26 April 2023
EMA/311929/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Camzyos

International non-proprietary name: mavacamten

Procedure No. EMEA/H/C/005457/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted

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Administrative information

Name of the medicinal product:	Camzyos
Applicant:	Bristol-Myers Squibb Pharma EEIG Plaza 254 Blanchardstown Corporate Park 2 Dublin 15 D15 T867 IRELAND
Active substance:	mavacamten
International Non-proprietary Name/Common Name:	mavacamten
Pharmaco-therapeutic group (ATC Code):	other cardiac preparations, other cardiac preparations (C01EB24)
Therapeutic indication(s):	Camzyos is indicated for the treatment of symptomatic (New York Heart Association, NYHA, class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients (see section 5.1).
Pharmaceutical form(s):	Capsule, hard
Strength(s):	2.5 mg, 5 mg, 10 mg and 15 mg
Route(s) of administration:	Oral use
Packaging:	Blister (PVC/PCTFE/alu)
Package size(s):	14 capsules and 28 capsules

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List of abbreviations

%CV	percent coefficient of variation
AAS	Atomic Absorption Spectrometry
ADAU	average daily activity unit
ADME	absorption, distribution, metabolism, and excretion
ADP	adenosine diphosphate
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANDA	Abbreviated New Drug Application (ANDA) is an application for a U.S. generic drug approval
AP	Applicant's Part (or Open Part) of a ASMF
APD	action potential duration
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASA	alcohol septal ablation
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (class)
ATP	adenosine triphosphate
AUC	area under the curve
Bid	twice daily
BMI	body mass index
BP	blood pressure
BSA	body surface area
CTD	Common Technical Document
CEAC	clinical event adjudication committee
CEP	Certificate of Suitability of the EP
CFU	Colony Forming Units
CI	confidence interval
Cmax	maximum (peak) serum concentration
CMH	Cochran-Mantel-Haenszel
CMR	cardiac magnetic resonance imaging
CMS	Concerned Member State
CNS	central nervous system
CoA	Certificate of Analysis
CPET	cardiopulmonary exercise testing
CRS	Chemical Reference Substance (official standard)
CSS	clinical summary score
cTn-I	cardiac troponin-I
CV	cardiovascular
CYP	cytochrome P450
D, d	day
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DoE	Design of experiments
DP	Decentralised (Application) Procedure
DPM	Drug Product Manufacturer
DRX state	disordered-relaxed state

DSC	Differential Scanning Calorimetry
ECG	electrocardiogram
ECHO	echocardiogram
ECI	event of clinical interest
eCRF	electronic case report form
ECVF	extracellular volume fraction
EDC	electronic data capture
EDL	extensor digitorum longus
EDQM	European Directorate for the Quality of Medicines
EOS	end of study
EOT	end of treatment
EP	European Pharmacopoeia
ERA	environmental risk assessment
ET	early termination
eTMF	electronic trial master file
FCR	Functional Related Characteristics
FPM	Finished Product Manufacturer
FSH	folllicle stimulating hormone
FT-IR	Fourier-transform infrared
GC	Gas chromatography
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCM	hypertrophic cardiomyopathy
HCMSQ	Hypertrophic Cardiomyopathy Symptom Questionnaire
HCT	Hydrochlorothiazide
HDPE	High Density Polyethylene
hERG	human Ether à go go-Related Gene
HIV	human immunodeficiency virus
HPLC	high performance liquid chromatography
HR	heart rate
hs	high sensitivity
HT	Holding time
ICD	implantable cardioverter-defibrillator
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IND	independent new drug (application)
IPC	In-process control
IPD	important protocol deviation
IR	Infrared
IRB	institutional review board
ITT	intention to treat
IU	International Units
IV	intravenous
IVM	in-vitro motility
IXRS	interactive response system
KCCQ-23	Kansas City Cardiomyopathy Questionnaire (23-item version)
LA	left atrium
LAVI	left atrial volume index
LDPE	Low Density Polyethylene
LGE	late gadolinium enhancement
LIMA	loaded in-vitro motility assay
LLOQ	lower limit of quantitation

LOA	Letter of Access
LOD	Limit of Detection
LOQ	Limit of Quantitation
LoQ	List of Questions
LS	least squares
LT	Less than
LV	left ventricular
LVEDVI	left ventricular end diastolic volume index
LVEF	left ventricular ejection fraction
LVESVI	left ventricular end systolic volume index
LVMI	left ventricular mass index
LVOT	left ventricular outflow tract
LVSV	left ventricular stroke volume
MA	Marketing Authorisation
MACE	major adverse cardiovascular event
MAH	Marketing Authorisation holder
MCF	myocardial contraction fraction
MEB	Medicines Evaluation Board
MedDRA	Medical Dictionary for Regulatory Activities
MET	metabolic equivalents of task
MHC	myosin heavy chain
MI	myocardial infarction
MMRM	mixed model for repeated measurements
MO	Major objection
MR	mitral regurgitation
MS	Mass Spectrometry
MYBPC3	myosin-binding protein-C
ND	Not detected
nHCM	nonobstructive hypertrophic cardiomyopathy
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NSTEMI	non-ST-elevated myocardial infarction
NSVT	nonsustained ventricular tachycardia
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
OC	Other concern
oHCM,	HOCM obstructive hypertrophic cardiomyopathy
OOS	Out of Specifications
PD	pharmacodynamic(s)
PDE	Permitted Daily Exposure
PE	Polyethylene
PGIC	Patient Global Impression of Change questionnaire
PGIS	Patient Global Impression of Severity questionnaire
Ph. Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PK	pharmacokinetic(s)
PO	per os
PP	Polypropylene
PRO	patient-reported outcome
PT	preferred term
PTAE	pretreatment adverse event
pVO2	peak oxygen consumption

PVC	Poly vinyl chloride
Q1, Q3	first quartile, third quartile
QD	once daily
QoL	quality of life
QOS	Quality Overall Summary
QTc	corrected QT interval
QTcF	QT interval with Fridericia correction
RER	respiratory exchange ratio
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of an ASMF
RRT	Relative retention time
RSD	Relative standard deviation
SAE	serious adverse event
SAM	systolic anterior motion
SAP	statistical analysis plan
SCD	sudden cardiac death
SD	standard deviation
SDV	source data verification
SDS	Sodium dodecyl sulphate
SMQ	Stardardized MedDRA Queries
SoB	shortness of breath (domain score)
SOC	system organ class
SOP	standard operating procedure
SPC	Summary of Product Characteristics
SRT	septal reduction therapy
SRX state	super-relaxed state
STEMI	ST-elevated myocardial infarction
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin
TC	telephone call
TEAE	treatment-emergent adverse event
TGA	Thermo-Gravimetric Analysis
TTE	transthoracic echocardiography
ULN	upper limit of normal
US	United StatesUSP/NF United States Pharmacopoeia/National Formulary
UV	Ultraviolet
VCO2	carbon dioxide production
Vis	Visible
VE	ventilatory efficiency
VE/VCO2	ratio of minute ventilation to carbon dioxide
VO2	oxygen consumption
Vss	volume of distribution at steady-state
VT	ventricular tachycardia
VUS	variant of uncertain significance
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire:Specific Health Problem
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bristol-Myers Squibb Pharma EEIG submitted on 24 June 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Camzyos, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 September 2019.

The applicant applied for the following indication: *Camzyos is indicated for the treatment of symptomatic (New York Heart Association, NYHA, class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients (see section 5.1).*

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0106/2019 on the agreement of a paediatric investigation plan (PIP) and a deferral and a waiver.

At the time of submission of the application, the EMEA-002231-PIP01-17 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. New active substance status

The applicant requested the active substance mavacamten contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a

medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following Scientific Advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
23 March 2017	EMA/CHMP/SAWP/159648/2017 (EMEA/H/SA/3493/1/2017/SME/III)	Angeles Alonso and Armin Koch

The applicant received Scientific Advice on 23 March 2017 EMA/CHMP/SAWP/159648/2017 (EMEA/H/SA/3493/1/2017/SME/III) for the development programme supporting the indication granted by the CHMP. The Scientific Advice pertained to the following quality, non-clinical and clinical aspects:

- The proposed starting materials and approach to establish specifications and in-process controls for the starting materials and process intermediates; the plan to select the batch size for registration stability batches for drug products of multiple strengths to be manufactured using a common blend; the plan to use All Color Capsules from Capsugel for primary stability batches to support the proposed shelf life of commercial printed capsules; the proposed primary stability plan for multiple strengths of drug product to determine commercial shelf life; the plan for stability data at the time of MAA; the proposed primary stability plan for multiple strengths of drug product to determine commercial shelf life.
- The approach to evaluate carcinogenic potential and whether the 2-year rat carcinogenicity study final report could be submitted post-approval.
- The approach to dosing and safety monitoring in the proposed Phase 2 and 3 studies (MYK-461-005 and MYK-461-008, respectively).
- The primary endpoint for dose-finding in the Phase 2 Study.
- The primary endpoint and effect size to support clinical benefit in the Phase 3 study.
- The proposed clinical development plan (Phase 2, Phase 3 and open-label safety extension study) and safety database for submission of an MAA.
- Whether in the context of the target population, morbidity / mortality trials will not be required for registration.
- Whether the proposed health-related and quality of life outcomes could be appropriate for inclusion in the Summary Product Characteristics.
- The planned clinical pharmacology testing strategy for the proposed indication.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Alar Irs

The application was received by the EMA on	24 June 2021
The procedure started on	30 September 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 December 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	23 December 2021
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	05 January 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 January 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 May 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	27 June 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	21 July 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	31 October 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	01 December 2022
The CHMP agreed on a 2nd list of outstanding issues in writing to be sent to the applicant on	15 December 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 January 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	08 February 2023
The CHMP agreed on a 3rd list of outstanding issues in writing to be sent to the applicant on	23 February 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 March 2023

The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	12 April 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Camzyos on	26 April 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant is proposing the following indication:

Camzyos is indicated for the treatment of symptomatic (New York Heart Association, NYHA, class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients (see section 5.1).

2.1.2. Epidemiology and risk factors

Prevalence of hypertrophic cardiomyopathy

Estimates of the prevalence of hypertrophic cardiomyopathy (HCM) in various countries range from 4 to 7 per 10,000, covering various time frames from 1997 through 2016 (Javidgonbadi et al. 2019) (Husser et al. 2018) (Pujades-Rodriguez et al. 2018) (Magnusson et al. 2017) (Adalsteinsdottir et al. 2014). A recent study by Lannou et al. estimated HCM prevalence in France at 10 per 10,000 (Lannou et al. 2020). However, this study used only inpatient records to identify HCM. Pujades-Rodriguez et al. 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 (Pujades-Rodriguez et al. 2018). Therefore, a study of HCM patients identified through inpatient records only would not provide an accurate estimate of disease prevalence.

The CARDIA study was the first to examine the prevalence of echocardiographic features of HCM (ie, hypertrophied, nondilated left ventricles and maximal wall thickness ≥15 mm that were not associated with systemic hypertension) in a general population of 4111 men and women (Maron et al. 1995). Although this study, as well as more recent population genetic studies (Semsarian et al. 2015), have shown a prevalence of HCM at approximately 1:500 or higher, most of the patients whose echocardiograph results met the criteria for HCM were asymptomatic and undiagnosed. This is supported by the observation that a majority of people with HCM are asymptomatic and do not receive an HCM diagnosis in their lifetime. In contrast, a recent analysis of a US claims database showed a prevalence of clinically established HCM of approximately 1:3000 (0.03%) (Maron et al. 2016). Thus, the number of patients with HCM who are diagnosed is much smaller, suggesting that most people with HCM experience a normal life span without limiting symptoms or the need for major treatments.

Prevalence of obstructive hypertrophic cardiomyopathy

Estimates of the proportion of patients with HCM who have obstructive HCM (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 that study, 22% of the HCM patients had oHCM (Javidgonbadi et al., 2019).

The prevalence of oHCM has been shown to increase with age. Husser et al., demonstrated that the prevalence of HCM in the German population increased from 7.4 per 100,000 persons (95% confidence interval [CI] 5.2–10.1) in 0 to 9- year-olds to 298.7 per 100,000 persons (95% CI 276.4–322.4) in patients > 80 years (Husser et al. 2018). 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 (EORP) the mean age of HCM diagnosis was 47

years, with 25th and 75th percentiles at 33 and 59 years of age, respectively (Charron et al. 2018). 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-olds and > 80 years, respectively), throughout a wide age range.

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.

2.1.3. Biologic features. Aetiology and pathogenesis

HCM

Hypertrophic cardiomyopathy is a primary myocardial disorder defined by left ventricular (LV) hypertrophy that cannot be explained by another cardiac or systemic disease (Marian and Braunwald 2017). HCM is a chronic, progressive disease of the cardiomyocyte, and largely of the cardiac sarcomere, with a diverse clinical presentation and course. HCM can be familial and is the most common genetic disease affecting the heart muscle. Mutations in cardiac myosin and other sarcomere proteins increase calcium sensitivity of myofilaments and can dysregulate sarcomere structure, favouring the formation of excess cross-bridges during systole and diastole, altering sarcomere kinetics, and increasing sarcomere energy utilization, resulting in ventricular hypercontractility accompanied by reduced LV compliance, which is reflected clinically as reduced ventricular chamber size, often supranormal ejection fraction, and diastolic dysfunction. (Spudich 2019; McNamara et al. 2017; Anderson et al. 2018; Adhikari et al. 2019; Toepfer et al. 2019; Sarkar et al. 2020; Toepfer et al. 2020). Over time, HCM leads to tissue remodelling, characterized histologically, by myocyte hypertrophy and disarray, microvascular remodelling, and fibrosis. Mutations in any of the structural genes of the sarcomere can be documented in approximately 40% of affected individuals overall and in about 60% of those with a family history of clinical disease (Ommen et al. 2020; Alfares et al. 2015; Elliott et al., 2014; Hershberger et al. 2009; Maron et al. 2012). Moreover, sarcomere hyperactivity underlying systolic and diastolic dysfunction in HCM has been reported regardless of aetiology (Hoskins et al. 2010) and often heralds the clinical onset of the disease (Ho 2011).

Obstructive HCM (oHCM)

Obstructive HCM (oHCM) and nonobstructive HCM (nHCM) are 2 subclassifications of HCM, based on the presence or absence of left ventricular outflow tract (LVOT) obstruction, defined as peak LV outflow gradient ≥30 mmHg at rest or with provocation (Elliott et al. 2014). Both subtypes of HCM are characterized by LV hypercontractility, hypertrophy, and reduced compliance. However, oHCM also has reduced LV outflow due to structural changes in the LVOT.

The precise mechanism of LVOT obstruction remains an active area of study, but it is attributed to a combination of abnormal ventricular geometry caused by septal hypertrophy, reduced ventricular cavity size, and pathologic elongation of the mitral valve (Sherrid et al. 2000). Ventricular obstruction produces increased LV systolic pressure and a variable array of subsequent abnormalities, including prolongation of ventricular relaxation, the elevation of LV diastolic pressure, mitral regurgitation, left atrial (LA) enlargement, atrial fibrillation, myocardial ischemia, and decreased forward cardiac output (Maron et al. 2003).

2.1.4. Clinical presentation, diagnosis

Subjects with oHCM experience progressive diminishing cardiac function and are at greater risk to develop heart failure and symptoms from systolic dysfunction and atrial fibrillation, which increases risk for thromboembolic stroke. Additionally, patients with HCM have an increased risk of sudden cardiac death (SCD), which is directly related to changes in cardiac structure and function, including LVOT gradient, maximal wall thickness, and left atrial volume index (LAVI). The risk of SCD ranges from 0.5% to 2% per year in adults with HCM (Maron et al., 2003; Ho et al., 2018; Elliott et al., 2014; Ommen et al., 2020). A study with long-term follow-up of 1101 oHCM patients showed a significant association between LVOT peak gradient > 30 mmHg and unfavourable outcomes, including disease progression (NYHA Class III or IV) or death from heart failure or stroke (Maron et al. 2003).

Patients with oHCM often experience symptoms which include shortness of breath at rest or with exertion, fatigue, chest pain, and limited exercise capacity that worsen over time in the absence of effective treatment. The presence and degree of symptoms vary across patients. While some experience few symptoms and minor limitations in daily activities, many experience significant debilitating consequences and high symptom burden with profound effects on their daily lives, livelihood, and families (Zaiser et al. 2020). Variability in symptom presentation may lead to delays in diagnosis, misdiagnosis, and receiving treatment that targets diseases other than HCM.

