[45] • Co-administration of mavacamten with the strong CYP3A4 inhibitor itraconazole is predicted by PBPK simulation to result in up to 59% and 40% increases in AUC0-24 and Cmax, respectively. • In CYP2C19 poor metabolizers, a 3.4 fold higher exposure is observed compared with normal metabolizers. With co-administration of strong CYP2C19 inhibitors, if 100% of the enzyme is inhibited, it is expected to result in up to 3.4 fold exposure relative to administration of mavacamten alone.
Risk factors and risk groups	Patients who may be receiving CYP2C19 or moderate or strong CYP3A4 inhibitors (prescription drugs, OTC medications, herbal products). CYP2C19 poor metabolizers may have increased mavacamten expsoures (up to 3 times) that can lead to an increased risk of systolic dysfunction compared to normal metabolizers.

Table 2.7.3.1-2: Important Potential Risk: Adverse events due to overexposure to mavacamten resulting from interaction with CYP2C19 inhibitors in ultrarapid and intermediate CYP2C19 metabolizers and moderate or strong CYP3A4 inhibitors in poor and normal CYP2C19 metabolizers

Adverse events due to overexposure to mavacamten resulting from interaction with CYP2C19 inhibitors in ultrarapid and intermediate CYP2C19 metabolizers and moderate or strong CYP3A4 inhibitors in poor and normal CYP2C19 metabolizers	
Preventability	Review concomitant medications (including OTC medications) prior to initiation and during ongoing mavacamten therapy and consider the potential for drug interactions. Concomitant treatment with strong CYP3A4 inhibitors in patients with CYP2C19 poor metaboliser phenotype and undetermined CYP2C19 phenotype, and concomitant treatment with the combination of a strong CYP2C19 inhibitor and a strong CYP3A4 inhibitor, is contraindicated.
Impact on the risk-benefit balance of the product	Drug-drug interactions with CYP2C19 and moderate or strong CYP3A4 inhibitors may increase the risk of adverse events. This is a preventable risk and is considered to have an impact on the benefit-risk balance.
Public health impact	The public health impact is considered low given the preventability of drug-drug interactions with CYP2C19 and CYP3A4 inhibitors.
MedDRA terms	Adverse events in subjects receiving CYP2C19 inhibitors or moderate or strong CYP3A4 inhibitors

Table 2.7.3.1-3: Important Potential Risk: Embryo-foetal Toxicity

Embryo-foetal Toxicity	
Potential mechanisms	The mechanism is unknown. There has been no observed exposure to mavacamten during human pregnancies. It is assumed that susceptibility to teratogenicity in humans may mirror that seen in animals.
Evidence source and strength of evidence	Nonclinical developmental toxicity study findings were suggestive of a teratogenic potential of mavacamten at therapeutic exposures.
Characterization of risk	Mavacamten may cause foetal harm in humans based on animal studies. Teratogenicity (cardiac/skeletal malformations) was observed in rat and rabbit studies at maternal exposures less than the maximum recommended human dose. Decreased foetal body weight and increase in post implantation loss were also observed. The risk of embryo-foetal toxicity due to paternal exposure in semen was assessed based on preclinical data, actual semen concentrations in healthy men volunteers, and the potential for these concentration levels to cause maternal systemic exposures that could be teratogenic. Based on measurements of mavacamten in semen of 4 male subjects who received 18.5 mg mavacamten for 28 days, it was concluded that the risk of teratogenic effects caused by mavacamten transferred by semen or other body fluids is negligible. No clinical data exists on the safety of mavacamten during human pregnancy.
Risk factors and risk groups	Females of childbearing potential who are not using highly effective contraception.
Preventability	Mavacamten is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. Oral contraceptives are safe to use while on mavacamten (Study MYK-461-010) as their metabolism is not significantly affected by mavacamten. Before initiation of treatment, women of childbearing potential must be informed of this risk to the foetus, must have a negative pregnancy test and must use effective contraception during treatment and for 6 months after treatment discontinuation. If a patient is suspected to be pregnant, mavacamten must be interrupted until pregnancy is excluded.
Impact on the risk-benefit balance of the product	This important potential risk may have impact on the benefit-risk balance of mavacamten. Communication on this risk and management to prevent pregnancy is available in the label and through additional risk minimisation measures.
Public health impact	Clear education and instructions are provided to prevent teratogenicity via the product label and additional risk minimisation measures. Mavacamten is contraindicated during pregnancy and in women of childbearing potential not using effective contraception. Major foetal abnormalities, if detected, will have a significant impact on quality of life or could be fatal in utero.
MedDRA terms	SMQ: Congenital, familial, and genetic disorder; Foetal disorders, Neonatal disorders, Pregnancy, labour and delivery complications and risk factors (excl abortions and stillbirth); Termination of pregnancy and risk of abortion

2.7.3.2 Presentation of the Missing Information

Table 2.7.3.2-1: Missing Information

Missing Information	**Evidence Source**
Population in need of further characterisation:	

Table 2.7.3.2-1: Missing Information

Patients with Class IV NYHA	Subjects with NYHA Class IV were not included in Study MYK-461-005. Patients with NYHA Class IV either have LVEF < 55% (exclusion criteria) or are at an increased risk of LV systolic dysfunction, may be considered candidates for SRT, and would have been unable to adequately perform CPET. There are little data in NYHA Class IV patients in Study MYK-461-017/CV027006 (only 1 patient enrolled).
Patients being treated with disopyramide	Disopyramide is a negative inotrope. Disopyramide is not a proven therapy for oHCM. It was decided to exclude disopyramide from the pivotal study pending further understanding of the safety profile of mavacamten in the indicated treatment population. There are limited data available from Study MYK-461-017. In Study MYK-461-017, the efficacy and safety results of patients receiving mavacamten and disopyramide were similar to those not receiving disopyramide.
Patients being treated with a combination of β-blockers and non-dihydropyridine calcium-channel blockers (verapamil/diltiazem)	Combination therapy with a β-blocker and either diltiazem or verapamil may be associated with greater effects on heart rate, blood pressure, and inotropy than either type alone. Mavacamten is also a negative inotrope. Therapy with a β-blocker or either diltiazem or verapamil as monotherapy was allowed in Study MYK-461-005 if the subject was on a stable dose of one of these agents and no dose adjustment was anticipated during the course of the study. However, combination therapy, in addition to mavacamten, was not allowed in Study MYK-461-005 pending a better understanding of the safety profile of mavacamten in oHCM. There are limited data on combination therapies in Study MYK-461-017. In Study MYK-461-017, the efficacy and safety results of patients receiving mavacamten in combination with β-blockers and nondihydropyridine calcium-channel blockers were similar to those receiving mavacamten monotherapy.
Long-term safety, including detrimental CV effects	In clinical studies, mavacamten has been administered to 260 oHCM patients for periods up to 30 months. In the oHCM clinical development program, 57 patients have been exposed to mavacamten for ≥ 12 to 18 months, 84 patients have been exposed for ≥ 18 to 24 months, 50 patients have been exposed for ≥ 24 to 30 months, and 27 patients have been exposed for > 30 months; therefore, the adverse effects following longer term treatment with mavacamten are still accruing to provide long-term efficacy and safety data, and to provide additional data on CV risk, and MACE in particular. In Study MYK-461-017, a total of 108 subjects entered the LTFU period which included 56 subjects initially randomized to mavacamten group and 52 subjects randomized to placebo group. During the LTFU period (LTFU started at Day 1 for patients randomized to mava and Week 16 for patients randomized to PBO), the mean (SD) duration of exposure to study therapy was 121.26 (28.771) weeks in the previous mavacamten group and 96.34 (34.492) weeks in the previous placebo group. To date, no known mavacamten adverse drug reactions that have a long latency, or are due to prolonged exposure, or are due to cumulative effects have been identified. While the development program showed mavacamten to have a positive benefit-risk profile, there is no evidence to suggest that mavacamten causes CV detriment. Long-term safety including detrimental CV effects is considered missing information because long-term data are limited.
Use during lactation	Lactating women are excluded from the mavacamten clinical studies. There have been no reports of lactation exposure in female subjects treated with mavacamten thus far in the clinical program. It is unknown whether mavacamten or its metabolites are excreted in human milk. Because of the unknown adverse effects of mavacamten in breastfed newborns/infants, women must not breast-feed during treatment with mavacamten.

Table 2.7.3.2-1: Missing Information

Safety in CYP2C19 poor metabolizers	Mavacamten is extensively metabolized, predominately by CYP2C19 (74%). Mavacamten terminal half-life is increased from 6-9 days in normal metabolizers to 23 days in poor CYP2C19 metabolizers. There are limited data on the safety of mavacamten in poor CYP2C19 metabolizers in clinical studies.