2.1.5. Management

Currently, there are no approved disease-specific or sarcomere-targeted therapies for oHCM in EU. The European Society of Cardiology (ESC) guideline states that in the absence of large randomized clinical studies, pharmacological therapy is administered on an empirical basis to improve functional capacity, reduce symptoms, and prevent disease progression. The current guideline relies on the use of established negative inotropic agents, including beta-blockers, non-dihydropyridine calcium channel blockers, and disopyramide, which results in a reduction of systolic anterior motion (SAM) of the mitral valve/septal contact and LVOT obstruction (Elliott et al. 2014) (Ommen et al. 2020):

Beta-blockers: Patients with symptomatic oHCM are treated initially with nonvasodilating beta-blockers titrated to maximally tolerated dose (Class I recommendation, level of evidence B in 2014 ESC and 2011 ACCF/AHA). Small and mostly retrospective studies suggest that oral propranolol can abolish or reduce resting and provocable LVOT obstruction and provide symptomatic benefit (Elliott et al. 2014; Ommen et al. 2020). However, there are no adequate, well-controlled, randomized, double-blind studies of these compounds, and no robust, evidence-based benefits in HCM have been shown. None of the recommendations in the current ESC or American College of Cardiology/American Heart Association (AHA) treatment guidelines for HCM are supported by Level A Evidence. The only medicinal products approved in Europe for use in the management of HCM are the beta-blockers propranolol (Austria, Belgium, Bulgaria, Cyprus, Estonia, Finland, France, Italy, Malta, Poland, Portugal, Romania, Spain and Sweden) and nadolol (France). While these pharmacological therapies, originally developed for other CV diseases, are partially effective in some but not all patients, there are tolerability issues that can limit the possibility to titrate these drugs up to an optimal dose (Papadakis et al. 2020). Fatigue and significant reductions in heart rate and blood pressure inhibit their effective use. Furthermore, by limiting increases in heart rate response to exercise, they limit functional capacity. Patients may also become intolerant when these drugs are used chronically at high doses. Beta-blockers with vasodilating properties should be avoided, as these can lead to a decrease in peripheral vascular resistance (afterload) that can exacerbate obstructive physiology in oHCM.

Non-dihydropyridine calcium channel blockers (CCB): Non-dihydropyridine calcium channel blockers inhibit calcium entry into excitable cells and thus blunt the ability of calcium to serve as an

intracellular messenger (Elliott et al. 2014; Ommen et al. 2020). Non-dihydropyridine calcium channel blockers have a limited role in the treatment of symptomatic oHCM due to the fact that their potentially beneficial, negative inotropic effects are partially counteracted by their gradient-enhancing vasodilatory properties and negative effects on cardiac conduction. As a result, guidelines suggest caution in the use of these agents in oHCM with significant gradients due to their potential adverse hemodynamic effects (Gersh et al., 2011; Houston & Stevens, 2014). Like beta-blockers, calcium channel blockers can cause adverse hemodynamic effects due to vasodilating properties, and patients may become intolerant when they are used chronically at high doses.

Anti-arrhythmic disopyramide: Disopyramide is a class IA anti-arrhythmic drug that is only recommended in the symptomatic oHCM population as add-on therapy for patients who do not obtain adequate relief of symptoms from the use of beta-blockers or CCBs alone. It has been shown to be effective in reducing LVOT obstruction and improving symptoms, likely through its negative inotropic effects. However, its use is limited by safety and tolerability concerns related to its anti-cholinergic side effects, and QT prolongation (Spoladore et al., 2012).

Nonpharmacological, invasive therapies, including septal myectomy and alcohol septal ablation (ASA), are available for patients with LVOT gradient ≥50 mmHg, NYHA Class III or IV, and/or recurrent exertional syncope despite maximal pharmacological therapy (Elliott et al. 2014). These procedures can be effective in reducing obstruction and improving LV outflow. However, they do not address the underlying myocardial disease and are not a permanent treatment, as residual or recurrent obstruction may occur and/or underlying diastolic dysfunction with symptoms may remain (Osman et al., 2019). Furthermore, these therapeutic options require specialized clinical settings and experienced surgeons with multidisciplinary teams that may not be available to all patients (Elliott et al. 2014; Ommen et al. 2020; Houston and Stevens 2014). For patients with end-stage disease, orthotopic cardiac transplantation is the only effective treatment option.

Implantable cardioverter-defibrillator (ICD): An ICD may be considered in HCM to prevent SCD. The ESC has developed an SCD risk calculator to inform recommendations for ICD implantation.

The main goals of treatment in HCM are control of symptoms and improvement of exercise limitation, abolition or reduction of dynamic intraventricular gradients, treatment of LV dysfunction and heart failure, control of atrial fibrillation and ventricular arrhythmias, and prevention of cardioembolism (Ammirati et al., 2016). Despite maximally tolerated treatment with current therapeutic options, many patients continue to show pathophysiological evidence of disease (e.g., LVOT gradient > 50 mmHg, systolic anterior motion (SAM) of the mitral valve, enlarged atria, elevated cardiac biomarkers) and/or impaired function (NYHA Class II-III and reduced patient-reported health status).

Patients with oHCM experience considerable symptoms, functional impairment, and poor quality of life. In a recent patient-focused meeting on HCM, 53% of patients reported that their medical treatment had “helped somewhat,” leaving many patients without treatment regimens that provide consistent and meaningful relief of their symptoms (Patient-Focused Drug Development Meeting on HCM, 26 June 2020) (Zaiser et al. 2020).

Therefore, the limited pharmacological and surgical options to treat the chronic and progressive symptomology of oHCM leave a significant treatment gap for oHCM patients and an unmet medical need for a targeted therapy that addresses the underlying disease pathophysiology of oHCM.

2.2. About the product

Mode of action.

Mavacamten is a selective, allosteric, and reversible cardiac myosin inhibitor. Mavacamten modulates the number of myosin heads that can enter power-generating states, thus reducing (or in HCM normalizing) the probability of force-producing systolic and residual diastolic cross-bridge formation. Mavacamten also shifts the overall myosin population towards an energy-sparing but recruitable, super-relaxed state. Excess cross-bridge formation and dysregulation of the super-relaxed state of myosin are mechanistic hallmarks of HCM, which can result in hyper-contractility, impaired relaxation, excess energy consumption, and myocardial wall stress. In HCM patients, cardiac myosin inhibition with mavacamten normalises contractility, reduces dynamic LVOT obstruction, and improves cardiac filling pressures and biomarkers of cardiac stress, improving symptoms and exercise capacity.

The approved indication is:

Camzyos is indicated for the treatment of symptomatic (New York Heart Association, NYHA, class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients (see section 5.1).

The approved posology is:

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 response by LVOT gradient with Valsalva manoeuvre 4 and 8 weeks after treatment initiation.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as hard capsule containing 2.5 mg, 5 mg, 10 mg or 15 mg of mavacamten as an active substance.

Other ingredients are:

Capsule content - silica, colloidal hydrated, mannitol (E421), hypromellose (E464), croscarmellose sodium (E468) and magnesium stearate;

Capsule shell

All strengths: gelatin, titanium dioxide (E171)

Camzyos 2.5 mg hard capsules: iron oxide black (E172), iron oxide red (E172)

Camzyos 5 mg hard capsules: iron oxide yellow (E172)

Camzyos 10 mg hard capsules: iron oxide red (E172)

Camzyos 15 mg hard capsules: iron oxide black (E172)

Printing ink - iron oxide black (E172), shellac (E904), propylene glycol (E1520), ammonia solution, concentrated (E527), potassium hydroxide (E525)

The product is available in polyvinylchloride (PVC) / polychlorotrifluoroethylene (PCTFE) / aluminium foil blister.

2.3.2. Active substance

General information

The chemical name of mavacamten is 6-[[(1S)-1-phenylethyl]amino]-3-propan-2-yl-1H-pyrimidine-2,4-dione corresponding to the molecular formula $C_{15}H_{19}N_3O_2$. It has a relative molecular mass of 273.33 g/mol and the following structure:

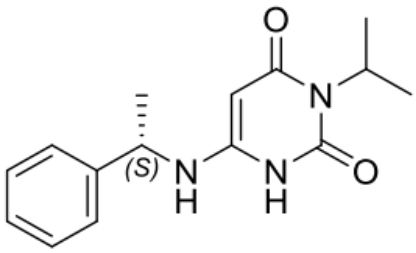


Figure 1: active substance structure

The chemical structure of mavacamten was elucidated by a combination of tests. Spectroscopic tests, including ^{1}H and ^{13}C nuclear magnetic resonance (NMR), Fourier-transform infrared (FT-IR), and ultraviolet-visible (UV-Vis), confirmed the linkage of the atoms and expected functional groups. Elemental analysis and mass spectrometry (MS) confirmed the molecular formula and molecular weight. Mavacamten exhibits stereoisomerism due to the presence of one chiral centres. Single crystal X-ray diffraction confirmed the absolute stereochemistry of the one chiral centre in mavacamten.

The active substance is a white to off-white non-hygroscopic solid. In all aqueous conditions and non-polar organic solvents, mavacamten is practically insoluble; mavacamten is freely soluble in polar organic solvents.

Extensive polymorph screening experiments have been performed using vapor diffusion, evaporation, polymer-induced crystallization, cooling, slurry conversion, anti-solvent addition, and reverse anti-solvent addition. Polymorph type A is controlled at the level of the active substance by XRPD.

Manufacture, characterisation and process controls

Mavacamten is synthesized in five main steps using three well defined starting materials with acceptable specifications.

One manufacturing site is proposed for the synthesis and manufacturing of the intermediates and active substance and one site for its micronisation.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program.

Throughout the development of the mavacamten active substance manufacturing process, the synthetic route has remained unchanged. Modifications and improvements were made to the process to facilitate scale-up and establish appropriate controls.

Although multivariate experiments were conducted to understand the impact of different factors in the synthetic route, no design space or model-based controls are claimed by the applicant. During the procedure, it has been clarified that normal operating ranges of all non-critical process parameters are fixed.

The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.
Mavacamten active substance is packaged in closed double polyethylene bags within high-density polyethylene drums. The double polyethylene bags comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification Error! Reference source not found.includes tests for appearance (visual), identification (FTIR and HPLC), enantiomeric impurity (by chiral reversed phase HPLC), assay (non-enantiospecific, by HPLC), individual unspecified and specified impurities and total impurities (HPLC), residue on ignition (Ph. Eur.), water content (Karl Fischer coulometric titration), particle size distribution (laser light diffraction analyse), polymorphic form (XRPD), residual solvent (GC method with flame ionization detection (FID)) and microbial enumeration testing (Ph. Eur.).

The active substance specification is considered acceptable and have been set based on relevant guidelines and batch data. The limits for assay and residue on ignition have been tightened, as requested.

Limits for impurities have been set in line with ICH Q3E. One of the specified impurities is controlled at the qualification threshold limit according to ICH Q3A, and was qualified in a 13-week oral toxicity study in rats.

Adequate justification was provided also for those parameters that were intentionally not included in the specification such as elemental impurities and potentially mutagenic impurities. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data (including three full scale PPQ and three full scale primary stability batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three full scale batches of active substance from the manufacturers stored in the intended commercial package for up to 60 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

Photostability testing following the ICH guideline Q1B was performed. The parameters tested are the same as for release, with the exception that identification, residue on ignition and residual solvents were not tested; this is accepted as these are not stability indicating. The analytical methods used were the same as for release and were stability indicating.

Photostability testing following the ICH guideline Q1B was performed on one batch.

Results on stress conditions, with stability samples packaged in covered glass vessels were also provide on two batches.

All tested parameters during long term, photostability and stress conditions were within the specifications. The indicative stability nature of the used HPLC method is also properly demonstrated.

The stability results indicate that the active substance manufactured by the proposed manufacturer is sufficiently stable. The stability results justify the proposed retest period of 60 months in the proposed container with no specific storage conditions.

2.3.3. Finished medicinal product

Description of the product and Pharmaceutical development

The description of each strength of the finished product is provided in Table 1 below. The different strengths can be differentiated based upon the colour of the capsule caps (light purple/ yellow/ pink/ gray) and imprint markings.

Table 1: Description of finished product

Strength	Description
2.5 mg	Size 2 hard gelatin capsule, light purple opaque cap imprinted with “2.5 mg” in black, and white opaque body imprinted with “Mava” in black, both in radial direction, containing white to off-white powder.
5 mg	Size 2 hard gelatin capsule, yellow opaque cap imprinted with “5 mg” in black, and white opaque body imprinted with “Mava” in black, both in radial direction, containing white to off-white powder.
10 mg	Size 2 hard gelatin capsule, pink opaque cap imprinted with “10 mg” in black, and white opaque body imprinted with “Mava” in black, both in radial direction, containing white to off-white powder.
15 mg	Size 2 hard gelatin capsule, gray opaque cap imprinted with “15 mg” in black and white opaque body imprinted with “Mava” in black, both in radial direction, containing white to off-white powder

2

The quality target product profile (QTPP) was defined as an immediate-release capsule in four strengths: 2.5 mg, 5 mg, 10 mg, and 15 mg, based on the properties of the active substance, intended use, characterisation of the finished product and intended patient population. The pharmaceutical development focused on those critical quality attributes (CQAs) that could be impacted by the finished product formulation or manufacturing process, namely: assay, content uniformity and dissolution. A

risk assessment of the active substance attributes was performed to evaluate the impact that each attribute could have on the finished product CQAs.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph Error! Reference source not found.of this report.

Excipient compatibility with the active substance was evaluated. The early development formulations were manufactured with mavacamten as an oral suspension, followed by tablets and capsules. Two capsule formulations were used during development. Capsule 1, based on the tablet formulation, was used during Phase 2 and initial Phase 3 clinical studies; Capsule 1 formulation was then optimised into Capsule 2, which was used primarily in the Phase 3 clinical studies. In the revised Capsule 2 formulation, the same excipients of Capsule 1 were used, The dissolution method was developed in parallel to the development of the formulation. The discriminatory power of the dissolution method was demonstrated by the evaluation of the impact on the dissolution profiles of different particle size of the active substance and different binder and lubricant levels.

Since both Capsule 1 and Capsule 2 formulations were used for the pivotal Phase 3 study, a relative bioavailability study was carried out confirming bioavailability similarity for Capsule 1 and Capsule 2 formulations. Dissolution data were presented in order to support the bridge in between the lower strengthof Capsule 1 and Capsule 2 formulations and within the formulations.

To address a multidisciplinary major objection (MO), a bioequivalence study has been conducted . The multidisciplinary major objection is considered resolved from the quality perspective.

The commercial manufacturing process for mavacamten capsules is comprised of conventional wet granulation, blending and encapsulation steps. Process conditions were identified through a systematic, risk-based approach. Based on these studies, a robust finished product manufacturing process for mavacamten capsules was developed that consistently produces a finished product that meets the defined CQAs.

The primary packaging is polyvinylchloride (PVC) / polychlorotrifluoroethylene (PCTFE) / aluminium foil blister. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of 8 main steps: pre-blending, wet granulation, fluid bed drying, milling, final blending and lubrication, encapsulation and packaging. The process is considered to be a standard manufacturing process, using standard unit operations and established equipment.

A description of the manufacturing process was presented and is considered acceptable.

The process parameters and in-process controls (IPCs) are in general set in line with the results of pharmaceutical development studies. The IPCs are adequate for this type of manufacturing process.

The specifications and certificates of analysis for bulk product packaging materials were submitted, as requested.

Full process validation has not been carried out. This approach is considered acceptable based on a detailed pre-validation risk assessment, process validation scheme in 3.2.R, and the fact that a solid oral dosage form that is manufactured by a standard manufacturing process

Product specification

The finished product release specifications Error! Reference source not found.include appropriate tests for this kind of dosage form: appearance (visual), water content (by volumetric Karl Fischer titration), identification, assay and impurities (specified, unspecified, total, all by HPLC (RT and UV)), uniformity of dosage units (content uniformity), dissolution (Ph. Eur., HPLC/UV), microbiological examination (Ph. Eur.).

The proposed specification for the finished product is in line with ICH Q6A, and it is acceptable for this type of dosage form. The specification parameters, analytical methods and acceptance criteria were satisfactorily described and justified. The limit for water was tightened, as requested.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

The limit for individual unspecified impurities was tightened in line with the requirements of ICH Q3B based on mavacamten maximum daily dose of 15 mg, as requested. Furthermore, two impurities were specified in the finished product specification with an acceptable limit , applicable for each. This is accepted.Upon request, the applicant provided additional dissolution data generated with the proposed commercial dissolution method; the dissolution limit was requested to be tightened for all strengths. A tighter specification limit for two strengths only was proposed and accepted. Based on additional dissolution data for the remaining two strengths the proposed limit was considered justified.

The parameters excluded from the finished product specification (i.e. chiral purity, residual solvents, elemental impurities, and potentially mutagenic impurities) were sufficiently justified.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on each component of the capsules on one batch of the finished product using a validated ICP-MS method were provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls.

As requested by the CHMP in a MO, the risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been updated during the procedure to consider in the risk assessment all suspected and actual root causes, in line with the “Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products” (EMA/409815/2020) and the “Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products” (EMA/369136/2020). Based on the updated, more detailed risk assessment, the additional data provided on the individual components and the literature references, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three full scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three registration stability batches for each strength of finished product stored for up to 24 months under long term conditions (30°C / 75% RH) and for up to six months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested in line with the shelf-life specificationError! Reference source not found..No significant changes have been observed. All observed individual and total related substance were well below their proposed specification limits. All results were within the proposed specification for both the long term and accelerated data.

In addition, one batch per strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant changes have been observed; the finished product is photostable.

One batch of 2.5 mg and 15 mg strength in blisters were stressed at -20°C/Ambient RH and at 40°C/75% RH for two days in three cycles, batches were tested for appearance, assay, related substances, dissolution, water content. No change with respect to all stability was observed.

The analytical procedure used for assay and impurities is stability indicating.

Based on available stability data, the proposed shelf-life of 3 years without special storage conditions as stated in the SmPC (section 6.3 and 6.4) are acceptable.

Adventitious agents

Gelatine obtained from bovine and/or porcine sources is used in the product (gelatine capsule). Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.3.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. In order to resolve the MOs raised during the procedure, adequate information to demonstrate equivalence of the capsule formulations used during clinical trials and proposed for marketing has been provided; the nitrosamine risk assessment has been updated and confirmed that no risk has been identified. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. Data has been presented to give reassurance on viral/TSE safety.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3.6. Recommendations for future quality development

Not applicable.

2.4. Non-clinical aspects

2.4.1. Introduction

Mavacamten (formerly known as MYK-461) is a novel small molecule specifically designed to directly modulate systolic and diastolic cardiac function at the source within the cardiomyocyte by selectively (but reversibly) inhibiting the enzymatic activity of myosin (adenosine triphosphate [ATP] turnover kinetics), the motor unit of the cardiac sarcomere.

In cardiac muscle, electrical depolarization and calcium (Ca^{2+}) entry into the myocytes (the targets of traditional inotropic agents) facilitates the activation of the sarcomeres, exposing myosin-binding sites on actin and initiating the molecular cascade that translates chemical energy into mechanical force. This fundamental force-producing process, known as myosin's chemo mechanical cycle, describes the conformational changes of each myosin motor as it 1) hydrolyses the high-energy ATP nucleotide into adenosine diphosphate (ADP) and inorganic phosphate (Pi); 2) transitions (as Pi is released) into a strongly bound cross-bridge with actin ("on-actin"), inducing a power stroke that provides contractile force and determines systolic kinetics; and 3) following ADP release, detaches from actin, determining the kinetics of diastolic relaxation. Mechanistic studies demonstrate that mavacamten directly slows cardiac myofibrillar ATP turnover (and therefore reduces cardiac contractile force) by allosterically inhibiting the release of Pi from myosin following ATP hydrolysis. This mode of inhibition prevents myosin from entering strongly bound "on-actin" states, effectively reducing the number of myosin heads that can form force producing cross-bridges, and thus, directly decreases sarcomere activity, myofilament tension, and at the ensemble level, overall myocyte systolic function. At rest, mavacamten also shifts the population of myosin heads readily available to interact with actin toward an energy-sparing "reserve" state with ultra-low ATP consumption rates, known as the super-relaxed (SRX) state. Under normal physiology, only a small fraction of all available myosin motors engages with actin during a cardiac cycle; the remainder are either primed for action, readily available to form cross-bridges, in a state known as the disordered-relaxed (DRX) state, or are sequestered, in reserve, in the SRX state. Mutations in genes encoding cardiac sarcomeric proteins, such as the myosin heavy chain (MHC) (MYH7 in humans/pigs and MYH6 in rodents) and myosin-binding protein-C (MYBPC3), contribute to functional derangements by releasing excess myosin heads from the SRX state favouring the formation of excess cross-bridges and increasing overall ATP use. In this setting, mavacamten has been shown to normalize (increase) the SRX population, restoring altered cross bridge kinetics and rescuing diastolic impairments. As such, mavacamten directly regulates cross bridge dynamics, and therefore can directly modulate cardiac systolic/diastolic behaviour in vivo. Mavacamten can also both normalize the excess residual cross-bridges that impair relaxation in HCM and reduce the heart's energy burden. Mavacamten's ability to decrease or, in HCM, normalize the number of available actin-binding myosin heads has been confirmed via biomechanical studies in skinned ventricular fibres across multiple species, including minipigs with pathogenic HCM mutations. Overall, mavacamten normalized the sarcomeres' enhanced sensitivity to Ca^{2+} in HCM, directly blunting hyperactivity, while preventing the excess diastolic tension caused by residual cross bridges. In cardiac myocytes, mavacamten decreases contraction in a dose-dependent manner, while increasing diastolic (resting) lengths and accelerating relaxation without impacting Ca^{2+} flux or electrical de-/re-polarization.

Therefore, targeted myosin inhibition with mavacamten results in a novel pharmacological profile: direct attenuation of contractile force at the sarcomere level which, unlike any traditional negative inotrope, occurs concomitantly with decreased diastolic tension and stresses due to a reduction in the number of residual (diastolic) cross-bridges.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

In vitro, mavacamten was demonstrated to be a selective and reversible inhibitor of basal cardiac myosin from bovine and human (IC50: 0.27 ± 0.02 µM and 0.52±0,09 µM, respectively) in absence of Ca2+ and in Ca2+-dependent regulated conditions (IC50: 0.53 ± 0.02 µM and 0.53±0.08 µM, respectively). Mavacamten inhibition of cardiac myosin was therefore achieved by inhibiting both basal ATPase activity as well as actin- and/or calcium activated ATPase rates. ATP turnover was decreased at both systolic and diastolic calcium levels. Inhibitory effects were reversible after rapid dilution.

Modest inhibition in fast skeletal muscle myosin from rabbit (basal IC50: 4.71 ± 0.20 µM) but not chicken smooth muscle was observed, suggesting specificity towards cardiac myosin. In contrast, mavacamten inhibited myosin in slow skeletal muscle (bovine masseter, IC50: 0.43 ± 0.05 µM). Binding to human myosin in known hypertrophy cardiomyopathy (HCM) mutations (R403Q, R453C, R719W, R723G, and G741E in MYH7) was in the low micromolar range (wild-type myosin 0.91 ± 0.047 µM and ranging from 0.65-1.31 µM for the mutations. In common laboratory animals, binding of mavacamten to cardiac myofibrils led to potent inhibition, similar to human myosin (IC50: 0.71 µM); in dog, rabbit, rat and mouse IC50 were 0.49 µM, 0.76 µM, 0.32 µM and 0.29 µM, respectively.

Mavacamten was able to dose dependently displace actin fibers in an IVM assay (EC50: 0.14 ± 0.05 µm) which was proportional to the dose-dependent reduction in gliding velocity (EC50: 0.24 ± 0.05µm). In the loaded motility assay, a single concentration of mavacamten resulted in reduced power (up to 38 ± 7%), likely due to inhibiting the formation of active cross-bridges. Mavacamten was shown to dose dependently reduce myosin activity in the DRX state and increased the population of myosin in the SRX state. These effects were partially reversible by addition of either ADP or Ca2+ in presence of mavacamten.

The mode of action of mavacamten was also investigated in human stem cell-derived cardiomyocytes where mavacamten dose dependently decreased contractility. A maximum effect was reached after 20 minutes for all concentrations tested (0.1-5 µM, IC50: 0.204µM). Beating rate was increased at all concentrations up to 1 µM where maximum contraction was reached. Mavacamten also dose dependently decreased sarcomere shortening during contraction and relaxation and increased the duration of contraction and relaxation as previously observed in bovine and rodent cardiac cells.

Ex-vivo experiments in rat, using healthy left ventricular myocytes incubated with mavacamten showed a dose-dependent inhibition of the shortening fraction and contraction velocity (IC50: 0.25µM), with maximal inhibition occurring at 3µM. The effects of mavacamten were independent of Ca2+ signalling and could be reversed by incubation with a β-adrenergic agonist, isoproterenol. Collectively these data demonstrated that mavacamten reduced contractility by a mechanism distinct from negative inotropes, which act by modulating calcium flux. Similarly, mavacamten dose dependently decreased tension in skinned left ventricular papillary muscle of rat and mini-pig independent of Ca^{2+} concentration.

In rat primary left ventricular myocytes, incubation of a single (0.25 µM) concentration of mavacamten resulted in the functional inhibition of the cardiac cells by reducing shortening fraction and velocity while accelerating relaxation. This state was reversed by co-incubation with isoproterenol, while maintaining lusitropy. Systolic and diastolic calcium-transient amplitudes were not affected by incubation with mavacamten. In isolated Langendorff-perfused rat hearts, mavacamten decreased inotropic indices (lower maximal rate of rise of left ventricular pressure, lower developed pressures) while accelerating relaxation without altering heart rate. Mavacamten also reduced end-diastolic pressures as well as estimated end-diastolic stiffness. Co-incubation with isoproterenol did not alter these responses.

Transgenic mice with mutations in troponin T resulting in pathogenic HCM phenotypes which displayed marked diastolic dysfunction with minimal fibrosis, were administered 0.83 mg/kg/day for 6 months. Mavacamten improved diastolic function while preserving fractional shortening. Administration of a mavacamten analog dose dependently hastened isovolumic relaxation and increased mitral-annulus early displacement. Together, these data suggest a proof of concept for the use of mavacamten in improving HCM in patients.

In summary, the mode of action of mavacamten as an inhibitor of myosin on cardiac muscle which decreases overall ATP turnover (utilization) at the sarcomere and blunts the responses of the cardiac myofilament to mechanical stresses, triggering direct, sarcomere-targeted, negative inotropy while both decreasing diastolic tensions and accelerating relaxation due to the reduction of residual cross-bridges has been sufficiently demonstrated in vitro and in vivo. Mavacamten was able to improve HCM phenotype in a transgenic mouse, thus further lending support to the proof of concept for mavacamten as a therapy in HCM.

Secondary pharmacodynamic studies

A kinome diversity screen (143 targets evaluated) was conducted to identify off-target binding after incubation with 10µM mavacamten. None of the targets showed relevant inhibition with rat GABAa showing a maximum inhibition of 38% at this concentration. Cytotoxicity of mavacamten was evaluated across 13 different cell lines following incubation for 48 hours at different concentrations. No meaningful cytotoxicity was induced by mavacamten in any cell line at any concentration. Literature evidence suggests that, while mavacamten binds to both myosin of smooth and skeletal muscle in vitro, there was no effect on skeletal performance at clinically relevant exposures. This was also reflected in the safety pharmacology studies which were devoid of notable effects on experiments which included forelimb/hindlimb grip strength as variables. Finally, literature evidence suggests a role for mavacamten in targeted myosin inhibition to correct both contractile and relaxation/filling deficiencies, thereby reducing myocardial stresses.

2.4.2.2. Safety pharmacology programme

CNS safety in vivo

Rats administered 1 mg/kg, 3 mg/kg or 10 mg/kg mavacamten did not show overt signs of CNS involvement in a standardized test battery including a functional observation battery or in evaluation of motor activity. A slight decrease in body temperature of 1°C was noted in the high dose group. The clinical relevance of this finding is unknown.

Cardiovascular safety in vitro

Minimal but statistically significant increased hERG inhibition of 5% and 9.6% in HEK293 cells was noted at 10µM and 60µM, respectively, compared to controls (1%). In contrast, the positive control terfenadine achieved a hERG inhibition of 80%. In subsequent assays with HEK293, rabbit purkinje fibers or stem cell-derived human cardiomyocytes, hERG showed comparable minimal inhibition at concentrations above 10 µM. The primary metabolite of mavacamten (MYK-1078) inhibited hERG by 4% at 40 µM. Prolonged incubation (16 hours) over a mavacamten or MYK-1078 concentration range (0.1-30 µM) similarly did not result in an appreciable inhibition of hERG channels. However, incubation with 30µM mavacamten for 48 hours resulted in 31.5% hERG inhibition. Neither mavacamten nor MYK-1078 produced statistically significant decreases in hERG surface expression, but not at levels to suggest activity as hERG trafficking inhibitors. Overall, it is not expected that mavacamten nor its primary metabolite would have the potential to inhibit hERG at clinically relevant concentrations based on in vitro data.

In HEK 293 and human ventricular myocytes, effects of mavacamten and MYK-1078 on action potential duration (APD) and acute and longer-term effects (48 hours incubation) on Nav1.5-late, Cav1.2, Kir6.2/SUR2A (IKatp), IKs, IK1, IKur, and Ito currents were evaluated across a concentration range (0.3-3-10-30 µM). Mavacamten dose dependently decreased APD in human myocytes (healthy and hypertrophied) and decreased AP triangulation. This was attributed to an increased inhibition of the late component of the sodium current (INa-late current) compared to its ability to block IKr, which was demonstrated in both healthy and hypertrophied human heart myocytes. In contrast, MYK-1078 moderately increased APD and mildly increased AP triangulation as result of increased IKr blockade compared to its ability to block INa-late. Comparing effects in healthy heart cells with diseased cells, mavacamten reduced INaL current more robustly in diseased cells. Neither mavacamten nor MYK-1078 affected the maximum AP upstroke velocity. Mavacamten did not significantly decrease hKv4.3-WT (voltage gated potassium channel) surface expression across a dose range of 0.01-30 µM, thus suggesting mavacamten is not a hKv4.3 trafficking inhibitor.

The APD shortening effects of mavacamten were also examined in healthy myocytes treated with 10nM dofetilide (a selective IKr antagonist). Dofetilide induced prolongation of the APD was subsequently reduced by incubation with mavacamten. Acute effects of mavacamten on ion channels showed no appreciable inhibition. At 30 µM, mavacamten changed ion current amplitudes ranging from +4.3% (Kir6.2/SUR2A) to -40.4% (Nav1.5, late). Similar modulation of ion currents was observed after prolonged incubation. The APD shortering profile without indications of proarrhythmic risk was also predicted in an in silico model.

No effects on resting membrane potential nor action potential parameters were observed in rabbit purkinje fibers incubated with mavacamten below 10µM. At 30 µM, a slight decrease in action potential duration at 50% of repolarization was observed but was not considered to be suggestive of an arrhythmogenic profile. MYK-1078 did not alter action potential duration in rabbit purkinje fibers and was thus also not considered to be arrhythmogenic. In stem cell-derived human cardiomycytes, mavacamten, MYK-1078 and a mavacamten analog (MYK 581) were shown to decrease cell motion. Short term incubation with mavacamten did not affect cardiac sodium channels but did so after 48 hours in a dose dependent fashion. However, this is paralleled by the changes in basal impedance twitch amplitude and subsequent twitch duration. Mavacamten nor its primary metabolite showed overt dysrhythmic activity in stem cell derived cardiomyocytes.