2.8 Summary of the Safety Concerns

The overall safety concerns, including important identified and potential risks and missing information for mavacamten are summarized in Table 2.8-1.

Table 2.8-1: Summary of Safety Concerns

Important identified risks	None
Important potential risks	Heart failure due to systolic dysfunction
	Adverse events due to overexposure to mavacamten resulting from interaction with CYP2C19 inhibitors in ultrarapid and intermediate CYP2C19 metabolizers and moderate or strong CYP3A4 inhibitors in poor and normal CYP2C19 metabolizers
	Embryo-foetal toxicity
Missing information	Patients with Class IV NYHA
	Patients being treated with disopyramide
	Patients being treated with a combination of β-blockers and non-dihydropyridine calcium-channel blockers (verapamil/diltiazem)
	Long-term safety, including detrimental CV effects
	Use during lactation
	Safety in CYP2C19 poor metabolizers

3 PART III: PHARMACOVIGILANCE PLAN

The pharmacovigilance plan provides details of pharmacovigilance activities/studies that are intended to proactively identify and/or characterize safety concerns and will inform risk mitigation strategies for the important identified and potential risks. Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme is provided in Annex 2. A summary of all pharmacovigilance study protocols in the pharmacovigilance programme is provided in Annex 3.

3.1 Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection

As part of routine pharmacovigilance activities, specific targeted questionnaires will be used to obtain structured information on reported suspected pregnancy exposures. Refer to Annex 4 for an example of these questionnaires.

The frequency of maternal, foetal, and infant outcomes among women with oHCM suspected exposure to mavacamten during pregnancy and/or lactation will be described within the PBRER. Infant outcomes will be followed-up for at least the first year of life.

3.2 Additional Pharmacovigilance Activities

A summary of PASS in the mavacamten pharmacovigilance plan is provided in Table 3.2-1.

Table 3.2-1: Post-Authorisation Safety Studies Short Name Summary

Study short name and title	Rationale and study objectives	Study design	Study population	Milestone(s)	Due Date(s)
Mavacamten Real-World Safety: a post-authorisation multi-national, long-term, observational study in patients with obstructive Hypertrophic Cardiomyopathy (oHCM) in the real-world setting in Europe (CV027013 [MAVEL-HCM])	The aim of this study is to evaluate the risk of clinically important cardiovascular safety-related outcomes among adult patients with symptomatic oHCM receiving mavacamten compared to non-mavacamten oHCM treatment in a real-world setting in Europe. The primary objectives of this study are: 1) To estimate the IRs of HF associated with exposure to mavacamten and with exposure to non-mavacamten oHCM treatment, among adult patients with symptomatic oHCM. 2) To estimate the risk of HF associated with exposure to mavacamten compared to non-mavacamten oHCM treatment, among adult patients with symptomatic oHCM The secondary objectives of this study are: 1) To estimate the IRs of clinically important CV and safety-related outcomes associated with exposure to mavacamten and with exposure to non-mavacamten oHCM treatment, among adult patients with symptomatic oHCM. 2) To estimate the risk of clinically important CV safety-related outcomes associated with expsoure to mavacamten compared with non-mavacamten oHCM treatment, among adult patients with symptomatic oHCM. The exploratory objectives of this study are: 1) To describe clinically important CV safety-related outcomes associated with exposure to mavacamten and with exposure to non-mavacamten oHCM treatment, among adult patients with symptomatic oHCM who are	Postmarketing longitudinal observational cohort study	Men and women at least 18 years of age who are diagnosed with oHCM who received mavacamten or non-mavacamten treatment	1. Protocol Submission 2. Interim CSR 3. Study progress report included in PBRER 4. Final CSR	Within 90 days after EC decision Within 1 year of the end of the 3-year patient enrollment period Submitted in accordance with the EURD List Within 1 year after the end of data collection

Table 3.2-1: Post-Authorisation Safety Studies Short Name Summary

Study short name and title	Rationale and study objectives	Study design	Study population	Milestone(s)	Due Date(s)
	concomitantly treated with CYP2C19 inhibitors and/or CYP3A4 inhibitors. 2) To describe clinically important cardiovasulcar safety-related outcomes associated with exposure to mavacamten oHCM treatment by CYP2C19 metaboliser phenotype among adult patients with symptomatic oHCM who are concomitantly treated with CYP2C19 inhibitors. 3) To describe the clinical responses (NYHA class, LVOT gradient, LVEF, NT-proBNP and cardiac troponin (eg, cTnT, cTnI) associated with exposure to mavacamten compared with non-mavacamten oHCM treatment, from baseline to specific follow-up timepoints, among adult patients with symptomatic oHCM. 4) To describe the occurrence of key intercurrent events (eg, serious infection, arrhythmia, major cardiac surgery) from first mavacamten prescription/dispensation date or matched prescription/dispensation date (ie, appropriate index date) to HF diagnosis or worsening HF (eg, hospitalisation for HF, treatment for HF, need for intravenous diuretic therapy in emergency or outpatient setting), in mavacamten and non-mavacamten groups, among adult patients with symptomatic oHCM.				

The following additional pharmacovigilance activities are not considered PASS per definition (GVP Module VIII), and are included in Table 3.3-1 under Category 3. These studies are detailed below:

CV0271148: Meta-analysis to assess CV outcome safety

This is a patient-level meta-analysis with all available placebo-controlled, double-blind, randomized Phase 3 and Phase 3b/4 studies with mavacamten (completed or ongoing before the end of 2023) contributing as secondary data sources for the assessment of CV safety in the symptomatic adult HCM population. The analysis will be performed after the placebo-controlled double-blind period of the last study is unblinded. Each clinical trial utilises the same intervention (mavacamten with similar dose strengths and clinically-guided titration) and comparator (placebo), while allowing standard-of-care treatment. This representation of the broad HCM patient population is considered appropriate for the purpose of CV risk elevation based on the mechanism of action of the drug and similarities in the nature of the disease and expected AE profile in different study populations.

The meta-analysis includes clinical trials in the symptomatic oHCM population (EXPLORER-HCM, VALOR-HCM, and EXPLORER-CN), and in the symptomatic nHCM population (ODYSSEY-HCM). The populations of EXPLORER-HCM, VALOR-HCM, and EXPLORER-CN include symptomatic oHCM patients with LVOT gradients at rest or with provocation (ie, Valsalva or exercise) ≥ 50 mmHg. The ODYSSEY-HCM trial includes patients LVOT gradient at rest < 30 mmHg and with provocation < 50 mmHg. The dose strengths of the oHCM and nHCM studies include those used in the approved label and all studies include clinically-guided titration schemes. Based on the mechanism of action of the drug and similarities in the nature of the disease, co-morbidities and expected safety profile, this broader symptomatic HCM patient population is considered appropriate for the purpose of CV risk evaluation.

MYK-461-007/CV027003 (MAVA-LTE): A Long-term Safety Extension Study of Mavacamten in Adults with Hypertrophic Cardiomyopathy Who Have Completed MAVERICK-HCM (MYK-461-006) or EXPLORER-HCM (MYK-461-005)

This is an ongoing, multicenter, dose-blinded, extension study evaluating the long-term safety and tolerability of mavacamten in subjects with symptomatic oHCM who completed the Phase 3 EXPLORER-HCM study through Week 38 (EXPLORER-LTE Cohort) and in subjects with symptomatic nHCM who completed the Phase 2 MAVERICK-HCM study through Week 24 (MAVERICK-LTE Cohort).

CV027012 (DISCOVER-HCM): Deliver Insights in Hypertrophic Cardiomyopathy and Observational Outcomes in Real-world: US Prospective Registry Study

This is an observational, multicenter registry of prospectively enrolled adult patients with symptomatic (NYHA functional class II-IV) oHCM in the US and Puerto Rico and LVEF ≥ 55% at enrollment. The registry aims to recruit an estimated 65 sites in the US and Puerto Rico to enroll at least 550 patients with oHCM including at least 350 patients initiating treatment with mavacamten at enrollment, once it is available. Enrollment is ongoing and is estimated to require two years.

The primary objective of this study is to estimate the incidence rate of new or worsening of HF due to systolic dysfunction (defined as symptomatic LVEF < 50%) among patients with symptomatic obstructive HCM during periods of exposure to mavacamten and non-mavacamten therapy.

CV027031 (ODYSSEY-HCM): A Randomized, Double-blind, Placebo-controlled Clinical Study to Evaluate Mavacamten in Adults with Symptomatic Non-obstructive Hypertrophic Cardiomyopathy

This Phase 3, double-blind, randomized, placebo-controlled, multicenter, international, parallel-group study is designed to evaluate the safety, tolerability, and efficacy of mavacamten compared with placebo in participants with symptomatic nHCM. The primary objective is to assess the efficacy of a 48-week course of mavacamten compared to placebo on patient-reported health status (symptoms and physical limitations) and on exercise capacity.