Cardiovascular and respiratory safety in vivo

Mavacamten administration to dogs and rats resulted in non-adverse changes of QTc. In the GLP compliant cardiovascular safety pharmacology, dogs dosed with 3 or 10 mg/kg but not 1 mg/kg developed dose dependent decreases in blood pressure and pulse pressure with compensatory increases in heart rate which were maintained for up to one week post dose. At 10 mg/kg QTc

prolongation at 1 week post dose, as well as increased respiratory rated and decreased tidal volume for up to 24 hours post dose were seen. The risk for mavacamten producing arrhythmia of either torsadogenic or non-torsadogenic origin was considered to be limited because ventricular restitution (QT/TQ) remained well below 1.0, which is the ratio of concern for reentrant arrhythmia. The ability of mavacamten to trigger an adaptive electrophysiological response in healthy hearts resulting in QT prolongation after sustained exposure was further evaluated in non-GLP studies in dog and rat. In the dog study, animals received 0 mg/kg PO bid on day 1, 1.5 mg/kg PO bid on day 2 and 0.3 mg/kg/day PO on days 3-15. The anticipated pharmacological effects of mavacamten (fractional shortening and increased left-ventricular end-diastolic dimensions) were also accompanied at first by a shortening of the QT-interval, but by the end of the study this turned into a statistically significant mild to moderate QTc prolongation (+19 ms (274 vs 255msc predose at the end of the study). The QT-prolongation was attributed primarily to lengthening of JTp interval (+19 ms on Day 15, 162 vs 144 ms predose) with negligible changes in the terminal portion of the T-wave suggesting preserved transmural repolarization and preserved late repolarizing currents. No changes in PR or QRS interval was noted which would suggest cardiac conduction. There were no additional notable findings for other haemodynamic parameters. From 3 mg/kg onward, cardiovascular effects were accompanied by vomiting, decreased activity, rapid breathing and decreased food consumption. At 10 mg/kg, animals had an increased respiratory rate and a decrease in tidal volume.

In the rat study, animals received 2 or 4 mg/kg/day for 7 days. In addition to the anticipated pharmacological effects, mavacamten statistically increased QT-intervals which were linearly correlated with increased left-ventricular end-diastolic dimensions. QT-prolongation was accompanied by downregulation of genes encoding Ito and IKATP currents.

Acute QT shortening, and longer-term QT prolongation was the result of adaptive responses to sustained myosin inhibition in ventricles with normal physiology due to changes in early repolarization currents, primarily by downregulation of the Ito and IKATP potassium channels in response to sustained myosin inhibition. In contrast, in HCM both these currents are already abrogated. Thus, it is considered that there is a decreased sensitivity of HCM hearts to mechanisms which lead to QT-prolongation after exposure to mavacamten in the healthy heart.

2.4.2.3. Pharmacodynamic drug interactions

Because mavacamten is intended as monotherapy, no pharmacodynamic drug interaction studies were performed.

2.4.3. Pharmacokinetics

Methods of analysis

Concentrations of mavacamten (MYK-461) and MYK-460 were measured in plasma of mice, rats, rabbits and dogs with validated LC-MS/MS methods. The methods were validated over the range of 1-2000 ng/mL. The validation was adequate regarding calibration, accuracy, precision, matrix effect, dilution integrity and stability. The methods used in the pharmacokinetic studies were considered fit for purpose.

Absorption

In vitro studies in Caco-2 cells showed high permeability and a low efflux ratio for mavacamten, indicating that the P-gp substrate potential is low.

Single dose pharmacokinetics were investigated in mice, rats, dogs and monkeys. Tmax after oral administration was 0.5 h in mice, 0.7 – 2.7 h in rats, 0.3 – 0.5 h in dogs and 0.7 h in monkeys. AUC and Cmax increased generally dose-proportionally in rats (dose range 1 to 10 mg/kg) and dogs (dose range 0.1 to 3 mg/kg), except that Cmax increased slightly less than dose-proportionally in dogs. Oral bioavailability compared to IV administration was complete in mice and 75%, 87% and 47% in rats, dogs and monkeys respectively. Volume of distribution was 3.8 L/kg in mice, 5.0 – 9.0 L/kg in rats, 7.0 L/kg in dogs and 11 L/kg in monkeys, which is beyond total body water in all species. After a single oral dose, clearance was 7.7 mL/min/kg in mice, 3.7 – 11 mL/min/kg in rats, 0.6 mL/min/kg in dogs and 3.0 mL/min/kg in monkeys, which is, respectively, about 8.5%, 10.6% <2% and 6.8% of liver blood flow. Elimination half-life was longer in dogs (130 – 161 h) than in other species (4.2 – 7.0 h in mice, 8.2 – 26 h in rats and 43 – 45 h in monkeys).

In a study in rats in which portal vein and femoral vein were cannulated, similar concentration-time profiles in portal vein and femoral vein indicate no relevant first pass effect in rats.

In multiple dose toxicokinetic studies, exposure to mavacamten increased approximately dose-proportionally in mice and dogs and dose-proportionally or slightly more than dose-proportionally in rats (especially at the later time points). In mice, slight accumulation was observed (accumulation ratio up to 1.8). In rats and dogs, significant accumulation was observed (up to approximately 6-fold in rats and up to approximately 9-fold in dogs). In rats, accumulation was observed up to 90 days, but not or only to a limited extent thereafter. In dogs, accumulation was observed primarily in the first half of the studies and not or limited thereafter. No consistent gender effect was observed in mice and dogs. In rats, exposure was slightly higher in females (maximally up to two-fold) at doses larger than 1 mg/kg. This can possibly be explained by a generally higher rate of metabolism in male rats and is not likely to be relevant for humans.

In rats, exposure was reduced in fed rats compared to fasted rats (ratio fed/fasted was 76% based on AUC_{0-24} and 69% based on $AUC_{0-\infty}$). In dogs, exposure was similar for fed and fasted dogs based on AUC_{0-96}. Based on $AUC_{0-\infty}$, relative bioavailability fed/fasted was 1.23 i.e. exposure was slightly higher in fed dogs compared to fasted dogs. Overall, there does not appear to be a clear food effect in the investigated animals.

The effect of different formulations on bioavailability was investigated in dogs. The bioavailability of mavacamten administered via capsules to dogs increased from 16% to 64% when mavacamten was micronized, reducing particle size from 88 µm to 4 µm. Also among the liquid suspension formulations, bioavailability was higher (increasing from 35% to 107%) at smaller particle size (decreased from 300 µm to 4 µm).

Distribution

In mice, plasma and heart tissue concentration-time profiles were investigated. Concentrations of mavacamten in heart tissue were approximately 3.5 x plasma concentrations after single oral dose and 2 – 3 x plasma concentrations after repeated dosing for 5 days. Heart tissue concentrations in mice did not increase over 5 days daily dosing of 2.5 mg/kg/day.

In a single dose oral tissue distribution study in pigmented rats, mavacamten-related radioactivity was widely and rapidly distributed. Peak concentrations were mostly achieved at 0.5 h after dosing. Radioactivity was highest in diaphragm, oesophagus, kidneys, liver, myocardium, salivary glands, adrenal glands, skeletal muscle, small intestine and stomach mucosa. Low levels were found in the CNS, which were below or almost below LOQ at 720 h after dosing. In non-pigmented skin, levels were comparable to pigmented skin, indicating no binding to melanin. In eyes of non-pigmented rats, peak levels in uveal tract were around half the peak levels in pigmented rats, indicating limited binding to melanin. In several organs / tissues, measurable levels were still found at 720 h after dosing, such as

diaphragm, eye uveal tract, kidneys and myocardium. Due to its presence in skin and eye, mavacamten should be investigated for its phototoxic potential. In a multiple-dose tissue distribution study in rats, concentrations in organs and tissues were generally slightly lower on day 7 than on day 1. Tissue to plasma ratios were approximately 3 in liver, kidney and oesophagus, 10 in myocardium and extensor digitorum longus muscle and 20 in soleus muscle.

In dogs, the distribution of mavacamten in cardiac and skeletal muscle was investigated after a single oral dose of 1.5 – 30 mg/kg. Concentrations at 7 days were similar between left ventricle, soleus muscle and extensor digitorum longus muscle, except at the highest dose of 30 mg/kg, where concentrations in the muscles were lower than in left ventricle but at this dose, dogs were euthanized in moribund condition at 1 h after dosing.

Protein binding of mavacamten-related radioactivity in plasma of mouse, rat, dog, cynomolgus monkey and human was 84%, 89%, 91%, 95% and 93% respectively and not concentration-dependent from 0.2 to 10 µM.

Blood-to-plasma ratios in blood from mouse, rat, dog, cynomolgus monkey and human were reported as 0.72, 0.82, 0.78, 0.82 and 0.79 in mouse, rat (~33%), dog (~25%), monkey and human (~30% in RBC). In an in vivo study in rats, a time effect in blood to plasma ratios was observed, with blood to plasma ratios lower than 1 shortly after administration and higher than 1 from one week after administration.

Placental transfer and excretion in milk were not studied.

Metabolism

After in vitro incubation of [^{14}C]mavacamten with liver microsomes or hepatocytes from mouse, rat, dog, monkey, and human, low levels of metabolites were found. In microsomes, less than 7.5% was metabolized. In hepatocytes, up to 20% was metabolized. Levels of metabolites were generally <5% of total radioactivity except for M4 in rat hepatocyte incubations which was found at 9% of total radioactivity. Metabolites found in human microsomes and hepatocytes were M1, M2 and M6 (<1% each). These metabolites were also found in the non-clinical species, except for dog hepatocytes where only M6 was found. M1 and M2 are both hydroxylated metabolites and M6 is formed by *N*-dealkylation of the phenylethyl group. M4 which was found in rat hepatocytes only, is a glucuronide of M1.

In an in vivo study in rats, parent compound was the main component in plasma, comprising 45% and 67% of total radioactivity in orally and IV dosed rats, respectively. In IV dosed rats, 2% of metabolite M1 was found. In plasma of orally dosed rats, none of the identified metabolites were found. A large part of mavacamten-related radioactivity in plasma appears unidentified (in orally dosed rats more than half of total radioactivity). Study NC-20-0025 contains information regarding identified and unidentified metabolites found in urine and bile, but there is no information regarding unidentified metabolites found in plasma. In urine, low amounts of parent compound were found (6-7% of total radioactivity). Metabolites found in urine were M1 (44% after oral and 19% after IV administration), M2 (14% oral and 8% IV), M4 (IV 24%, oral only minor amount) and unidentified metabolite c (16% oral, 14% IV) and small amounts of M8 and several unidentified metabolites. In bile, only a small amount of parent compound was found (3.9%). Main metabolite in bile was M4 (glucuronide of M1, 56%), followed by M8 and M1 (11% and 10%) and a low amount of M2. Also a considerable amount of unidentified metabolite i was found (25%), which most likely is a glucuronide linked metabolite, as well as minor amounts of several other unidentified metabolites.

In a 6-week study in rats, percentages of MYK-460 relative to mavacamten in plasma of rats (0.18 – 0.44% for Cmax and 0.03 – 0.26% for AUC) were similar to the amount of MYK-460 present at the start of the study (0.22%), indicating no conversion of mavacamten to MYK-460 in vivo in rats. In

dogs, percentages of MYK-460 relative to mavacamten on day 1 were somewhat higher (0.51 – 1.7%) than the amount of MYK-460 present at the start of the study (0.21%). The ratio of MYK-460 to mavacamten did however not increase over a period of 6 weeks.

Excretion

After oral administration to bile duct-intact rats, 58% was excreted in faeces, 23% in urine and 1.7% in expired air. After IV administration to bile duct-cannulated rats, 41% was excreted in bile, 7.6% in faeces and 31% in urine. A total of 8% was recovered from carcass and 6% from other sources such as cage rinse and cage wash. The recovery was at least 94% and therefore sufficient.

2.4.4. Toxicology

2.4.4.1. Single dose toxicity

In a non-GLP oral toxicity study with dogs, administration of 30 mg/kg mavacamten resulted in extreme hypoactivity, unproductive retching (female only), and decreased capillary refill time (male only) approximately 1 hour following dose administration, resulting in animals being sacrificed in moribund condition. The doses up to 7 mg/kg were well tolerated without signs of toxicity. Gross necropsy and histopathology were not conducted.

2.4.4.2. Repeat dose toxicity

The pivotal GLP-studies up to 26 and 39 weeks of duration and the highest tested dose level of 3 mg/kg/day were conducted in rats and dogs, respectively. The main adverse effects seen in both species were observed in the heart and are considered related to the primary pharmacodynamic action of the substance. Cardiac failure at the top tested dose levels caused increased mortality and early euthanasia of the test animals (rats: ≥1.2 mg/kg/day, corresponding to AUC0-24 ≥9150 ng x h/mL; dogs: ≥0.45 mg/kg/day (males), corresponding to AUC0-24 = 17200 ng x h/mL). Effects observed in other organs and tissues (centrilobular hepatocellular necrosis, centrilobular congestion/vacuolation; pulmonary congestion/oedema, spleen oedema) seen in both species are considered secondary to the cardiac failure and reduced cardiac output. In rats, adverse heart changes included increased heart weight correlated with cardiac hypertrophy, myocardial and endocardial degeneration/inflammation, cartilaginous/osseous metaplasia (chorda tendineae) and valvular inflammatory cell infiltrate/inflammation. The ventricular and atrial dilatation seen at all dose levels in the 3-months study was ascribed by the applicant to an artefact during the tissue processing, as these findings were not confirmed in the 26 weeks study at the same dose levels. As the effect was indeed not observed upon longer exposure duration at the same dose levels, this is endorsed. Decreased systolic function (an increase in end diastolic and systolic chamber size and an associated reduction in indices of global left ventricular systolic performance (LV ejection fraction and fractional shortening) was seen in the 26-week study at the dose level of 1.2 mg/kg/day (AUC0-24 of ≥8490 ng x h/mL) which resolved after the recovery period. Increased levels of NT-proANP (cardiac biomarker indicative of heart stress) were measured (non-GLP) in the 3 months study at the dose level of 2.0/1.2 mg/kg/day at week 6 and at the end of dosing. NT-proANP is the biologically inactive fragment of the ANP prohormone which is secreted from the heart in response to atrial stretching or through stimulation by angiotensin II and endothelin. The most important stimulus for the release of this hormone into circulation is stretching of myocyte fibres. The expression and secretion of ANP increase significantly in pathological states accompanied by stretching the heart chambers, volume overload, and ischemic injury, such as heart failure and myocardial infarction. However, the individual variability in the NT-proANP levels in the

study was high, also in controls and pretest animals, and correlated poorly with histopathological findings. The levels of another cardiac biomarker NT-proBNP in the 26 week study at the same dose level were not affected. Also slightly higher troponin I levels were measured after the recovery period in the 3-months study in four high dose rats; in 3 out of 4 rats this correlated with increased heart weights compared to the controls. However, as the increased troponin I levels were seen only after the 4-week recovery period and no evidence of cardiac necrosis was observed, the relevance of this finding is also questionable.

The findings in dogs were in general comparable to the findings in rats. In general, mostly somewhat higher exposure was achieved at the same dose levels in male animals compared to females. Male dogs appeared to be more sensitive to mavacamten toxicity, with the dose level of 0.45 mg/kg/day causing mortality in the 13-week study in males but not in females (AUC0-24 = 17200 ng x h/mL in males vs 12300 ng x h/mL in females). The applicant suggested that this apparently higher male sensitivity to toxicity of mavacamten was caused by a higher exposure achieved in male dogs, which is supported by the toxicokinetic data from the 6-week and 3-month dog studies. Cardiac failure seen at this dose level was consistent with increased NT-proBNP levels in two males, one humanely euthanized on day 72 and one euthanized early as scheduled (dosing stopped earlier) on day 74. Therefore the highest dose level in the 39-week study was lower in males than in females (0.3 vs 0.45 mg/kg/day). Next to histopathological changes, ECG changes (increased heart rate and QTc prolongation) were reported starting from the dose level of 0.18 mg/kg/day in the 13- and 39-week studies (AUC0-24 ≥ 3800 ng x h/mL); also QRS interval was prolonged in females administered 0.45 mg/kg/day (AUC0-24 = 12500 ng x h/mL) in the 39 week study. The changes were reversible in the recovery animals. It is noted that QTc interval prolongation was also seen in the healthy volunteers in the clinical studies and was considered to be not related to a direct drug effect on repolarizing currents, but rather to an indirect drug effect mediated by the on-target reduction in systolic cardiac function. Exposure to mavacamten decreases normal contractility in healthy hearts, whereas it normalizes hypercontractility in obstructive hypertrophic cardiomyopathy. Thus the ECG effects seen in healthy animals are not expected to be relevant for patients. Cardiac ventricle dilation was seen in the 13-week study at 0.45 mg/kg/day at the necropsy of the early decedents and in one surviving female. Ventricular dilatation, associated with substantial increases in mean left ventricular (LV) end-diastolic and mean LV end-systolic volumes and a substantial reduction in mean LV ejection fraction, was also seen in the echocardiogram evaluation in the high-dose males and females (0.30 and 0.45 mg/kg/day, respectively) in the 39-week study. These effects reversed by week 4 of the recovery phase and were still absent after 12 weeks of recovery. As the observed ECG changes (increased heart rate and QTc prolongation) at 0.18 mg/kg/day were minor and reversible in the recovery animals, the NOAEL in the 13- and 39-week dog studies was set at 0.18 mg/kg/day (AUC ≥3800 ng x h/mL).

2.4.4.3. Genotoxicity

Mavacamten gave negative results in the Ames test up to the limit concentration of 5000 µg/plate and in the in vitro micronucleus assay in human lymphocytes, tested up to cytotoxic concentrations, both with and without metabolic activation. An in vivo bone marrow micronucleus test in rats dosed up to 8 mg/kg (MTD) for 2 consecutive days was negative. As the bone marrow is a highly perfused tissue and the test substance was measured in plasma, the bone marrow exposure is considered adequately demonstrated. Based on the results of the in vitro and in vivo tests, mavacamten is concluded to be not genotoxic.

2.4.4.4. Carcinogenicity

Carcinogenicity of mavacamten was studied in the 104-week study with Sprague-Dawley rats and 6 months study with transgenic RasH2 mice. The maximal achieved exposures (AUC0-24) were 3640 (M) and 2810 (F) ng x h/mL in rats and 30000 (M) and 50400 (F) ng x h/mL in mice. Administration of mavacamten did not affect survival. No gross necropsy or histopathological lesions were seen in both species which were attributed to the treatment. Mavacamten showed no carcinogenic potential when administered for 104 weeks to rats or 6 months to transgenic mice.

2.4.4.5. Reproductive and developmental toxicity

In the GLP-compliant FEED study, mavacamten did not show adverse effects on male or female fertility and early embryonic development up to the highest tested dose of 1.2 mg/kg/day. The toxicokinetic analysis has not been performed in the study; therefore, the applicant estimates the exposure based on the results of the 3-month repeated dose toxicity study at which the same dose levels were tested. This can be accepted; however, the achieved exposure levels were below the anticipated clinical exposure (0.4 and 0.8 in males and females, respectively), and the study as such is therefore considered insufficient to draw the conclusion about the potential effects of mavacamten on fertility and early embryonic development in the clinical settings. Such a risk is, however, not anticipated based on the pharmacological profile of mavacamten and the available data on secondary pharmacodynamics.

Developmental toxicity of mavacamten was tested in two GLP-compliant studies with rats and rabbits. In rats, increased post-implantation loss and reduced foetal body weight were seen at the dose level of 1.5 mg/kg/day (maternal AUC0-24 = 16500 ng x h/mL) in the absence of maternal toxicity. Consistent with a lower foetal weight, delayed ossification consisting of increased incidences of incomplete ossification of cervical and thoracic vertebrae, and paws (phalanxes and metatarsals) was seen at the same dose level. At the same dose level, also skeletal and visceral malformations were observed. Skeletal malformations were manifested mainly as fused sternebrae (19 foetuses from 10 litters), whereas visceral malformations were observed in 2 foetuses from 2 litters and included one complete situs inversus and one foetus with the absence of the right atrioventricular valve associated with a ventricular septum defect. Although the visceral effects were considered only in two foetuses, they were still considered related to the test substance administration based on their nature and the active substance pharmacodynamic mode of action; furthermore, situs inversus and a ventricular septum effect were also observed in 2 foetuses from 2 litters which were found dead in the pre-and post-natal developmental toxicity study. Based on the result of the study, the NOAEL for developmental toxicity was set at 0.7 mg/kg/day (maternal AUC0-24 = 5690 ng x h/mL, exposure multiple of the anticipated clinical exposure of 0.3), whereas the NOAEL for maternal toxicity was set at the highest tested dose of 1.5 mg/kg/day (maternal AUC0-24 = 16500 ng x h/mL).

In rabbits, maternal toxicity, manifested as lower body weight gain and lower food consumption, was seen from the dose level of 1.2 mg/kg/day (maternal AUC0-24 = 16500 ng x h/mL). At the highest tested dose of 2 mg/kg/day 2 females died prematurely; a mild bilateral ventricular dilatation was observed in both animals at gross necropsy. There were no effects on the number of corpora lutea, post-implantation loss, number of live foetuses or mean foetal weight. External, skeletal and visceral malformations were seen from the dose level of 1.2 mg/kg/day. A dose-dependent increase in the number of foetuses with cleft palate was seen from 1.2 mg/kg/day. At 2.0 mg/kg/day great vessels malformations (dilatation of pulmonary trunk and/or aortic arch) were noted in 4 foetuses from 4 litters, and fused sternebrae were seen in 38 foetuses from 10 litters. Based on the results of the

study, the NOAEL for both maternal and developmental toxicity was set at the lowest tested dose of 0.6 mg/kg/day (maternal AUC0-24 = 7160 ng x h/mL).

In the rabbit study, mavacamten was detected in the embryos and extra-embryonic tissues (foetal envelopes, placenta, amniotic fluid) ca. 24 hours after dosing on GD12. Mavacamten was distributed in these tissues, with individual embryonic tissue to plasma concentration ratios ranging from 0.09 to 0.15 across the dose levels; however, as the analyses were not performed under GLP, the results are considered to serve indicative purposes only.

Based on the results of the developmental toxicity studies, mavacamten demonstrated a potential for foetal toxicity and teratogenicity in two species and should be regarded as a potential human developmental toxicant. The maternal plasma concentrations at the NOAEL were below the anticipated clinical exposure at the maximal recommended human dose. Considering that the observed effects were seen at maternal exposure levels below the anticipated clinical exposure and the observed effects are considered to be related to the pharmacologic mode of action, the use of mavacamten is contraindicated during pregnancy and in women of child-beating potential (WOCBP), unless the conditions listed in Section 4.6 of SmPC are met.

It is further proposed by the applicant to add the following sentence to the SmPC: “Women of childbearing potential must use effective contraception during treatment and for 6 months after discontinuation of Camzyos, since it takes approximately 5 half-lives (approximately 45 days for CYP2C19 normal metabolisers and 115 days for CYP2C19 poor metabolisers) to eliminate mavacamten from the body after treatment discontinuation (see sections 4.4 and 5.2).” Therefore, before initiation of treatmentin women of childbearing potential, a negative pregnancy test result must be available and counselling should be provided regarding the serious risk to the foetus. The period of 6 months has been calculated as a 5 half-life times of mavacamten in poor CYP2C19 metabolizers. While this is endorsed, it is noted that the half-life times are calculated based on the single dose studies, and for mavacamten significant accumulation after repeated dosing was noted (up to factor 8 in humans). The applicant was asked to justify whether a period of 5 half-life times is sufficient, considering accumulation of mavacamten in humans, and to compare the plasma levels of mavacamten after this period to the plasma concentrations in maternal animals at which developmental effects were noted. The applicant has provided the results of the PBPK modelling which indicated that the predicted mean mavacamten concentrations 4 months after end of treatment would be at least factor 5 lower than the NOEL levels and at least factor 9 lower than the LOAEL levels in the rabbit and rat EFD studies. It is therefore concluded that the recommendation of the 6-month waiting period after the treatment in Section 4.6 of the SmPC is supported by the available data and is considered to offer sufficient protection against potential adverse effects on the foetus in women of childbearing potential.

In the GLP-compliant pre- and postnatal developmental toxicity study, mavacamten was administered to pregnant dams from GD6 to PND20 at the dose levels of 0 (vehicle controls), 0.3, 0.75 and 1.5 mg/kg/day. The toxicokinetic analysis was not performed, but maternal exposure was estimated from the results of the developmental toxicity study with rats in which maternal F0 AUC0-24 of 16500 ng x h/mL was achieved on GD12 at the same dose level. Pup exposure and excretion of mavacamten in the milk of lactating dams were not evaluated. Intact offspring that were found dead or euthanized for humane reasons during PND 0–4 were necropsied using a fresh dissection technique, which included examination of the heart and major vessels. The pups which were not selected as F1 generation were subjected to gross necropsy on PND 21. The selected F1 generation pups were kept untreated and assessed for sexual developmental landmarks (balano-preputial separation, vaginal patency), sensory function and neurobehavioral development. The F1 animals not selected for breeding were necropsied on PND 73-78; F1 animals selected for breeding were euthanized in PND 123-128 (males) or GD 15 (females). The ovaries and uterus were examined for number and distribution of corpora lutea,

implantation sites, embryos, and early resorptions. Tissues with gross lesions were preserved, but no histopathological evaluation was conducted.

Mavacamten administration did not cause maternal toxicity or adverse effects on the number of implantation sites, unaccounted-for sites, gestation length and parturition in F0 females. No statistically significant effects were also seen on the mean number of F1 pups born, live litter size, percentage of males per litter at birth, and postnatal survival. However, it is noted that, although not statistically significant, a higher number of pups was found dead or euthanized in extremis from PND 0 to the selection of F1 generation (pups (litter): 3(1), 6(3), 6(6) and 12(7)). Visceral malformation consisting of an intraventricular septal defect (1 mm in diameter opening in the anterior portion of the septum, an absent bicuspid valve, and a small tricuspid valve) was noted for one foetus in the 1.5 mg/kg/day group, while situs inversus (the trachea, oesophagus, heart, great and major vessels were laterally transposed) and lobular dysgenesis of the lungs (only 1 lobe present) were noted for one foetus in the 0.75 mg/kg/day group. No other malformations were noted. Although the incidence of the observed findings was very low, they are consistent with the findings reported in the developmental toxicity with rats and are therefore considered to be likely related to the mavacamten administration. Therefore the lowest tested dose level of 0.3 mg/kg/day is considered the NOAEL for developmental defects. The necropsy of non-selected F1 pups on PND21 was uneventful.

No adverse effects on development, fertility and reproductive performance were seen in the F1 generation kept untreated until PND128 (males) and GD15 (females). Reproductive performance, mean numbers of corpora lutea, implantation sites, and intrauterine survival of the F2 embryos were not different from controls in the treated F1 animals. Also no effects on embryo-foetal development were noted in the F2 generation foetuses. Based on the results of the study, the highest administered dose level of 1.5 mg/kg/day is considered to be the NOAEL for F0 maternal toxicity and F1 reproductive and maternal toxicity.

No studies in juvenile animals were performed. As mavacamten is developed for the treatment of symptomatic obstructive hypertrophic cardiomyopathy in adult patients, juvenile studies are not warranted.

2.4.4.6. Toxicokinetic data

Exposure to mavacamten increased approximately dose-proportionally in mice and dogs and dose-proportionally or slightly more than dose-proportionally in rats (especially at the later time points). In mice, slight accumulation was observed (accumulation ratio up to 1.8). In rats and dogs, significant accumulation was observed (up to approximately 6-fold in rats and up to approximately 9-fold in dogs). In rats, accumulation was observed up to 90 days, but not or only to a limited extent thereafter. In dogs, accumulation was observed primarily in the first half of the studies and not or limited thereafter. No consistent gender effect was observed in mice and dogs. In rats, exposure was slightly higher in females (maximally up to two-fold) at doses larger than 1 mg/kg. This can possibly be explained by a generally higher rate of metabolism in male rats and is not likely to be relevant for humans.

Exposure was low in non-clinical species. Only in mice, exposures higher than the expected clinical exposure were reached (up to 8x the human exposure). In rats and dogs, exposures were below the expected clinical exposure in all studies.

In the embryo-foetal development study in rats, exposure in the pregnant females increased slightly more than dose-proportionally. In the embryo-foetal development study in rabbits, exposure in the pregnant females increased approximately dose-proportionally. Exposure in the foetuses was not investigated.

2.4.4.7. Local Tolerance

As mavacamten is intended to be taken orally and no local gastro-intestinal tract reactions were noted in the available toxicity studies, no local tolerance studies are warranted.

2.4.4.8. Other toxicity studies

No separate studies were conducted on antigenicity, immunotoxicity and the dependence potential of mavacamten. As mavacamten is a small molecule, no antigenic response is expected. The available repeated dose toxicity studies gave no indication of adverse effects on primary and secondary lymphatic organs and tissues. Available repeated dose toxicity studies did not indicate any adverse effects on the central nervous system.

As the metabolic profile of mavacamten was similar between the preclinical species and humans, and all metabolites detected in plasma were <10% of the parent, no separate studies on metabolites are required.

The applicant has presented the overview of the batches used in the preclinical studies. In addition, a 3-month repeated dose oral toxicity study was conducted with rats in which two batches of mavacamten were tested, one with pure substance and another spiked with a specified impurity . Administration of both batches at a dose level of 0.3 mg/kg/day caused higher body weight and body weight gain, as well as higher heart, adrenal and spleen weights in female animals. No effects were noted in males. The exposures to mavacamten were comparable between the batches. No differences in the toxicological profiles were noted between the two batches. Although the amount of the specified impurity may have been too low to detect meaningful effects, the study is considered sufficient to consider the specified impurity qualified up to the proposed specification limit.

For the second specified impurity, the specification limit is proposed based on the qualification threshold in accordance with ICH Q3A guideline. The substance is classified as ICH M7 class 5 substance according to (Q)SAR expert-rule based prediction using Lhasa Limited Derek Nexus Version 6.1 and (Q)SAR statistical-based prediction using Leadscope Inc. Leadscope Model Applier Version 3.0.

2.4.5. Ecotoxicity/environmental risk assessment

Summary of main study results

Substance (INN/Invented Name): Mavacamten			
CAS-number (if available):			
PBT screening		Result	Conclusion
Bioaccumulation potential- log K_{ow}	OECD107	2.9 pH 5 and 7	Potential PBT (N)
Phase I			
Calculation	Value	Unit	Conclusion
$PEC_{surface\ water}$, refined (prevalence, literature)	0.011	µg/L	> 0.01 threshold (Y)

Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	Test protocol	Results			Remarks
Adsorption-Desorption	OECD 106 or …	*P.M.*			
Ready Biodegradability Test	OECD 301LETTER	*P.M.*			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	*P.M.*			
Phase IIa Effect studies					
Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	*P.M.*	µg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	*P.M.*	µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	*P.M.*	µg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	*P.M.*	µg/L	
Phase IIb Studies					
Bioaccumulation/*Species*	OECD 305	BCF	*P.M.*	L/kg	
Aerobic and anaerobic transformation in soil	OECD 307	DT50 %CO_2	*P.M.*		
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect	*P.M.*	mg/ kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	*P.M.*	mg/ kg	
Earthworm, Acute Toxicity Tests/*Species*	OECD 207	NOEC	*P.M.*	mg/ kg	
Collembola, Reproduction Test/*Species*	ISO 11267	NOEC	*P.M.*	mg/ kg	
Sediment dwelling organism/*Species*		NOEC	*P.M.*	mg/ kg	

2.4.6. Discussion on non-clinical aspects

Pharmacology

A cytotoxicity assay with mavacamten showed no evidence of cytotoxicity in an assay which evaluated cell count, nuclear size, DNA structure, mitochondrial membrane potential, mitochondrial mass, or cytochrome c release in HepG2 cells. Increased cell membrane permeability was noted at minimum and half-maximal concentrations of 4.08 and >10µM, respectively. Increased cell permeability was not associated with cytotoxicity in vitro at concentrations up to 7-fold higher than the minimum effective concentration for increased cell permeability. In dog and rat, there were no findings that could be correlated to increased cell permeability. Increased cell permeability in HepG2 cells was not considered toxicologically relevant by the applicant, which is acknowledged.

In safety pharmacology studies in rat and dog, QT prolongation was observed after dosing with mavacamten. After extensive in vitro studies to evaluate the mechanism behind this effect, the QT-prolongation was considered to be hERG independent with low torsadogenic or proarrhythmic risk. It was considered likely that the acute QT shortening, and longer-term QT prolongation was the result of adaptive responses to sustained myosin inhibition in ventricles with normal physiology due to changes in early repolarization currents, primarily by downregulation of the Ito and IKATP potassium channels in response to sustained myosin inhibition. In contrast, in HCM, both these currents are already abrogated. In addition, INaL is also upregulated in HCM, which is a current that is moderately inhibited by mavacamten with potentially beneficial effects in mavacamten. Therefore, in HCM, the moderate but consistent INaL blockade by mavacamten coupled with its salutary functional effects most likely offset any mild downregulation of early repolarizing currents, leading to a neutral QT/APD response, or even shortening, as observed in HCM. Thus, it is considered that there is a decreased sensitivity of HCM hearts to mechanisms that lead to QT-prolongation after exposure to mavacamten in the healthy heart.