CV027004 (HORIZON-HCM): A Phase 3, Open-label, Single-arm, Clinical Study to Evaluate Efficacy, Safety and Tolerability of Mavacamten in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy

This Phase 3 open-label, single-arm, study is designed to evaluate the efficacy, safety, and tolerability of a 30-week course of mavacamten and the long-term effects of mavacamten in Japanese participants with symptomatic obstructive HCM. To evaluate the effect of a 30-week course of mavacamten on post exercise peak LVOT gradient as determined by Doppler echocardiography.

3.3 Summary Table of Additional Pharmacovigilance Activities

Table 3.3-1: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Mavacamten Real-World Safety: a post-authorisation multi-national, long-term, observational study in patients with obstructive Hypertrophic Cardiomyopathy (oHCM) in the real-world setting in Europe (CV027013 [MAVEL-HCM]) (PASS) Planned	The primary objectives of this study are: 1) To estimate the IRs of HF associated with exposure to mavacamten and with exposure to non-mavacamten oHCM treatment, among adult patients with symptomatic oHCM 2) To estimate the risk of HF associated with exposure to mavacamten compared with non-mavacamten oHCM treatment, among adult patients with symptomatic oHCM The secondary objectives of this study are: 1) To estimate the IRs of clinically important CV safety-related outcomes associated with exposure to mavacamten and with exposure to non-mavacamten oHCM treatment, among adult patients with symptomatic oHCM 2) To estimate the risk of clinically important CV safety-related outcomes associated with exposure to mavacamten compared with non-mavacamten oHCM treatment, among adult patients with symptomatic oHCM. The exploratory objectives of this study are:	• Heart failure due to systolic dysfunction • Patients with Class IV NYHA • Patients being treated with disopyramide • Patients being treated with a combination of β-blockers and nondihydropyridine calcium-channel blockers (verapamil/diltiazem) • Long-term safety, including detrimental CV effects	1. Protocol Submission 2. Interim CSR 3. Study progress report included in PBRER 4. Final CSR	Within 90 days after EC decision Within 1 year of the end of the 3-year patient enrollment period Submitted in accordance with the EURD List Within 1 year after the end of data collection

Table 3.3-1: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
	1) To describe clinically important CV safety-related outcomes associated with expsoure to mavacamten and with exposure to non-mavacamten oHCM treatment, among adult patients with symptomatic oHCM who are concomitantly treated with CYP2C19 inhibitors and/or CYP3A4 inhibitors 2) To describe clinically important CV safety-related outcomes associated with exposure to mavacamten oHCM treatment by CYP2C19 metaboliser phenotype among adult patients with symptomatic oHCM who are concomitantly treated with CYP2C19 inhbitors 3) To describe the clinical responses (NYHA class, LVOT gradient, lVEF, NT-proBNP and cardiac troponin (eg, cTnT, cTnI), associated with exposure to mavacamten compared with non-mavacamten oHCM treatment from baseline to specific follow-up timepoints, among adult patients with symptomatic oHCM 4) To describe the occurrence of key intercurrent events (eg, serious infection, arrhythmia, major cardiac surgery) from first mavacamten prescription/dispensation date or matched prescribption/dispensation date (ie, appropriate index date) to HF diagnosis or worsening HF (eg, hospitalisation for HF, treatment for HF, need for intravenous diuretic therapy in emergency or outpatient setting) in mavacamten and non-mavacamten groups, among adult patients with symptomatic oHCM.			

Table 3.3-1: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
CV0271148: Meta-analysis to assess CV outcome safety Ongoing	The primary objective of the study is to assess whether the risk of major CV events defined as e-MACE in the mavacamten group is non-inferior to risk in the placebo group.[a] The secondary objective of the study is to assess the effect of mavacamten treatment on other CV safety outcomes, including the individual components of e-MACE, and all-cause mortality. The meta-analysis includes clinical trials in the symptomatic oHCM population (EXPLORER-HCM, VALOR-HCM, and EXPLORER-CN), and in the symptomatic nHCM population (ODYSSEY-HCM).	• Long-term safety, including detrimental CV effects	1. Protocol submission 2. Study progress report included in PBRER 3. Final CSR	Within 90 days after EC decision Submitted in accordance with the EURD list Completed within 1 year after all studies have been unblinded
MYK-461-007/CV027003 (MAVA LTE): A Long-term Safety Extension Study of Mavacamten (MYK 461) in Adults with Hypertrophic Cardiomyopathy Who Have Completed the MAVERICK-HCM (MYK-461-006) or EXPLORER-HCM (MYK-461-005) Trials Ongoing	This is an ongoing, multicenter, dose-blinded, extension study evaluating the long-term safety and tolerability of mavacamten in subjects with symptomatic oHCM who completed the Phase 3 EXPLORER-HCM study through Week 38 (EXPLORER-LTE Cohort) and in subjects with symptomatic nHCM who completed the Phase 2 MAVERICK-HCM study through Week 24 (MAVERICK-LTE Cohort).	• Heart failure due to systolic dysfunction • Long-term safety, including detrimental CV effects	1. Final CSR	Nov-2026

Table 3.3-1: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
CV027012 (DISCOVER-HCM): Deliver Insights on Safety in Hypertrophic Cardiomyopathy and Observe Endpoints in Real-world Ongoing	This is an observational, multicenter registry of prospectively enrolled adult patients with symptomatic (NYHA functional class II-IV) oHCM in the US and Puerto Rico and LVEF ≥ 55% at enrollment. The registry aims to recruit an estimated 65 sites in the US and Puerto Rico to enroll at least 550 patients with oHCM including at least 350 patients initiating treatment with mavacamten at enrollment, once it is available. Enrollment is estimated to require two years.	• Heart failure due to systolic dysfunction • Patients with Class IV NYHA • Patients being treated with disopyramide • Patients being treated with a combination of β-blockers and non-dihydropyridine calcium-channel blockers (verapamil/diltiazem) • Long-term safety, including detrimental CV effects	1. Interim CSR 2. Study progress report 3. Final CSR	Within 1 year of the end of the 2-year patient selection period Annually for the first 6 years Within 1 year after the end of data collection
CV027031 (ODYSSEY-HCM): A Randomized, Double-blind, Placebo-controlled Clinical Study to Evaluate Mavacamten in Adults with Symptomatic Non-obstructive Hypertrophic Cardiomyopathy Ongoing	This Phase 3, double-blind, randomized, placebo-controlled, multicenter, international, parallel-group study is designed to evaluate the safety, tolerability, and efficacy of mavacamten compared with placebo in participants with symptomatic nHCM. The primary objective is to assess the efficacy of a 48-week course of mavacamten compared to placebo on patient-reported health status (symptoms and physical limitations) and on exercise capacity.	• Safety in CYP2C19 poor metabolizers	1. Final CSR	Jun-2026

Table 3.3-1: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
CV027004 (HORIZON-HCM): A Phase 3, Open-label, Single-arm, Clinical Study to Evaluate Efficacy, Safety and Tolerability of Mavacamten in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy Ongoing	This Phase 3 open-label, single-arm, study is designed to evaluate the efficacy, safety, and tolerability of a 30-week course of mavacamten and the long-term effects of mavacamten in Japanese participants with symptomatic obstructive HCM. To evaluate the effect of a 30-week course of mavacamten on post exercise peak LVOT gradient as determined by Doppler echocardiography.	• Safety in CYP2C19 poor metabolizers	1. Final CSR	Jun-2027

[a] e-MACE event is defined as a composite of adjudicated events of CV death, non-fatal MI, non-fatal stroke, hospitalisation for heart failure, hospitalisation for arrhythmia, other CV hospitalisation (for events other than heart failure or arrhythmia), or appropriate shock therapy from ICD.