Pharmacokinetics

Concentrations of mavacamten (MYK-461) and MYK-460 were measured in plasma of mice, rats, rabbits and dogs with validated LC-MS/MS methods. The validation was adequate regarding calibration, accuracy, precision, matrix effect and dilution integrity. Stability at room temperature was not reported in rats and dogs. In the response, the applicant stated that after ~22 hours, -18.6% difference was noted in rat plasma and -5.3% difference in dog plasma compared to a fresh sample, when stored at room temperature during method development. During the analyses of the samples, samples were only at room temperature during the extraction procedure, for maximally 2 h. Possible degradation during 2 h is not expected to have had a significant effect on the results.

Oral bioavailability compared to IV administration was complete in mice and 75%, 87% and 47% in rats, dogs and monkeys, respectively. The bioavailability of mavacamten administered via capsules to dogs increased from 16% to 64% when mavacamten was micronized.

In rats, mavacamten-related radioactivity was highest in the diaphragm, oesophagus, kidneys, liver, myocardium, salivary glands, adrenal glands, skeletal muscle, small intestine and stomach mucosa. Low levels were found in the CNS. Mavacamten-related radioactivity was found in the skin and eye, indicating that mavacamten should be investigated for its phototoxic potential.

Blood-to-plasma ratios in blood from mouse, rat, dog, cynomolgus monkey and human were reported as 0.72, 0.82, 0.78, 0.82 and 0.79 in mouse, rat (~33%), dog (~25%), monkey and human (~30% in RBC). This indicates no preferential distribution to red blood cells.

After in vitro incubation of [^{14}C]mavacamten with liver microsomes or hepatocytes from mouse, rat, dog, monkey, and human, low levels of metabolites (generally <5%) were found. In an in vivo study in rats, parent compound was the main component in plasma, comprising 45% and 67% of total radioactivity in orally and IV dosed rats, respectively. Unidentified metabolites were found in plasma, urine and bile of rats in considerable amounts. Although clinically, there is uncertainty regarding the metabolite profile in CYP2C19 poor metabolisers, this cannot be solved in the rat. Moreover, in the rat study, plasma was only sampled up to 72 h. It should be solved clinically. The issue regarding the unidentified metabolites in the rat is not further pursued.

After oral administration to bile duct-intact rats, 58% was excreted in faeces, 23% in urine and 1.7% in expired air. After IV administration to bile duct-cannulated rats, 41% was excreted in bile, 7.6% in faeces and 31% in urine.

Toxicology

The toxicological behaviour of mavacamten was investigated in accordance with the requirements of ICH M3(R2). Pivotal GLP-compliant studies were conducted in rats and dogs as test species. It is noted that the achieved exposure in the conducted studies was below the anticipated clinical exposure at the MRHD, as the dosing levels were limited by severe cardiac toxicity and lethality in the healthy test animals. Due to this, the studies may not have been sufficient to assess the potential secondary pharmacologic effects of mavacamten; however, as there were no significant safety concerns identified in the submitted pharmacological studies, this limitation can be accepted.

Single doses of mavacamten up to 7 mg/kg were well tolerated without signs of toxicity in dogs, while administration of 30 mg/kg mavacamten resulted in animals being sacrificed in moribund condition.

Repeated dose toxicity was investigated in the studies of up to 26 weeks duration in rats and up to 39 weeks duration in dogs, with the animals dosed up to 3 mg/kg/day. The main adverse effects seen in both species were observed in the heart and are considered related to the primary pharmacodynamic action of the substance. Cardiac failure at the top tested dose levels caused increased mortality and early euthanasia of the test animals (rats: ≥1.2 mg/kg/day, corresponding to AUC0-24 ≥9150 ng x h/mL; dogs: ≥0.45 mg/kg/day (males), corresponding to AUC0-24 = 17200 ng x h/mL). Effects observed in other organs and tissues in both species (centrilobular hepatocellular necrosis, centrilobular congestion/vacuolation; pulmonary congestion/oedema, spleen oedema) are considered secondary to the cardiac failure and reduced cardiac output. In rats, adverse heart changes included increased heart weight correlated with cardiac hypertrophy, myocardial and endocardial degeneration/inflammation, cartilaginous/osseous metaplasia and valvular inflammation. Decreased systolic function was seen in the 26-week study at the dose level of 1.2 mg/kg/day (AUC0-24 of ≥8490 ng x h/mL), which resolved after the recovery period. There was no consistent effect on the levels of cardiac stress biomarkers (NT-proANP, NT-proBNP and troponin I).

The findings in dogs were in general comparable to the findings in rats. In general, mostly somewhat higher exposure was achieved at the same dose levels in male animals compared to females. Male dogs appeared to be more sensitive to mavacamten toxicity, with the dose level of 0.45 mg/kg/day causing mortality and early euthanasia in the 13-week study in males but not in females (AUC_{0-24} = 17200 ng x h/mL in males vs 12300 ng x h/mL in females). The applicant suggested that this apparently higher male sensitivity to toxicity of mavacamten was caused by a higher exposure achieved in male dogs, which is supported by the toxicokinetic data from the 6-week and 3-month dog studies. Next to histopathological changes, increased heart rate and QTc prolongation were reported at ≥0.18 mg/kg/day in the 13- and 39-week studies ($AUC0_{-24}$ ≥3800 ng x h/mL); also, QRS interval was prolonged in females administered 0.45 mg/kg/day (AUC_{0-24} = 12500 ng x h/mL) in the 39-week study. The changes were reversible upon recovery. The QTc interval prolongation is considered to be

an indirect effect mediated by the on-target reduction in systolic cardiac function and not relevant for patients with obstructive hypertrophic cardiomyopathy, for whom cardiac hypercontractivity is normally observed. Cardiac ventricular dilation, reversible upon recovery, was seen in the 13-week study at 0.45 mg/kg/day at the necropsy of the early decedents and one surviving female, and in the 39-week study in the high-dose males and females (0.30 and 0.45 mg/kg/day, respectively).

The compliant genotoxicity package indicated that mavacamten is not genotoxic. Mavacamten showed no carcinogenic potential when administered for 104 weeks to rats or for 6 months to transgenic mice.

Mavacamten did not show adverse effects on male or female fertility and early embryonic development up to the highest tested dose of 1.2 mg/kg/day. However, as the achieved exposure levels in the submitted FEED study were below the anticipated clinical exposure, this study is not considered to provide sufficient evidence for the lack of effects of mavacamten on fertility. However, it is acknowledged that secondary pharmacodynamics data do not indicate possible concerns. In the developmental toxicity studies with rats and rabbits, mavacamten showed fetotoxic and teratogenic potential in both species at maternal exposure levels below the anticipated clinical exposure at the MRHD. In rats, increased post-implantation loss, reduced foetal body weight and skeletal and visceral malformations were seen in the absence of maternal toxicity. Skeletal malformations were manifested mainly as fused sternebrae, whereas visceral malformations were observed in 2 foetuses of two litters and included one complete situs inversus and one foetus with the absence of the right atrioventricular valve associated with a ventricular septum defect. Although the visceral effects were observed only in two foetuses, they were still considered related to the test substance administration based on their nature, the same effects seen in the pre- and postnatal developmental toxicity rat study and the active substance pharmacodynamic mode of action. In rabbits, external, skeletal and visceral malformations were observed, with a dose-dependent increase in the number of foetuses with cleft palate from 1.2 mg/kg/day and great vessels malformations (dilatation of pulmonary trunk and/or aortic arch) and fused sternebrae at 2 mg/kg/day. Mavacamten was detected in rabbit embryos and extra-embryonic tissues (foetal envelopes, placenta, amniotic fluid) ca. 24 hours after dosing on GD12, with individual embryonic tissue to plasma concentration ratios ranging from 0.09 to 0.15 across the dose levels (non-GLP measurements). Considering that mavacamten demonstrated clear teratogenic potential in two species at maternal exposure levels below the anticipated clinical exposure, and the observed effects are considered to be related to the pharmacologic mode of action, the use of mavacamten is contraindicated during pregnancy and in women of child-bearing potential, unless the conditions listed in Section 4.6 of the SmPC are met.

It is further proposed by the applicant to add the following sentence to the SmPC: “Women of childbearing potential must use effective contraception during treatment and for 6 months after discontinuation of Camzyos, since it takes approximately 5 half-lives (approximately 45 days for CYP2C19 normal metabolisers and 115 days for CYP2C19 poor metabolisers) to eliminate mavacamten from the body after treatment discontinuation.” Therefore, before initiation of treatmentin women of childbearing potential, a negative pregnancy test result must be available and counselling should be provided regarding the serious risk to the foetus. The applicant has provided the results of the PBPK modelling which indicated that the predicted mean mavacamten concentrations 4 months after end of treatment would be at least factor 5 lower than the NOEL levels and at least factor 9 lower than the LOAEL levels in the rabbit and rat EFD studies. It is therefore concluded that the recommendation of the 4-month waiting period after the treatment in Section 4.6 of the SmPC is supported by the available data and is considered to offer sufficient protection against potential adverse effects on the foetus in women of childbearing potential.

In the pre- and postnatal developmental toxicity study, mavacamten administration did not cause maternal toxicity or adverse effects on the number of implantation sites, unaccounted-for sites,

gestation length and parturition in F0 females up to the highest tested dose level of 1.5 mg/kg/day. No statistically significant effects were also seen on the mean number of F1 pups born, live litter size, percentage of males per litter at birth, and postnatal survival. Visceral malformations manifested as an intraventricular septal defect (1 mm in diameter opening in the anterior portion of the septum, an absent bicuspid valve, and a small tricuspid valve) and one situs inversus (laterally transposed trachea, oesophagus, heart, great and major vessels) with lobular dysgenesis of the lungs (only 1 lobe present) were noted for one foetus in the 1.5 mg/kg/day and one foetus in the 0.75 mg/kg/day groups, respectively. Although the incidence of the observed findings was very low, they are consistent with the findings reported in the developmental toxicity with rats and are therefore considered to be likely related to the mavacamten administration. Therefore the lowest tested dose level of 0.3 mg/kg/day is considered the NOAEL for developmental defects. Mavacamten did not cause adverse effects on the development, fertility and reproductive performance of the F1 generation and on embryo-foetal development of the F2 generation foetuses. The highest administered dose level of 1.5 mg/kg/day is considered to be the NOAEL for F0 maternal toxicity and F1 reproductive and maternal toxicity. The toxicokinetic analysis was not performed, but maternal exposure was estimated from the results of the developmental toxicity study with rats in which maternal F0 AUC_{0-24} of 16500 ng x h/mL was achieved on GD12 at the same dose level. Pup exposure and excretion of mavacamten in the milk of lactating dams were not evaluated.

As mavacamten is developed for the treatment of symptomatic obstructive hypertrophic cardiomyopathy in adult patients, juvenile studies are not warranted.

No local tolerance studies were conducted. This is endorsed because mavacamten is intended to be taken orally, and no local gastro-intestinal tract reactions are noted in the available toxicity studies.

No antigenicity or immunotoxicity studies have been conducted. As mavacamten is a small molecule, no antigenic response is expected. In addition, the available repeated dose toxicity studies gave no indication of adverse effects on primary and secondary lymphatic organs and tissues.

No separate dependence studies have been conducted. Available repeated dose toxicity studies did not indicate any adverse effects on the central nervous system.

As toxicokinetic data indicate the distribution of mavacamten to skin and eyes, the applicant is requested to investigate its phototoxic potential in accordance with ICH M3 (R2) guideline. The applicant has provided the results of the UV-VIS absorbance of mavacamten which indicate the molar extinction coefficient (MEC) of 246 L/mol x cm in the wavelength range of 290-700 ng. Based on this mavacanten is not considered to be sufficiently photoreactive to result in direct cytotoxicity.

As the metabolic profile of mavacamten was similar between the preclinical species and humans, and all metabolites detected in plasma were <10% of the parent, no separate studies on metabolites are considered necessary.

Based on the conducted studies, the specified impurity s considered qualified up to the proposed specification limit. For the second specified impurity, the specification limit is proposed based on the qualification threshold in accordance with ICH Q3A guideline. According to Section 3.2.S.3.2.5 of the provided dossier, the substance is classified as ICH M7 class 5 substance; as it is predicted to be not mutagenic both by an expert-rule based and statistical-based QSARs.

Mavacamten is considered not to be PBT, nor vPvB.

2.4.7. Conclusion on the non-clinical aspects

Overall, the preclinical toxicology program was conducted according to ICH M3 guideline requirements.

The pivotal studies conducted in rats and dogs demonstrated adverse effects in the heart, which are considered related to the primary pharmacodynamic action of mavacamten. It is noted that the achieved exposure in the conducted studies was below the anticipated clinical exposure at the MRHD, as the dosing levels were limited by severe cardiac toxicity and lethality in the healthy test animals. Due to this, the studies may not have been sufficient to assess the potential secondary pharmacologic effects of mavacamten; however, as there were no significant safety concerns identified in the submitted pharmacological studies, this limitation was accepted. Adverse effects seen in the repeated dose studies included increased heart weight, cardiac hypertrophy, myocardial and endocardial degeneration/inflammation, cartilaginous/osseous metaplasia (rats), valvular inflammation, ECG changes (increased heart rate, QTc and QRS prolongation in dogs) and ventricular dilation. The ECG changes and ventricular dilation were reversible in recovery animals. At high dose levels, cardiac failure was seen, causing mortality and early euthanasia of the test animals. Effects observed in other organs and tissues (centrilobular hepatocellular necrosis, centrilobular congestion/vacuolation, pulmonary congestion/oedema, spleen oedema) were considered secondary to the cardiac failure and reduced cardiac output.

Mavacamten is not genotoxic or carcinogenic and does not adversely affect fertility at the tested dose levels. Developmental toxicity studies in rats and rabbits demonstrated embryo-foetal toxicity in both species at maternal exposure levels below the anticipated clinical exposure at the MRHD, which is considered to be related to its pharmacologic mode of action. Mavacamten is suspected of causing congenital malformations when administered to pregnant women and is therefore contraindicated during pregnancy and in women of child-bearing potential, unless the conditions listed in Section 4.6 of the SmPC are met. Women of childbearing potential must use effective contraception during treatment and for 6 months after discontinuation. No information is available on its excretion in animal milk.

In summary, mavacamten is considered approvable from the preclinical point of view.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 3 Error! Reference source not found.outlines the clinical studies that support the use of mavacamten for treatment of oHCM, including

- 12 Phase 1 clinical pharmacology studies
- 2 Phase 2 studies
    - 1 Phase 2, open-label, pilot study in subjects with symptomatic oHCM (MYK-461-004 [PIONEER-HCM]);

- 1 Phase 2, double-blind, placebo-controlled study in subjects with symptomatic nHCM (MYK-461-006 [MAVERICK-HCM]);

- 2 pivotal Phase 3, double-blind, placebo-controlled studies in subjects with symptomatic NYHA Class II-III oHCM (MYK-461-005 [EXPLORER-HCM]) and in subjects with symptomatic oHCM who were referred for consideration of septal reduction therapy (SRT)(MYK-461-017/CV027006 [VALOR-HCM]). VALOR-HCM includes a long-term follow-up (LTFU) period.
- 2 ongoing, long-term extension (LTE) studies (MYK-461-007 [MAVA-LTE] and MYK-461-008 [PIONEER-OLE]) that provide longer-term data in subjects previously enrolled in the pivotal Phase 3 study and the Phase 2 studies.

As of the 31-Aug-2021 (07-Feb-2022 for the RCT portion of MYK-461-017), all studies are complete, with the exception of the 2 ongoing LTE studies and the VALOR-HCM study.