4 PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no PAES planned.

5 PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

5.1 Routine Risk Minimisation Measures

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Heart failure due to systolic dysfunction	**Routine risk communication:** The SmPC addresses the risk of heart failure due to systolic dysfunction in Section 4.4. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendations for systolic dysfunction monitoring and management are included in SmPC Sections 4.2 and 4.4. **Other routine risk minimisation measures beyond the Product Information:** None
Adverse events due to overexposure to mavacamten resulting from interaction with CYP2C19 inhibitors in ultrarapid and intermediate CYP2C19 metabolizers and moderate or strong CYP3A4 inhibitors in poor and normal CYP2C19 metabolizers	**Routine risk communication:** The SmPC addresses the risks of adverse events due to overexposure to mavacamten resulting from interaction with CYP2C19 inhibitors in ultrarapid and intermediate CYP2C19 metabolizers and moderate or strong CYP3A4 inhibitors in poor and normal CYP2C19 metabolizers in Sections 4.4 and 4.5. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendations for monitoring for the risk of systolic dysfunction due to drug interactions and appropriate dosage modifications are included in SmPC Sections 4.2, 4.4, and 4.5. **Other routine risk minimisation measures beyond the Product Information:** None
Embryo-foetal toxicity	**Routine risk communication:** The SmPC addresses the risks of embryo-foetal toxicity in Sections 4.3, 4.4, 4.6, and 5.3. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Information on how to minimise the risk of foetal toxicity is included in SmPC Section 4.4 and Section 4.6. **Other routine risk minimisation measures beyond the Product Information:** None
Patients with Class IV NYHA	**Routine risk communication:** The SmPC describes the indication (for the treatment of symptomatic NYHA Class II-III oHCM) in Sections 4.1 and 5.1. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None
Patients being treated with disopyramide	**Routine risk communication:** The SmPC addresses the risk of use of disopyramide in Section 4.4. It also reflects exclusion of patients on disopyramide from EXPLORER-HCM in Section 5.1.

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Information on the monitoring of patients during concomitant use of mavacamten with disopyramide is included in SmPC Section 4.4. **Other routine risk minimisation measures beyond the Product Information:** None
Patients being treated with a combination of β-blockers and non-dihydropyridine calcium-channel blockers (verapamil/diltiazem)	**Routine risk communication:** The SmPC addresses the risk of treatment with a combination of β-blockers and non-dihydropyridine calcium-channel blockers (verapamil/diltiazem) in Sections 4.4 and 4.5 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Information on the monitoring of mavacamten patients taking β-blockers in combination with verapamil or diltiazem is included in SmPC Sections 4.4 and 4.5. **Other routine risk minimisation measures beyond the Product Information:** None
Long-term safety, including detrimental CV effects	**Routine risk communication:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None
Use during lactation	**Routine risk communication:** The SmPC addresses the unknown adverse effects of mavacamten in breastfed newborns/infants in Section 4.6. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measure beyond the Product Information:** None
Safety in CYP2C19 poor metabolizers	**Routine risk communication:** The SmPC addresses the safe use of mavacamten in CYP2C19 poor metabolizers in Section 4.2 and 4.5. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measure beyond the Product Information:** None

5.2 Additional Risk Minimisation Measures

Additional risk minimisation measures are reflected in Table 5.2-1. Details of proposed additional risk minimisation activities are provided in Annex 6.

Table 5.2-1: Additional Risk Minimisation Measures

HCP Checklist	**Objectives:** For further awareness to prescribers of important potential risks of heart failure due to systolic dysfunction, adverse events due to overexposure to mavacamten resulting from interaction with CYP2C19 inhibitors in ultrapid and intermediate CYP2C19 metabolizers and moderate or strong CYP3A4 inhibitors in poor and normal CYP2C19 metabolizers, and embryo-foetal toxicity. **Rationale for the additional risk minimsation activity:** The Checklist will support the communication of critical tasks and actions by the prescriber throughout the patient's cycle of treatment with mavacamten; before starting treatment, during treatment, and after treatment has been discontinued. **Target audience and planned distribution path:** Prescribers **Plans to evaluate the effectiveness of the interventions and criteria for success:** As part of routine pharmacovigilance practice, in the event of a mavacamten pregnancy exposure, a PSF will be used to obtain follow-up information. The PSF contains adequate elements concerning pregnancy exposure and outcome as well as potential exposure during breastfeeding. Also, on a regular basis, signal detection will be performed as part of routine pharmacovigilance monitoring, to monitor any changes in the occurrence, nature, and outcome of the important safety concerns including heart failure due to systolic dysfunction, adverse events due to overexposure to mavacamten resulting from interaction with CYP2C19 inhibitors in ultrarapid and intermediate CYP2C19 metabolizers and moderate or strong CYP3A4 inhibitors in poor and normal CYP2C19 metabolizers, and embryo-foetal toxicity as described below: • review of individual case reports of pregnancy with abnormal outcomes • review of individual case reports of heart failure for the nature and outcome • aggregate review of pregnancy cases and cases with fatal outcomes • routine disproportionality analysis using the Global Safety Database, including reports to monitor the changes in the occurrence. A summary of the results, if concerns are identified, will be presented and discussed in the PBRER.
Patient Card and Patient Guide	**Objectives:** To raise further awareness on important potential risks of heart failure due to systolic dysfunction, adverse events due to overexposure to mavacamten resulting from interaction with CYP2C19 inhibitors in ultrarapid and intermediate CYP2C19 metabolizers and moderate or strong CYP3A4 inhibitors in poor and normal CYP2C19 metabolizers, and embryo-foetal toxicity. Embryo-foetal toxicity risk information will be presented separately from other risk information, and will be presented as a tear-out in the Patient Guide so it may be removed for patients that the embryo-foetal toxicity risk does not apply.

Table 5.2-1: Additional Risk Minimisation Measures

	Rationale for the additional risk minimisation activity: Education will support the communication of critical safety measures to patients, such as notifying your doctor if you experience symptoms of heart failure, do not start or stop any medications without talking to your doctor, and avoiding pregnancy **Target audience and planned distribution path:** Patients via prescribers. **Plans to evaluate the effectiveness of the interventions and criteria for success:** As part of routine pharmacovigilance practice, in the event of a mavacamten pregnancy exposure, a PSF will be used to obtain follow-up information. The PSF contains adequate elements concerning pregnancy exposure and outcome as well as potential exposure during breastfeeding. Also, on a regular basis, signal detection will be performed as part of routine pharmacovigilance monitoring, to monitor any changes in the occurrence, nature, and outcome of the important safety concerns including heart failure due to systolic dysfunction, adverse events due to overexposure to mavacamten resulting from interaction with CYP2C19 inhibitors in ultrarapid and intermediate CYP2C19 metabolizers and moderate or strong CYP3A4 inhibitors in poor and normal CYP2C19 metabolizers, and embryo-foetal toxicity as described below: • review of individual case reports of pregnancy with abnormal outcomes • review of individual case reports of heart failure for the nature and outcome • aggregate review of pregnancy cases and cases with fatal outcomes • routine disproportionality analysis using the Global Safety Database, including reports to monitor the changes in the occurrence. A summary of the results, if concerns are identified, will be presented and discussed in the PBRER.

5.3 Summary of Risk Minimisation Measures

A summary of risk minimisation measures and pharmacovigilance activities by safety concern is provided in Table 5.3-1.

Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Heart failure due to systolic dysfunction	**Routine risk minimisation measures:** SmPC Section 4.4.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: • HCP Checklist • Patient Card and Patient Guide	**Additional pharmacovigilance activities:** • MAVA-LTE (MYK-461-007/CV027003) • DISCOVER-HCM (CV027012) Planned post-authorisation safety studies: • Mavacamten Real-World Safety: a post-authorisation multi-national, long-term, observational study in patients with obstructive Hypertrophic Cardiomyopathy (oHCM) in the real-world setting in Europe (CV027013 [MAVEL-HCM])
Adverse events due to overexposure to mavacamten resulting from interaction with CYP2C19 inhibitors in ultrarapid and intermediate CYP2C19 metabolizers and moderate or strong CYP3A4 inhibitors in poor and normal CYP2C19 metabolizers	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.4, and 4.5 **Additional risk minimisation measures**: • HCP Checklist • Patient Card and Patient Guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Embryo-foetal toxicity	**Routine risk minimisation measures:** SmPC Sections 4.4, 4.6, and 5.3 **Additional risk minimisation measures**: • HCP Checklist • Patient Card and Patient Guide	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Pregnancy Specific Targeted Questionnaire **Additional pharmacovigilance activities:** None
Patients with Class IV NYHA	**Routine risk minimisation measures:** SmPC Sections 4.1 and 5.1 **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** • DISCOVER-HCM (CV027012) Planned post-authorisation safety studies: • Mavacamten Real-World Safety: a post-authorisation multi-national, long-term, observational study in patients with obstructive Hypertrophic Cardiomyopathy (oHCM) in the real-world setting in Europe (CV027013 [MAVEL-HCM])

Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Patients being treated with disopyramide	**Routine risk minimisation measures:** SmPC Sections 4.4 and 5.1 **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** • DISCOVER-HCM (CV027012) Planned post-authorisation safety studies: • Mavacamten Real-World Safety: a post-authorisation multi-national, long-term, observational study in patients with obstructive Hypertrophic Cardiomyopathy (oHCM) in the real-world setting in Europe (CV027013 [MAVEL-HCM])
Patients being treated with a combination of β-blockers and non-dihydropyridine calcium-channel blockers (verapamil/diltiazem)	**Routine risk minimisation measures:** SmPC Sections 4.4 and 4.5 **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** • DISCOVER-HCM (CV027012) Planned post-authorisation safety studies: • Mavacamten Real-World Safety: a post-authorisation multi-national, long-term, observational study in patients with obstructive Hypertrophic Cardiomyopathy (oHCM) in the real-world setting in Europe (CV027013 [MAVEL-HCM])
Long-term safety, including detrimental CV effects	**Routine risk minimisation measures:** None **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** • MAVA-LTE (MYK-461-007/CV027003) • DISCOVER-HCM (CV027012) • CV0271148: Meta-analysis to assess CV outcome safety Planned post-authorisation safety studies: • Mavacamten Real-World Safety: a post-authorisation multi-national, long-term, observational study in patients with obstructive Hypertrophic Cardiomyopathy (oHCM) in the real-world setting in Europe (CV027013 [MAVEL-HCM])

Table 5.3-1: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use during lactation	**Routine risk minimisation measures:** SmPC Section 4.6	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Pregnancy Specific Targeted Questionnaire
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None.
Safety in CYP2C19 poor metabolizers	**Routine risk minimisation measures:** SmPC Sections 4.2 and 4.5	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** • HORIZON-HCM (CV027004) (oHCM) • ODYSSEY-HCM (CV027031) (nHCM)

6 SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for CAMZYOS (mavacamten)

This is a summary of the risk management plan (RMP) for CAMZYOS The RMP details important risks of CAMZYOS, how these risks can be minimised, and how more information will be obtained about CAMZYOS's risks and uncertainties (missing information).

CAMZYOS's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how CAMZYOS should be used.

This summary of the RMP for CAMZYOS should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of CAMZYOS's RMP.

I. The medicine and what it is used for

CAMZYOS is authorised for the treatment of symptomatic (New York Heart Association, NYHA, class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients (see SmPC for the full indication). It contains mavacamten as the active substance and it is given by oral administration.

Further information about the evaluation of CAMZYOS's benefits can be found in CAMZYOS's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/camzyos

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of CAMZYOS, together with measures to minimise such risks and the proposed studies for learning more about CAMZYOS's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks

Together, these measures constitute *routine risk minimisation* measures.

In the case of CAMZYOS, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Benefit-Risk Evaluation Report (PBRER) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of CAMZYOS is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of CAMZYOS are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of CAMZYOS. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information

Important identified risks	None
Important potential risks	Heart failure due to systolic dysfunction
	Adverse events due to overexposure to mavacamten resulting from interaction with CYP2C19 inhibitors in ultrarapid and intermediate CYP2C19 metabolizers and moderate or strong CYP3A4 inhibitors in poor and normal CYP2C19 metabolizers
	Embryo-foetal toxicity
Missing information	Patients with Class IV NYHA
	Patients being treated with disopyramide
	Patients being treated with a combination of β-blockers and non-dihydropyridine calcium-channel blockers (verapamil/diltiazem)
	Long-term safety, including detrimental cardiovascular (CV) effects
	Use during lactation
	Safety in CYP2C19 poor metabolizers

II.B Summary of important risks

Important potential risks

Heart failure due to systolic dysfunction

Important potential risks

Evidence for linking the risk to the medicine	Systolic dysfunction (reversible) has been reported in mavacamten clinical trials. Heart failure due to **s**ystolic dysfunction represents a clinical outcome of an exaggerated on-target effect (excessive decrease in myocardial contractility) of mavacamten that has been seen alone or in combination with intercurrent illnesses (eg, uncontrolled atrial fibrillation, serious infection, stress cardiomyopathy) in clinical trials. Systolic dysfunction has been reversible in the clinical program upon dose discontinuation and down titration. Excessive or prolonged reduction in ejection fraction can be life-threatening.
Risk factors and risk groups	History of significant ischemic events, history of arrhythmias, and history of systolic dysfunction are identified as prior risk factors for developing systolic dysfunction leading to heart failure. Intercurrent events of stress cardiomyopathy, atrial fibrillation, infection, arrhythmias with rapid ventricular rate, ischemia, and higher mavacamten concentrations may contribute to new events of systolic dysfunction or make it more difficult to control. Drug-drug interactions with CYP2C19 inhibitors or moderate or strong CYP3A4 inhibitors.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Additional risk minimisation measures: • HCP Checklist • Patient Card and Patient Guide
Additional pharmacovigilance activities	• Mavacamten Real-World Safety: a post-authorisation multi-national, long-term, observational study in patients with obstructive Hypertrophic Cardiomyopathy (oHCM) in the real-world setting in Europe (PASS; CV027013 [MAVEL-HCM]) • MAVA-LTE (MYK-461-007/CV027003) • DISCOVER-HCM (CV027012)
Adverse events due to overexposure to mavacamten resulting from interaction with CYP2C19 inhibitors in ulrarapid and intermediate CYP2C19 metabolizers and moderate or strong CYP3A4 inhibitors in poor and normal CYP2C19 metabolizers	
Evidence for linking the risk to the medicine	Pharmacokinetic parameters from in vitro studies, population PK modeling and drug interaction studies in healthy volunteers, demonstrated metabolism largely by CYP2C19 and CYP3A4 and increased mavacamten concentrations in the presence of CYP2C19 and moderate or strong CYP3A4 inhibitors. In the pivotal EXPLORER study, 7 (6%) subjects in the mavacamten group and 2 (2%) subjects in the placebo group experienced reversible reductions in left ventricular ejection fraction (LVEF) to < 50% (median 48%: range 35-49%) while on treatment. Among 7 subjects in the mavacamten group with on-treatment LVEF reduction to < 50%, concentration levels were not highly correlated with the changes (eg, 4 of 7 events of LVEF < 50% occurred with mavacamten plasma concentrations < 700 ng/mL, and 3 of 7 occurred with mavacamten concentrations > 700 ng/mL). Therefore, elevation in plasma concentration did not consistently precede changes in LVEF. In all 7 patients treated with mavacamten, LVEF recovered following interruption of mavacamten and none of them were associated with an event of heart failure.

Important potential risks

Risk factors and risk groups	Patients who may be receiving CYP2C19 or moderate or strong CYP3A4 inhibitors (prescription drugs, over the counter [OTC] medications, herbal products). CYP2C19 poor metabolizers may have increased mavacamten expsoures (up to 3 times) that can lead to an increased risk of systolic dysfunction compared to normal metabolizers.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.4 and 4.5 Additional risk minimisation measures: • HCP Checklist • Patient Card and Patient Guide
Embryo-foetal toxicity	
Evidence for linking the risk to the medicine	Nonclinical developmental toxicity study findings were suggestive of a teratogenic potential of mavacamten at therapeutic exposures.
Risk factors and risk groups	Females of childbearing potential who are not using highly effective contraception.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4, 4.6, and 5.3 Additional risk minimisation measures: • HCP Checklist • Patient Card and Patient Guide

Missing information

Patients with Class IV NYHA	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.1 and 5.1
Additional pharmacovigilance activities	• Mavacamten Real-World Safety: a post-authorisation multi-national, long-term, observational study in patients with obstructive Hypertrophic Cardiomyopathy (oHCM) in the real-world setting in Europe (PASS; CV027013 [MAVEL-HCM]) • DISCOVER-HCM (CV027012) See section II.C of this summary for an overview of the post-authorisation development plan.
Patients being treated with disopyramide	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4 and 5.1
Additional pharmacovigilance activities	• Mavacamten Real-World Safety: a post-authorisation multi-national, long-term, observational study in patients with obstructive Hypertrophic Cardiomyopathy (oHCM) in the real-world setting in Europe (PASS; CV027013 [MAVEL-HCM]) • DISCOVER-HCM (CV027012) See section II.C of this summary for an overview of the post-authorisation development plan.
Patients being treated with a combination of β-blockers and non-dihydropyridine calcium-channel blockers (verapamil/diltiazem)	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4 and 4.5

Missing information

Additional pharmacovigilance activities	• Mavacamten Real-World Safety: a post-authorisation multi-national, long-term, observational study in patients with obstructive Hypertrophic Cardiomyopathy (oHCM) in the real-world setting in Europe (PASS; CV027013 [MAVEL-HCM]) • DISCOVER-HCM (CV027012) See section II.C of this summary for an overview of the post-authorisation development plan.
Long-term safety, including detrimental CV effects	
Risk minimisation measures	Routine risk minimisation measures: None
Additional pharmacovigilance activities	• Mavacamten Real-World Safety: a post-authorisation multi-national, long-term, observational study in patients with obstructive Hypertrophic Cardiomyopathy (oHCM) in the real-world setting in Europe (PASS; CV027013 [MAVEL-HCM]) • MAVA-LTE (MYK-461-007/CV027003) • DISCOVER-HCM (CV027012) • CV0271148: Meta-analysis to assess CV outcome safety See section II.C of this summary for an overview of the post-authorisation development plan.
Use during lactation	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6
Safety in CYP2C19 poor metabolizers	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2 and 4.5
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • HORIZON-HCM (CV027004) (oHCM) • ODYSSEY-HCM (CV027031) (Nonobstructive hypertrophic cardiomyopathy [nHCM])

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of CAMZYOS.