Table 3. Summary of mavacamten clinical studies

Study Number (Name)	Study Title Study Status	Study Population Number of Subjects	Dosing Regimen (All drug was administered by mouth)
Phase 1 Studies			
MYK-461-001	Safety, Tolerability, Preliminary Pharmacokinetics and Pharmacodynamics of Single Ascending Oral Doses of MYK-461 in Patient Volunteers with Hypertrophic Cardiomyopathy	Adults with HCM n = 15	Single dose, suspension 48, 96, and 144 mg in 8 aliquots every 15 minutes
MYK-461-002	Safety, Tolerability, Preliminary Pharmacokinetics and Pharmacodynamics of Single Ascending Oral Doses of MYK-461 in Healthy Volunteers	Healthy adult males n = 48	Single dose, suspension 1 and 2 mg; 6, 12, 24, and 48 mg in 8 aliquots every 15 minutes
MYK-461-003	A Phase 1, Double-blind, Randomized, Placebo-controlled, Ascending Multiple Oral Dose Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacokinetics of MYK-461 in Healthy Volunteers	Healthy adults n = 60	Multiple doses (28 days), tablet 1 mg BID, 3 mg BID, 12.5 mg QD, 18.5 mg QD, and 25 mg QD
MYK-461-009	An Open-label Drug Interaction Study to Assess the Effects of Verapamil on MYK-461 Pharmacokinetics in Healthy Subjects	Healthy adults n = 25	Single dose, tablet Mavacamten cohort: 25 mg on Day 1 Mavacamten + verapamil cohort: Verapamil sustained-release 240 mg followed 4 hours later by mavacamten 25 mg on Day 1 and daily verapamil sustained release 240 mg through Day 28

Study Number (Name)	Study Title Study Status	Study Population Number of Subjects	Dosing Regimen (All drug was administered by mouth)
MYK-461-010	An Open-label Pharmacokinetic Drug-Drug Interaction Study Between Mavacamten and Estrogen- and Progestin-based Hormonal Contraception in Healthy Women	Healthy adult females n = 13	Multiple doses (17 days), tablet Period 1: 35 µg ethinyl estradiol + 1 mg norethindrone on Day 1 Period 2 (after 7-10 day washout): 25-mg loading dose of mavacamten on Day 1 and a second 25-mg loading dose on Day 2, followed by a daily dose of 15 mg on Days 3 to 17, for a total of 17 doses; 35 µg ethinyl estradiol + 1 mg norethindrone on Day 17

Study Number (Name)	Study Title Study Status	Study Population Number of Subjects	Dosing Regimen (All drug was administered by mouth)
MYK-461-011	Open-label Study of the Pharmacokinetics of MYK-461 in Healthy Japanese and Caucasian Subjects	Healthy Japanese and Caucasian adults n = 28	Single-dose, tablet Japanese: single dose of 5, 15, or 25 mg Caucasians: single dose of 25 mg
MYK-461-012	An Open-label Study of the Pharmacokinetics of Single-dose Mavacamten in Healthy Adults Who Are Normal or Poor CYP2C19 Metabolizers Based on Genotype	Healthy Asian adults, normal or poor CYP2C19 metabolizers n = 16	Single-dose, capsule Mavacamten 15 mg
MYK-461-013	An Open-label, Single-dose, Mass-balance Study to Assess the Absorption, Metabolism, and Excretion of [14C]-Mavacamten in Healthy Males	Healthy adult males n = 6	Single-dose, capsule Mavacamten 15 mg [14C] labeled
MYK-461-014	The Relative Bioavailability of the Intended Commercial Capsule Formulation vs. the Initial Capsule Formulation of Mavacamten and the Effect of Food on its Pharmacokinetics	Healthy subjects n = 24	Single-dose, capsule Mavacamten 15 mg: • initial capsule, fasted • intended commercial capsule, fasted • intended commercial capsule, fed
MYK-461-015	A Phase 1, Open-label, Nonrandomized, 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	Adult participants with normal and reduced (Child Pugh Class A and B) hepatic function n = 27	Single-dose, capsule Mavacamten 25 mg

Study Number (Name)	Study Title Study Status	Study Population Number of Subjects	Dosing Regimen (All drug was administered by mouth)
MYK-461-016	The Effect of Mavacamten on the Pharmacokinetics of the CYP3A4 Substrate, Midazolam, in Healthy Participants	Healthy adults n = 13	Multiple doses (16 days), capsule Midazolam 5 mg on Day 1 Mavacamten 25 mg on Days 2 and 3 Mavacamten 15 mg on Days 4-17 Midazolam 5 mg on Day 17
MYK-461-018	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 Completed	Healthy adults n = 28	Single-dose, capsule Mavacamten cohort: 15 mg on Day 1 Mavacamten + omeprazole cohort: omeprazole 20 mg daily from Day -3 to Day 28 and mavacamten 15 mg on Day 1
Phase 2 Studies			
MYK-461-004 (PIONEER-HCM)	A 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 (PIONEER-HCM) Completed	Adults with symptomatic oHCM Part A: n = 11 Part B: n = 10	Mavacamten tablet: 2, 5, 10, 15, or 20 mg once daily for 12 weeks Part A: Starting dose of 10 mg for subjects who weigh ≤ 60 kg and 15 mg for subjects who weigh > 60 kg Part B: Starting dose 2 mg Parts A and B may have had dose adjustments beginning Week 4
MYK-461-006 (MAVERICK-HCM)	A Randomized, Double-blind, Placebo-controlled, Concentration-guided, Exploratory Study of Mavacamten (MYK-461) in Patients with Symptomatic Non-obstructive Hypertrophic Cardiomyopathy (nHCM) and Preserved Left Ventricular Ejection Fraction (MAVERICK-HCM) Completed	Adults with symptomatic nHCM n = 59 (mavacamten 40, placebo 19)	Mavacamten capsule: 2.5, 5, 10, or 15 mg QD, or placebo, adjusted for plasma drug levels, for 16 weeks The starting dose was mavacamten 5 mg once daily. At Week 6, doses were adjusted based on plasma concentrations at Week 4 to achieve target mavacamten concentrations.

Study Number (Name)	Study Title Study Status	Study Population Number of Subjects	Dosing Regimen (All drug was administered by mouth)
Phase 3 Studies			
MYK-461-005 (EXPLORER-HCM)	A Randomized, Double-blind, Placebo-controlled Clinical Study to Evaluate Mavacamten (MYK-461) in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy (EXPLORER-HCM)	Adults with symptomatic oHCM n = 251 (mavacamten 123, placebo 128)	Mavacamten capsule 2.5, 5, 10, or 15 mg or placebo once daily for 30 weeks The starting dose was mavacamten 5 mg once daily; dose adjustments were possible at Weeks 6, 8, 10, 14, 18, 22, 26 Dose increase was only possible at Week 8 or 14.

MYK-461-017 (VALOR-HCM)	A Randomized, Double-blind, Placebo-controlled Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy Who Are Eligible for Septal Reduction Therapy (VALOR-HCM)	Adults with symptomatic oHCM who were referred for consideration of septal reduction therapy (SRT) withing 12 months prior screening Double-Blind Period n = 112 (mavacamten 56, placebo 56) Active-Controlled Period/LTFU n = 108 mavacamten (former mavacamten 56, former placebo 52)	Double-Blind Period *randomization to Week 16* Starting regimen: mavacamten 5 mg QD or matched placebo Up-titration evaluation at Weeks 8 and 12 based on the LVEF and LVOT gradient measured by ECHO (max dose: 15 mg) Down-titration evaluation at Week 4 for safety, or any time if LVEF <50% Active-Controlled Period *Week 16 to 32* Placebo arm crosses over to mavacamten at Week 16 with the same 5 mg starting dose and equivalent adjustment schedule (up-titration at 8 and 12 weeks of exposure; down-titration at 4 weeks of exposure) as the mavacamten group during the placebo-controlled period During the active controlled period, patients who started on mavacamten at Day 1 remain on mavacamten therapy with no scheduled dose changes. LTE Period *Week 32 to 128* All patients remain on mavacamten with potential dose titration based on ECHO parameters. LTFU Day 1 of the first mavacamten dose until EOT for the mavacamten group, and from Week 16 until EOT for the “placebo to mavacamten” group.
LTE Studies			
MYK-461-007	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 (MAVA-LTE) Ongoing	Adults with symptomatic nHCM (n = 44) or oHCM (n = 231)	Mavacamten capsule 2.5, 5, 10, or 15 mg QD for up to 5 years

MYK-461-008	An Open-label Extension Study of Mavacamten (MYK-461) in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy Previously Enrolled in Study MYK-461-004 (PIONEER-HCM) (PIONEER-OLE) Ongoing	Adults with symptomatic oHCM (n = 13)	Mavacamten capsule 5, 10, or 15 mg QD; 5 mg starting dose for up to 5 years

BID = twice daily; CYP = cytochrome P450; ECHO = electrocardiogram; EOT = end of treatment; HCM = hypertrophic cardiomyopathy; LTE = long-term extension; LTFU = long-term follow-up; MAVA = mavacamten; nHCM = nonobstructive hypertrophic cardiomyopathy; oHCM = obstructive hypertrophic cardiomyopathy; OLE = open-label extension; QD = once daily

2.5.2. Clinical pharmacology

Pharmacokinetics

Mavacamten is a reversible inhibitor of cardiac myosin that is developed for the treatment of obstructive hypertrophic cardiomyopathy (oHCM) in adults. The recommended starting dose is 2.5 mg orally once daily for CYP2C19 poor metabolisers and 5 mg orally once daily for CYP2C19 intermediate, normal, rapid and ultra-rapid metabolisers (non-poor metabolisers). After 4 weeks, the dose should be decreased to 2.5 mg once daily or dosing should be paused if on 2.5 mg if the LVOT gradient with Valsalva manoeuvre is <20 mmHg. Twelve weeks after treatment initiation, the dose may be stepwise increased to a maximum of 5 mg once daily for CYP2C19 poor metabolisers and a maximum of 15 mg once daily for CYP2C19 intermediate, normal, rapid and ultra-rapid metabolisers in case of persistent symptoms of obstructive hypertrophic cardiomyopathy and LVOT gradient with Valsalva manoeuvre >30 mmHg and LVEF > 55%. The dose is administered once daily independent of a meal. Available strengths are 2.5 mg, 5 mg, 10 mg and 15 mg hard capsules.

The clinical pharmacology of mavacamten was assessed in healthy volunteers (11 studies) and patients with obstructive hypertrophic cardiomyopathy (1 study). Dedicated healthy volunteer studies assessed the effect of food, relative bioavailability, intrinsic factors (race and hepatic impairment), and several drug-drug interactions (DDI) on the pharmacokinetics of mavacamten. Furthermore, a mass-balance study characterised the absorption, metabolism, and excretion of mavacamten. In addition, sparse blood samples were obtained in clinical efficacy and safety studies (6 studies). Furthermore, several *in vitro* studies were performed investigating the permeability, plasma protein binding, blood-to-plasma ratio, metabolic stability in human liver microsomes and human hepatocytes and if mavacamten was a substrate of CYP enzymes and transporters. Furthermore, *in vitro* studies were performed to investigate whether mavacamten was an inhibitor or inducer of CYP enzymes or transporters.

Physicochemical properties

Mavacamten ($C_{15}H_{19}N_3O_2$) has a molecular weight of 273.33 g/mol and a pKa of 9.03 ± 0.09. Furthermore, mavacamten is poorly soluble in water (pH independent over the physiologically relevant pH range). Mavacamten can be considered a BCS class II compound, since mavacamten has low solubility and high absorption *in vivo*.

Mavacamten has one chiral centre and is in the (S)-configuration. No inter-conversion to the R-enantiomer occurs *in vivo*.

Analytical methods

Mavacamten was analysed in K_2-EDTA plasma using LC-MS/MS. Four high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods were developed for the quantitation of mavacamten from human plasma and urine. Based on the provided data, the analytical methods used to determine mavacamten in plasma appear to be sufficiently validated.

Population pharmacokinetic (PopPK) modelling

The applicant submitted two population pharmacokinetic analyses that were developed using observations of healthy volunteers, obstructive hypertrophic cardiomyopathy patients and non-obstructive hypertrophic cardiomyopathy patients. For healthy volunteers, mainly dense samples were collected, whereas for patient data, only samples at trough and 1- or 2-hours post-dosing were available. Actual sampling and dosing times were however used.

The final model consists of a two-compartment model with first-order elimination and first-order absorption (including lag time). Several covariates were found to be influential in the models (i.e. body weight, CYP2C19 genotype, disease status (i.e. healthy volunteers versus patients), concomitant administration of omeprazole or disopyramide, formulation, food intake and dose. The pharmacokinetics appear to be quite unpredictable for individual subjects. However, on a population level, the models capture the variability adequately. The PopPK models are not able to predict the food effect on the pharmacokinetics of mavacamten, as clear misspecifications could be observed in the pcVPCs of the first analysis. In the second population pharmacokinetic model, submitted later in the procedure, no goodness-of-fit diagnostics stratified by food effect were provided. After correcting the influence of several covariates in the population pharmacokinetic model, patients with oHCM were estimated to have a higher exposure than healthy subjects. The reason for this observation remains unknown. The equations of the second population pharmacokinetic model, including model parameters and goodness-of-fit diagnostics, are displayed below.

$CL2C19 = (1 \times CL_{2C19IM}) \times (1 \times CL_{2C19PM}) \times (1 \times CL_{2C19RM}) \times (1 \times CL_{2C19UM}) \times (1 \times CL_{Unknown,missing})$

$CL_{TV} = CL_{Ref} \times CL2C19 \times (BW/BW_{Ref})^{0.75} \times (1 + CL_{female}) \times (1 \times CL_{HS}) \times (1 \times CL_{OMEP}) \times (1 \times CL_{ESOMEP}) \times (1 \times CL_{DPYR})$

$Q_{TV} = Q_{Ref} \times (BW/BW_{Ref})^{0.75}$

$V2_{TV} = V2_{Ref} \times (BW/BW_{Ref})^{V2BW}$

$V3_{TV} = V3_{Ref} \times (BW/BW_{Ref})^{V2BW}$

$K_{a,TV} = K_{a,\,Ref} \times (LNZDOSE_i / LNZDOSE_{Ref})^{KaLNZDOSE} \times (1 + K_{a,\,solution}) \times (1 + K_{a,\,fast}) \times (1 + K_{a,\,fed})$

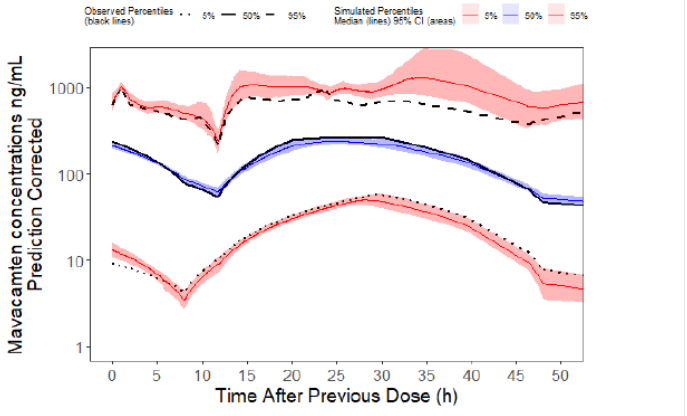
$F_{TV} = F_{solution} \times (LNZDOSE_i / LNZDOSE_{Ref})^{FLNZDOSE} \times (1 + F_{female}) \times (1 + F_{fast}) \times (1 + F_{fed})$,

Where: HS = healthy subjects, OMEP = omeprazole, ESOMEP = esomeprazole, DPYR = disopyramide, LNZDOSE = last non-zero dose, 2C19 = CYP2C19 phenotype (PM = poor-metaboliser, IM = intermediate metaboliser or *2/*17, RM = rapid metaboliser, UM = ultra-rapid metaboliser, Unknown or missing), Reference bodyweight = 84, EP = exponential residual error and EP14 = Exponential residual error for study MYK-461-014.