II.C.2 Other studies in post-authorisation development plan

Category 3 on-going and planned additional pharmacovigilance activities

Study short name and title	Rationale and study objectives
CV027013 (MAVEL-HCM): Mavacamten Real-World Safety: a post-authorisation multi-national, long-term, observational study in patients with obstructive Hypertrophic Cardiomyopathy	The primary objectives of this study are: 1) To estimate the IRs of HF associated with exposure to mavacamten and with exposure to non-mavacamten oHCM treatment, among adult patients with symptomatic oHCM

Category 3 on-going and planned additional pharmacovigilance activities

Study short name and title	Rationale and study objectives
(oHCM) in the real-world setting in Europe	2) To estimate the risk of HF associated with exposure to mavacamten compared with non-mavacamten oHCM treatment, among adult patients with symptomatic oHCM. The secondary objectives of this study are: 1) To estimate the IRs of clinically important CV safety-related outcomes associated with exposure to mavacamten and with exposure to non-mavacamten oHCM treatment, among adult patients with symptomatic oHCM 2) To estimate the risk of clinically important CV safety-related outcomes associated with exposure to mavacamten compared with non-mavacamten oHCM treatment, among adult patients with symptomatic oHCM The exploratory objectives of this study are: 1) To describe clinically important CV safety-related outcomes associated with exposure to mavacamten and with exposure to non-mavacamten oHCM treatment, among adult patients with symptomatic oHCM who are concomitantly treated with CYP2C19 and/or CYP3A4 inhibitors 2) To describe clinically important CV safety-related outcomes associated with exposure to mavacamten oHCM treatment by CYP2C19 metaboliser phenotype among adult patients with symptomatic oHCM who are concomitantly treated with CYP2C19 inhibitors 3) To describe the clinical responses (NYHA class, LVOT gradient, LVEF, NT-proBNP and cardiac troponin (eg, cTnT, cTnI), associated with expsoure to mavacamten compared with non-mavacamten oHCM treatment from baseline to specific follow-up timepoints, among adult patients with symptomatic oHCM. 4) To describe the occurrence of key intercurrent events (eg, serious infection, arrhythmia, major cardiac surgery) from first mavacamten prescription/dispensation date or matched prescription/dispensation date (ie, appropriate index date) to HF diagnosis or worsening HF (eg, hospitalisation for HF, treatment for HF, need for intravenous diuretic therapy in emergency or outpatient setting) in mavacamten and non-mavacamten groups, among adult patients with symptomatic oHCM.
CV0271148: Meta-analysis to assess CV outcome safety	This is a patient-level meta-analysis with all available placebo-controlled, double-blind, randomized Phase 3 and Phase 3b/4 studies with mavacamten (completed or ongoing before the end of 2023) contributing as secondary data sources for the assessment of CV safety in the symptomatic adult HCM population. The analysis will be performed after the placeob-controlled double-blind period of the last study is unblinded. Each clinical trial utilizes the same intervention (mavacamten with similar dose strengths and clinically-guided titration) and comparator (placebo), while allowing standard-of-care treatment. This representation of the broad HCM patient population is considered appropriate for the purpose of CV risk evaluation based on the mechanism of action of the drug and similarities in the nature of the disease and expected AE profile in the different study populations. The primary objective of this study is to assess whether the risk of major CV events defined as expanded MACE (e-MACE) in the mavacamten group is non-inferior to risk in the placebo group.[a] The secondary objective of this study is to assess the effect of mavacamten treatment on other CV safety

Category 3 on-going and planned additional pharmacovigilance activities

Study short name and title	Rationale and study objectives
	outcomes, including the individual components of e-MACE, and all-cause mortality. The meta-analysis includes clinical trials in the symptomatic oHCM population (EXPLORER-HCM, VALOR-HCM, and EXPLORER-CN), and in the symptomatic nHCM population (ODYSSEY-HCM).
MYK-461-007/CV027003 (MAVA-LTE) - A Long-term Safety Extension Study of Mavacamten in Adults with Hypertrophic Cardiomyopathy Who Have Completed the MAVERICK-HCM or EXPLORER-HCM Trials	The primary objective of this study is as follows: • To assess the long-term safety and tolerability of mavacamten in participants with HCM previously enrolled in 1 of 2 placebo-controlled trials: MAVERICK HCM for non-obstructive HCM (nHCM) and EXPLORER HCM for obstructive HCM (oHCM) The secondary objectives of this study are as follows: • To assess the long-term effects of mavacamten on symptoms and echocardiographic measures of cardiac function • To assess left ventricular outflow tract (LVOT) obstruction as determined by Doppler echocardiography in the EXPLORER-LTE Cohort The exploratory objective of this study was as follows: • To assess the long-term effects of mavacamten on disease biomarker
CV027012 (DISCOVER-HCM) - Deliver Insights in Hypertrophic Cardiomyopathy and Observational Outcomes in Real-world: United States Prospective Registry Study	This is an observational, multicenter registry of prospectively enrolled adult patients with symptomatic (NYHA functional class II-IV) oHCM in the US and Puerto Rico and LVEF ≥ 55% at enrollment. The registry aims to recruit an estimated 65 sites in the US and Puerto Rico to enroll at least 550 patients with oHCM including at least 350 patients initiating treatment with mavacamten at enrollment, once it is available. Enrollment is estimated to require two years.
CV027031 (ODYSSEY-HCM): A Randomized, Double-blind, Placebo-controlled Clinical Study to Evaluate Mavacamten in Adults with Symptomatic Non-obstructive Hypertrophic Cardiomyopathy	This Phase 3, double-blind, randomized, placebo-controlled, multicenter, international, parallel-group study is designed to evaluate the safety, tolerability, and efficacy of mavacamten compared with placebo in participants with symptomatic nHCM. The primary objective is to assess the efficacy of a 48-week course of mavacamten compared to placebo on patient-reported health status (symptoms and physical limitations) and on exercise capacity.
CV027004 (HORIZON-HCM): A Phase 3, Open-label, Single-arm, Clinical Study to Evaluate Efficacy, Safety and Tolerability of Mavacamten in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy	This Phase 3 open-label, single-arm, study is designed to evaluate the efficacy, safety, and tolerability of a 30-week course of mavacamten and the long-term effects of mavacamten in Japanese participants with symptomatic obstructive HCM. To evaluate the effect of a 30-week course of mavacamten on post exercise peak LVOT gradient as determined by Doppler echocardiography.

[a] e-MACE event is defined as a composite of adjudicated events of CV death, non-fatal MI, non-fatal stroke, hospitalisation for heart failure, hospitalisation for arrhythmia, other CV hospitalisation (for events other than heart failure or arrhythmia), or appropriate shock therapy from ICD.

APPENDIX 2: CLINICAL TRIAL EXPOSURE TABLES

4 page(s) excluding cover page

APPENDIX 2: CLINICAL TRIAL EXPOSURE TABLES

Table 1: Duration of Exposure - nHCM

Duration of Exposure	Participants	Person Years
<= 1 month	0	0.0
>1 to 3 months	5	1.1
>3 to 6 months	8	2.5
>6 to 12 months	3	2.4
>12 to 18 months	1	1.4
>18 to 24 months	2	3.8
>24 to 30 months	24	55.0
> 30 months	11	30.7
Total	54	96.9

Studies included: MYK-461-006 and MYK-461-007.

Duration of exposure for a subject in a single study is defined as last dose - first dose + 1.

For subjects that received mavacamten in more than one study, the total duration of exposure from all studies is presented.

Data extraction: Final study data were used for this analysis except for the following ongoing studies MYK-461-007 (28OCT2021), MYK-461-008 (12OCT2021), if included. Data cutoff: 31AUG2021.

Source: /myk461/hcm/rmp/rmp2022/version1/prog/t_exp_1.sas v9.4 12APR2022:17:27

Table 2: Duration of Exposure - All Other Indications (no HCM)

Duration of Exposure	Participants	Person Years
<= 1 month	281	5.5
>1 to 3 months	0	0.0
>3 to 6 months	0	0.0
>6 to 12 months	0	0.0
>12 to 18 months	0	0.0
>18 to 24 months	0	0.0
>24 months	0	0.0
Total	281	5.5

Studies included: MYK-461-001, MYK-461-002, MYK-461-003, MYK-461-009, MYK-461-010, MYK-461-011, MYK-461-012, MYK-461-013, MYK-461-014, MYK-461-015, MYK-461-016, MYK-461-018. MYK-461-001 is a Phase-1 study in subjects with HCM. All other studies are Phase-1 studies in healthy volunteers.

Includes healthy volunteer, dose finding, liquid formulation studies.

Duration of exposure for a subject in a single study is defined as last dose - first dose + 1.

For subjects that received mavacamten in more than one study, the total duration of exposure from all studies is presented.

Data extraction: Final study data were used for this analysis except for the following ongoing studies MYK-461-007 (22DEC2020), MYK-461-008 (23DEC2020), if included. Data cutoff: 30OCT2020.

Source: /myk461/hcm/adhoc/rmp_request_eu/version1/prog/t_exp_1.sas v9.4 04FEB2021:16:27

Table 3: Clinical Exposure by Age Group and Gender nHCM

	Participants			Person Years		
Age Group	Male	Female	Total	Male	Female	Total
<18	0	0	0	0.0	0.0	0.0
18 to 44	4	8	12	7.8	17.4	25.2
45 to 64	12	14	26	20.3	31.6	51.9
65 to 74	7	7	14	3.7	13.7	17.4
75 to 84	1	1	2	2.0	0.3	2.4
85 and over	0	0	0	0.0	0.0	0.0
Total	24	30	54	33.9	63.1	96.9

Studies included: MYK-461-006 and MYK-461-007.
Duration of exposure for a subject in a single study is defined as last dose - first dose + 1.
For subjects that received mavacamten in more than one study, the total duration of exposure from all studies is presented.
Data extraction: Final study data were used for this analysis except for the following ongoing studies MYK-461-007 (28OCT2021), MYK-461-008 (12OCT2021), if included. Data cutoff: 31AUG2021.
Source: /myk461/hcm/rmp/rmp2022/version1/prog/t_exp_3.sas v9.4 12APR2022:17:27

Table 4: Clinical Exposure by Age Group and Gender- All Other Indications (no HCM)

	Participants			Person Years		
Age Group	Male	Female	Total	Male	Female	Total
<18	0	0	0	0.0	0.0	0.0
18 to 44	130	56	186	3.5	1.6	5.0
45 to 64	42	43	85	0.2	0.3	0.5
65 to 74	5	5	10	<0.1	<0.1	<0.1
75 to 84	0	0	0	0.0	0.0	0.0
85 and over	0	0	0	0.0	0.0	0.0
Total	177	104	281	3.6	1.9	5.5

Studies included: MYK-461-001, MYK-461-002, MYK-461-003, MYK-461-009, MYK-461-010, MYK-461-011, MYK-461-012, MYK-461-013, MYK-461-014, MYK-461-015, MYK-461-016, MYK-461-018. MYK-461-001 is a Phase-1 study in subjects with HCM. All other studies are Phase-1 studies in healthy volunteers.
Includes healthy volunteer, dose finding, liquid formulation studies.
Duration of exposure for a subject in a single study is defined as last dose - first dose + 1.
For subjects that received mavacamten in more than one study, the total duration of exposure from all studies is presented.
Data extraction: Final study data were used for this analysis except for the following ongoing studies MYK-461-007 (22DEC2020), MYK-461-008 (23DEC2020), if included. Data cutoff: 30OCT2020.
Source: /myk461/hcm/adhoc/rmp_request_eu/version1/prog/t_exp_3.sas v9.4 04FEB2021:16:27

Table 5: Clinical Exposure by Dose - nHCM

Dose of Exposure	Participants	Person Years
2.5 mg	6	4.1
5 mg	54	53.1
10 mg	20	19.0
15 mg	11	18.8
Total	NA	95.1

Studies included: MYK-461-006 and MYK-461-007.
A subject may have received more than one dose level of mavacamten and be counted in more than one dose level.
The time during dose interruption is not included in this analysis.
Data extraction: Final study data were used for this analysis except for the following ongoing studies MYK-461-007 (28OCT2021), MYK-461-008 (12OCT2021), if included. Data cutoff: 31AUG2021.
Source: /myk461/hcm/rmp/rmp2022/version1/prog/t_exp_4.sas v9.4 12APR2022:17:27

Table 6: Clinical Exposure by Dose - All Other Indications (no HCM)

Dose of Exposure	Participants	Person Years
1 mg	6	<0.1
1 mg BID	10	0.8
2 mg	6	<0.1
3 mg BID	10	0.8
5 mg	4	<0.1
6 mg	6	<0.1
12 mg	6	<0.1
12.5 mg QD	10	0.7
15 mg	102	1.3
18.5 mg QD	10	0.8
24 mg	6	<0.1
25 mg	94	0.3
25 mg QD	10	0.7
25.8 mg*	1	<0.1
25.9 mg*	3	<0.1
26 mg*	2	<0.1
48 mg	10	<0.1
96 mg	6	<0.1
144 mg	5	<0.1
Total	NA	5.5

Studies included: MYK-461-001, MYK-461-002, MYK-461-003, MYK-461-009, MYK-461-010, MYK-461-011, MYK-461-012, MYK-461-013, MYK-461-014, MYK-461-015, MYK-461-016, MYK-461-018. MYK-461-001 is a Phase-1 study in subjects with HCM. All other studies are Phase-1 studies in healthy volunteers.

Includes healthy volunteer, dose finding, liquid formulation studies.

The time during dose interruption is not included in this analysis.

A subject may have received more than one dose level of mavacamten and be counted in more than one dose level.

*Liquid formulations in study MYK-461-013.

Data extraction: Final study data were used for this analysis except for the following ongoing studies MYK-461-007 (22DEC2020), MYK-461-008 (23DEC2020), if included. Data cutoff: 30OCT2020.

Source: /myk461/hcm/adhoc/rmp_request_eu/version1/prog/t_exp_4.sas v9.4 04FEB2021:16:27

Table 7: Clinical Exposure by Ethnic or Racial Origin - nHCM

Ethnic Origin	Participants	Person Years
White	48	85.0
Black or African American	2	4.9
Asian	1	0.3
Unknown/Missing	3	6.6
Total	54	96.9

Studies included: MYK-461-006 and MYK-461-007.

Duration of exposure for a subject in a single study is defined as last dose - first dose + 1.

For subjects that received mavacamten in more than one study, the total duration of exposure from all studies is presented.

Data extraction: Final study data were used for this analysis except for the following ongoing studies MYK-461-007 (28OCT2021), MYK-461-008 (12OCT2021), if included. Data cutoff: 31AUG2021.

Source: /myk461/hcm/rmp/rmp2022/version1/prog/t_exp_5.sas v9.4 12APR2022:17:27

Table 8: Clinical Exposure by Ethnic or Racial Origin - All Other Indications (no HCM)

Ethnic Origin	Participants	Person Years
White	178	4.0
Black or African American	33	0.5
Asian	60	0.7
Native Hawaiian or Other Pacific Islander	1	<0.1
Multiple	3	<0.1
Other	3	<0.1
Unknown/Missing	3	0.2
Total	281	5.5

Studies included: MYK-461-001, MYK-461-002, MYK-461-003, MYK-461-009, MYK-461-010, MYK-461-011, MYK-461-012, MYK-461-013, MYK-461-014, MYK-461-015, MYK-461-016, MYK-461-018. MYK-461-001 is a Phase-1 study in subjects with HCM. All other studies are Phase-1 studies in healthy volunteers.

Includes healthy volunteer, dose finding, liquid formulation studies.

Duration of exposure for a subject in a single study is defined as last dose - first dose + 1.

For subjects that received mavacamten in more than one study, the total duration of exposure from all studies is presented.

Data extraction: Final study data were used for this analysis except for the following ongoing studies MYK-461-007 (22DEC2020), MYK-461-008 (23DEC2020), if included. Data cutoff: 30OCT2020.

Source: /myk461/hcm/adhoc/rmp_request_eu/version1/prog/t_exp_5.sas v9.4 04FEB2021:16:27

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

See below for the targeted questions as an example of the BMS Pregnancy Surveillance Form, which contains adequate elements concerning pregnancy exposure (Part I) and outcome (Part II) as well as potential exposure during breastfeeding (Part III).

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

Prior to the launch of CAMZYOS in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed to educate Healthcare Professionals (HCPs) and patients on important risks associated with CAMZYOS.

The MAH shall ensure that in each Member State where CAMZYOS is marketed, all HCPs who prescribe CAMZYOS have access to/are provided with the Healthcare Professional Information Pack:

- Information on where to find the latest Summary of Product Characteristics (SmPC)
- HCP Checklist
- Patient Guide
- Patient Card

The HCP Checklist will contain the following messages:

Prior to starting treatment

For patients of childbearing potential

- Confirm a negative pregnancy test
- Educate on the risk of embryo-foetal toxicity associated with CAMZYOS
- Counsel on the need to avoid pregnancy and the need for an effective form of contraception during treatment with CAMZYOS and for 6 months following discontinuation
- Instruct patients to contact you or another member of your healthcare team immediately if they become pregnant or suspect they may be pregnant

For all patients

- Complete an echocardiogram assessment and confirm the patient's left ventricular ejection fraction (LVEF) is ≥ 55% before starting treatment.
- Patients should be genotyped for CYP2C19 phenotype in order to determine appropriate CAMZYOS dose.
- Assess for potential interactions involving CAMZYOS and any medicine (including prescription and over-the-counter medicines), herbal supplements and grapefruit juice. Detailed guidance on dose modifications/contraindications with concomitant medicines, based on the patient's CYP2C19 phenotype status, is included in the Summary of Product Characteristics (Table 1 and Table 2 of Section 4).
- Inform the patient of the risk of heart failure associated with CAMZYOS and that they must consult their healthcare professional or seek medical attention immediately if they experience

worsening, persistent or new shortness of breath, chest pain, fatigue, palpitations or leg swelling.

- Counsel the patient on the risk of potential interactions involving CAMZYOS and not to start or stop taking any medications or change the dose of any medication they are taking without talking to you first.
- Provide the patient with the Patient Guide and highlight the Patient Card within the guide

During treatment at each clinical visit (as described in the Summary of Product Characteristics)

For patients of childbearing potential

- Remind patients of the risk of embryo-foetal toxicity associated with CAMZYOS
- Counsel on the need to avoid pregnancy and the need for an effective form of contraception during treatment and for 6 months following discontinuation
- Periodically check pregnancy status throughout treatment
- Instruct patients to contact you or another member of your healthcare team immediately if they become pregnant or suspect they may be pregnant

For all patients

- Confirm LVEF is ≥50% by echocardiogram assessment. If at any visit LVEF is <50%, interrupt treatment for at least 4 weeks and until LVEF is ≥50%.
- Assess the LVOT gradient with Valsalva manoeuvre and adjust the dose per the guidance provided in the Summary of Product Characteristics Section 4.2.
- Assess the patient for signs, symptoms and clinical findings of heart failure per the guidance provided in the Summary of Product Characteristics Sections 4.2 and 4.4.
- Assess for intercurrent illnesses such as infections or arrhythmia (e.g., atrial fibrillation or other uncontrolled tachyarrhythmia).
- Assess for interactions involving CAMZYOS and any medicine (including prescription and over-the-counter medicines), herbal supplements and grapefruit juice that the patient has newly started, has changed the dose of or plans on taking in the future. Detailed guidance on dose modifications/contraindications with concomitant medicines, based on the patient's CYP2C19 phenotype status, is included in the Summary of Product Characteristics (Table 1 and Table 2 of Section 4).
- Remind the patient of the risks associated with CAMZYOS and that they must consult their HCP or seek medical attention immediately if they experience worsening, persistent or new shortness of breath, chest pain, fatigue, palpitations or leg swelling.
- Counsel the patient on the risks of potential interactions involving CAMZYOS.
- Counsel the patient on actions to take in case of an overdose and missed or delayed doses.
- Provide the patient with the Patient Guide and Patient Card if needed.

After treatment

For patients of childbearing potential

- Counsel patients on the need to avoid pregnancy and the need for an effective form of contraception for 6 months following discontinuation of CAMZYOS.

The Patient Card will contain the following key messages:

- Patient instructions: Carry this card with you at all times. Tell any healthcare professional who sees you that you are taking CAMZYOS
- CAMZYOS is indicated for the treatment of symptomatic obstructive hypertrophic cardiomyopathy. Refer to the Patient Guide and package leaflet for more information, or contact <insert local BMS contact>

Safety information for patients of childbearing potential (to appear first on the card):

- CAMZYOS may cause harm to an unborn baby if used during pregnancy
- CAMZYOS must not be taken if you are pregnant or are of childbearing potential and are not using an effective method of contraception
- If you are able to get pregnant, you must use an effective method of contraception throughout treatment and for 6 months after your last dose
- Talk to your doctor if you are considering becoming pregnant
- If you suspect you may be pregnant or are pregnant, you must inform your prescriber or doctor immediately.

Safety information for all patients:

- Tell your prescriber or doctor or seek other medical attention immediately if you experience new or worsening symptoms of heart failure, including shortness of breath, chest pain, fatigue, a racing heart (palpitations), or leg swelling
- Tell your prescriber or doctor of any new or existing medical conditions
- Tell your prescriber, doctor, or pharmacist about your treatment with CAMZYOS before starting any new medicines (including prescriptions and those available over-the-counter) or herbal supplements, since some of them can increase the amount of CAMZYOS in your body and make it more likely for you to get side effects (some of which may be severe). Do not stop taking or change the dose of any medicine or herbal supplement that you are already taking without talking to your doctor or pharmacist first, as other medicines can affect the way CAMZYOS works.

Please complete this section or ask your prescriber of CAMZYOS to complete it.

Patient's name:

Name of prescriber:

Office phone number:

After-hours phone number:

Hospital name (if applicable):

The Patient Guide will contain the following key messages:

Embryo-foetal toxicity risk messages listed first as a tear out page:

- If you are of childbearing potential, please review the information below before you start treatment with CAMZYOS and keep this page for your reference.
- CAMZYOS must not be taken if you are pregnant or if you are of childbearing potential and are not using an effective method of contraception (birth control) as CAMZYOS may cause harm to an unborn baby.
- If you are able to get pregnant, you will need a confirmed negative pregnancy test before you start taking CAMZYOS.
- You must use an effective method of contraception throughout treatment and for 6 months after your last dose of CAMZYOS. You should discuss with your doctor which method(s) of contraception is/are the most suitable for you.
- Talk to your doctor if you are considering becoming pregnant
- If you suspect you may be pregnant or are pregnant while receiving CAMZYOS, tell your prescriber or doctor immediately. You prescriber or doctor will discuss your treatment options with you.

On the following pages:

- Carry the Patient Card with you at all times and tell any healthcare professional who sees you that you are taking CAMZYOS
- Brief description of echocardiograms and why they are important
- CAMZYOS and heart failure
  - Heart failure due to systolic dysfunction is a serious and sometimes fatal condition.
  - Tell your prescriber or doctor, or seek other medical attention immediately if you experience new or worsening symptoms of heart failure, including shortness of breath, chest pain, fatigue, a racing heart (palpitations), or leg swelling
  - Tell your prescriber or doctor of any new or existing medical condition(s) you experience before and during treatment with CAMZYOS.
- CAMZYOS and interactions
  - Some medicines, including those available over-the-counter, and some herbal supplements can affect the amount of CAMZYOS in your body and make it more likely for you to get side effects (some of which may be severe).
  - Tell your prescriber, doctor, or pharmacist about all of the prescription medicines, over-the-counter medicines and herbal supplements you take, even if you do not take them every day.
  - Do not start taking, stop taking, or change the dose of any of your medicines or herbal supplements without talking to your prescriber, doctor, or pharmacist.
  - Some examples of products that may affect how much CAMZYOS is in your body are shown in Table 1. Please note, these examples are a guide and are not considered a comprehensive list of all possible medicines that may fit this category. Intermittent use of

products that might affect the levels of CAMZYOS in your body include prescription and over-the-counter medicines, herbal supplements and grapefruit juice is not recommended.

- Products listed in Table 1 “Examples of products that may affect CAMZYOS”:
  - Omeprazole, esomeprazole
  - Verapamil, diltiazem
  - Clarithromycin, rifampicin
  - Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
  - Fluoxetine, fluvoxamine
  - Ritonavir, cobicistat
  - Grapefruit juice

- When should I seek medical attention
  - Tell any healthcare professional who sees you if any side effects occur while taking CAMZYOS, even those not discussed in this Patient Guide.
  - Tell your prescriber or doctor, or seek other medical attention immediately if you experience new or worsening symptoms of heart failure, including shortness of breath, chest pain, fatigue, a racing heart (palpitations), or leg swelling.