Table PK 1. Population pharmacokinetic model parameter estimates

Parameter	Estimate	%RSE	
CL/F (L/hr)	0.932	5	
BW-CL/F	0.75 [Fixed]	--	
CL_{2C19PM}	-0.725	3	
CL_{2C19IM}	-0.327	10	
CL_{2C19RM}	-0.0229	250	
CL_{2C19UM}	0.228	55	
$CL_{2C19UnkMet}$	-0.142	41	
CL_{HS}	0.253	22	
CL_{OMEP}	-0.334	10	
CL_{EGFR}	0.217	42	
CL_{ESOMEP}	-0.42	6	
CL_{female}	0.287	19	
CL_{DPYR}	0.962	23	
V2/F (L)	6.61	13	
BW-V2/F	0.792	9	
V3/F (L)	253	2	
BW-V3/F	0.792	9	
Q/F (L/hr)	16.5	4	
BW-Q/F	0.75 [Fixed]	--	
KA (hr-1)	0.301	22	
$KA_{Solution}$	0.681	24	
KA_{Fasted} (HS only)	0.87	60	
KA_{Fed} (HS only)	0 [Fixed]	--	
$KA_{LNZDOSE}$	-0.136	25	
ALAG1 (hr)	0.192	6	
$ALAG1_{LNZDOSE}$	-0.0866	47	
F	1 [Fixed]	--	
$F_{Solution}$	-0.193	21	
$F_{LNZDOSE}$	0.078	15	
F_{Fasted} (HS only)	-0.31	8	
F_{Fed} (HS only)	-0.429	7	
F_{Female}	0.0976	29	
Random Effect	**Estimate**	**%RSE**	**Shrinkage (%)**
IIV on CL/F	54.2%	3	0.85
CL-V2/F correlation	-2.54%	243	
IIV on V2/F	132%	8	42.8
CL-V3/F correlation	59%	8	
V2-V3/F correlation	2.2%	275	
IIV on V3/F	22.7%	5	16.3
IIV on KA	41.1%	14	50.2
IIV on Q/F	23.1%	8	48.2
IIV on RUV	44.1%	7	2.79
Residual Error	**Estimate**	**%RSE**	
EP	0.0292	4	1.39
EP14	0.48	21	1.39

Figure PK 1. Prediction-corrected visual predictive check



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Physiologically based pharmacokinetic (PBPK) modelling

A PBPK model was used to investigate the effect of a strong CYP3A4 inhibitor on the PK of mavacamten in CYP2C19 normal and poor metabolisers. The PBPK model was not sufficiently able to predict the PK in CYP2C19 poor metabolisers. Furthermore, the applicant included fm values for the contribution of CYP2C19, 3A4 and 2C9. However, *in vitro* data indicated that CYP3A5 was also involved in the metabolism to a significant extent. V_{max} and K_m were not determined for each CYP enzyme and an incorrect approach to determine the contribution of each CYP enzyme to the overall metabolism was used. The contribution of each CYP may be concentration-dependent, and mavacamten showed more than a dose-proportional increase in exposure (indicating saturation of the metabolism since it is not a substrate of P-glycoprotein). Overall, the contribution of CYP2C19, 3A4 and 3A5 may be different at higher/lower concentrations and depends on the CYP2C19 and CYP3A4 and 3A5 phenotypes. Overall, the PBPK model is currently not sufficient to waive clinical DDI studies.

In addition, PBPK modelling was used to investigate the induction potential towards CYP2B6 via CAR and the inhibition potential towards MATE1. Limited model qualification was provided for the prediction of induction for CYP2B6 and MATE1 inhibition. Therefore, the PBPK model was not sufficiently qualified to conclude that mavacamten does not induce CYP2B6 via CAR in CYP2C19 poor metabolisers receiving the highest dose. However, it is proposed by the CHMP that CYP2C19 poor metabolisers are restricted from treatment with dosages higher than 5 mg; therefore, this induction potential is likely not to occur in clinical practice. The PBPK model was not sufficiently qualified to conclude that mavacamten does not inhibit MATE1 at clinically relevant doses following repeated dosing.

Absorption

The pharmacokinetics of mavacamten in healthy volunteers was investigated following a single dose over a dosing range from 1 mg to 25 mg and following multiple dosing over a dose range of 12.5 to 18.5 mg once daily for 28 days. Following a single dose, mavacamten is rapidly absorbed in plasma in healthy subjects. Median plasma t_{max} was around 2 hours.

No absolute oral bioavailability study was performed. Therefore, the exact oral bioavailability of the commercial formulation is unknown. Based on the data of the mass balance study (<4% of the radioactivity was eliminated in the first 48 hours and 85% is eliminated via urine), the absorption can be considered high (>85%). At C_{max}, 80.3% of the radioactivity in plasma was parent compound. In contrast, co-administration with CYP3A4 inhibitor resulted in an increase of 1.5-fold in C_{max} indicating first-pass metabolism by CYP3A4 in the intestine or liver. This indicates that the absolute oral bioavailability can be estimated to be ~60-80%.

Co-administration of mavacamten with a high-fat meal decreased the C_{max} with 55% and the AUC with 13%. The decrease in AUC was not considered clinically relevant. The effect of a normal-fat meal on the C_{max} and AUC is unknown, but likely less than the high-fat meal. In pivotal efficacy and safety study 005, mavacamten was taken without regard of food. It is therefore agreed that mavacamten may be given independent of food.

In the clinical studies, the inter-individual variability for C_{max} ranged from 15% to 57% and for AUC ranged from 24% to 67% in subjects that were normal to rapid CYP2C19 metabolisers. The PopPK model estimated an inter-individual variability of 59%.

The C_{max} appears to increase more than dose proportional over the concentration range 1 mg to 2 mg and dose proportional from 2 mg to 25 mg in CYP2C19 normal metabolisers. The AUC appears to increase more than dose proportional over the concentration range 1 mg to 5 mg and dose proportional from 5 mg to 25 mg in CYP2C19 normal metabolisers. In CYP2C19 poor metabolisers the

dose is proportional over the clinical dose range of 2.5 mg to 5 mg and dosages are restricted to a maximum dose of 5 mg for poor metabolisers.

The accumulation was 2.2-fold for the C_{max} and 7.3-fold for the AUC_{0-24} following a dose of 12.5 mg once daily in CYP2C19 normal metabolisers. Similar accumulation is expected over a dose range of 5 to 15 mg (C_{max} and AUC are dose-proportional). However, the AUC is more than dose proportional from 2.5 mg to 5 mg dose range and the accumulation may thus be different at dosages <5 mg. Also, the degree of accumulation is dependent on the CYP2C19 phenotype. No information is available on the accumulation of mavacamten for the other CYP2C19 phenotypes (poor metaboliser, intermediate metaboliser, rapid metaboliser and ultra-rapid metaboliser) over the clinical dose range.

Five different formulations were used in the clinical studies: oral suspension, tablet campaign 1, tablet campaign 2, capsule 1 and capsule 2. A bioequivalence study was performed between the 15 mg capsule 1 formulation and 15 mg capsule 2 formulation (intended commercial formulation). Bioequivalence was shown between the two formulations. The 10 mg capsule 2 formulation strength can be waived via a biowaiver of strengths (see Quality AR). However, the two lower strengths of the capsule 2 formulation (2.5 mg and 5 mg) cannot be agreed based on a biowaiver of strength (the strengths were manufactured by the same manufacturing process and have the same qualitative composition, but the composition of the strengths is not quantitatively proportional and the dissolution was not similar). A bioequivalence study with the 5 mg strength (3 times) versus with the 15 mg capsule 2 formulation is needed to show that the different strengths are switchable. It was agreed to study this post-authorisation. Currently the SmPC has a warning regarding the switchability between the different available strengths.

Distribution

Mavacamten has an *in vitro* plasma protein binding of 93% and a blood-to-plasma ration of 0.79 ± 0.12. Thus, mavacamten has a high plasma protein binding and does not significantly distribute to red blood cells. The protein binding was also assessed *in vivo* in the hepatic impairment study and ranged between 97 to 98% in subjects with normal or reduced hepatic function (independent of the hepatic function).

Mavacamten has a large apparent volume of distribution of 114 L to 206 L. A limited amount is distribution to semen at clinical dosages (ratio of 0.04).

Metabolism

The *in vitro* and *in vivo* metabolism rate of mavacamten is slow. Only 4% was metabolised after 1-hour of incubation with human liver microsomes and 4-hour with human hepatocytes. In the mass balance study, the majority of mavacamten radioactivity is eliminated as metabolite and only a very small fraction as a parent in urine (<2%) and faeces (<1%).

In plasma of CYP2C19 normal metabolisers, the majority of radioactivity was parent compound (67-77%), and all metabolites were present for <10% (the main metabolites M2 and M46 were present for 2.3-4.6% and 1.4-7.9% of the total radioactivity, respectively). The majority is eliminated as metabolite, and <3% is eliminated as parent in the excreta. In urine, M2 is the main metabolite and represents ~50% of the excreted radioactivity (together with M13). Overall, this indicates that mavacamten is metabolised to a significant extent and based on the excreta data M2 is most likely the main metabolite formed. Furthermore, the metabolite profile in CYP2C19-poor metabolisers is partly unknown. Plasma samples from study 012 in CYP2C19-poor metabolisers and normal metabolisers

were used to investigate the presence of mavacamten and metabolites M2 (formed by CYP2C19), M6 (formed by CYP3A) and M8. No other metabolites were measured. Metabolites M2 and M8 were only present to a very limited extent or not measured in CYP2C19 poor metabolisers. M6 AUC in poor metabolisers was similar to that in CYP2C19 normal metabolisers. It is unknown if other metabolites are formed in CYP2C19-poor metabolisers. Based on the provided data, it cannot be concluded that no other metabolites are formed in CYP2C19 poor metabolisers compared to CYP2C19 normal metabolisers. Furthermore, most metabolites were observed in the excreta and not in plasma.

Based on *in vitro* and mass balance studies, mavacamten metabolism involves mainly CYP2C19 and to a lesser extent CYP3A4, and 3A5 and to an even lesser extent by CYP2C9 in CYP2C19 normal to extensive metabolisers. In CYP2C19 poor metabolisers, mavacamten is metabolised by CYP3A4, 3A5 and 2C9. Involvement of UGT enzymes in biotransformation appears marginal in CYP2C19 normal to extensive metabolisers as the very limited amount of metabolites excreted in urine were found to be glucuronides. The contribution of glucuronidation in CYP2C19-poor metabolisers is unknown.

Transporters

The applicant performed *in vitro* studies investigating if mavacamten is a substrate of P-glycoprotein and hepatic uptake transporters (OATP1B1, OATP1B3, OATP2B1, OCT1 and NTCP) and the transporters OAT1, OAT3 and OCT2. Based on these studies, mavacamten is not a substrate of P-glycoprotein, OATP1B1, OATP1B3, OATP2B1, OCT1, OCT2, NTCP, OAT1 and OAT3. Thus, hepatic uptake does not appear to be the rate limiting step in the clearance of mavacamten.

No studies were performed investigating if mavacamten is a substrate of BCRP. No *in vitro* study is needed to investigate if mavacamten is a substrate of BCRP, since the bioavailability appears to be high and the majority is eliminated as metabolite via urine.

Excretion

The excretion of mavacamten related radioactivity is mainly via urine, only a small fraction (<10%) is eliminated via faeces. The elimination is slow and depends on the CYP2C19 phenotype; the elimination half-life of mavacamten ranged from 72 h in ultra-rapid metabolisers to 533 h in poor metabolisers. The elimination half-life was ~150 h in CYP2C19 normal metabolisers.

Pharmacokinetics in hypertrophic cardiomyopathy patients

The pharmacokinetics of mavacamten were investigated in patients with hypertrophic cardiomyopathy following a single ascending oral dose of mavacamten (48 mg, 96 mg and 144 mg) divided into 8 aliquots administered over a 2 h period. The PK in healthy volunteers following a single dose of 48 mg mavacamten divided into 8 aliquots 15 minutes apart was compared to the PK in patients with obstructive hypertrophic cardiomyopathy (see Table below). The t_{max} and AUC_{0-24} are comparable, but the C_{max} and AUC_{0-inf} is lower in patients compared to healthy volunteers. The elimination half-life is around half in patients compared to healthy volunteers.

parameter	healthy volunteers (n=6)	patients with obstructive hypertrophic cardiomyopathy (n=3)	comparison
t_{max} (h)	2.1 (1.5-3.0)	2.5 (1.5-3)	-
C_{max} (ng/mL)	894 (CV%=36)	657 (CV%=44)	0.73
AUC_{0-24h} (ng×h/mL)	4218 (CV%=37)	4403 (CV%=51)	1.04
AUC_{0-inf} (ng×h/mL)	36654 (CV%=94)	18500 (CV%=67)	0.50
$t_{½}$ (h)	187 ± 56	88 ± 18	0.47

No dedicated PK studies were performed following the administration of a single dose administered at once over the clinical dose range (2.5 to 15 mg) or following repeated dosing. Sparse blood sampling was performed in clinical studies 004 (n=21), 005 (n=123), 006 (n=39), 007 (n=90), and 008 (n=13), and Population PK modelling was used to predict the PK. Based on the PopPK modelling, the applicant concluded that patients with obstructive hypertrophic cardiomyopathy exhibited a higher exposure than healthy subjects.

In patients that are CYP2C19 normal metabolisers, the predicted C_{max} is 945 ng/mL, and AUC is 20.000 ng × h/mL at steady state following once-daily dosing with 15 mg mavacamten. Similar exposure is expected in CYP2C19 poor metabolisers at steady state treated with 5 mg mavacamten once-daily.

Special populations

Genetic polymorphism

Mavacamten is mainly cleared by metabolism via CYP2C19 once it is systemically available in CYP2C19 intermediate to ultra-rapid metabolisers. However, metabolism by CYP3A plays a role during absorption and first-pass metabolism in these subjects (C_{max} of mavacamten was increased 1.5-fold following concomitant administration with a moderate CYP3A inhibitor). Furthermore, *in vitro* data indicates that CYP3A5 is able to metabolise mavacamten to a more significant extent than CYP3A4. The potential effect of genetic polymorphisms in CYP3A5 on the PK of mavacamten, especially in CYP2C19 poor metabolisers is unknown.
Based on the PK data in subjects with different CYP2C19 metabolising status, the PK of mavacamten depends highly on the CYP2C19 metabolic status (see Table below) with a 2.2-fold higher C_{max} and a 6.9-fold higher AUC in poor metabolisers compared to ultra-rapid metabolisers. The C_{max}/dose was 1.8-fold higher in poor metabolisers and 1.2-fold lower in ultra-rapid metabolisers compared to normal metabolisers. The AUC/dose was 4.6-fold higher in poor metabolisers and 1.6-fold lower in ultra-rapid metabolisers compared to normal metabolisers.

parameter	poor metaboliser (n=10)	intermediate metaboliser (n=32)	normal metaboliser (n=60)	rapid metaboliser (n=19)	ultra-rapid metaboliser (n=8)
C_{max}/dose	33.7 (CV%=31)	24.0 (CV%=30)	18.6 (CV%=49)	19.9 (CV%=44)	15.4 (CV%=29)
AUC/dose	2949 (CV%=24)	987 (CV%=35)	613 (CV%=46)	508 (CV%=66)	425 (CV%=48)
$t_{½}$ (h)	533 (CV%=28)	179 (CV%=58)	116 (CV%=87)	105 (CV%=80)	71.6 (CV%=61)

Impaired renal function

No dedicated renal impairment study was performed. In the population pharmacokinetic model, renal function was not identified as a significant covariate for subjects with eGFR levels down to 29.5 mL/min/1.73 m^2. It can be agreed with the applicant that mild to moderate impaired renal function is not expected to translate in a significant increase in plasma exposure to mavacamten. Severe renal impairment is known to affect the metabolism capacity of the liver. Thus, severe renal impairment may have an effect on the PK of mavacamten. The effect of severe renal impairment was not investigated in clinical studies.

Impaired hepatic function

Mild and moderate hepatic impairment did not influence C_{max} of mavacamten (1.1-fold increase), but significantly increased the plasma exposure (AUC; approximately 1.7 to 3.9-fold higher plasma exposure) and half-life of mavacamten. However, the subjects in the mild hepatic impairment group had higher AUCs than subjects in the moderate hepatic impairment group. Furthermore, the elimination half-life increased >2.5-fold in subjects with mild and moderate hepatic impairment compared to normal hepatic function. No adjustment of the starting dose of 2.5 mg is needed in CYP2C19 poor metabolisers or for patients for which the CYP2C19 status is unknown. However, the dose should be reduced by half or more in subjects with mild (Child-Pugh class A) and moderate (Child-Pugh class B) hepatic impairment. No dose recommendation can be made for patients with severe hepatic impairment (Child-Pugh class C), because mavacamten has not been studied in patients with severe hepatic impairment.

Age

The influence of age (age range: 18–83 years) was investigated using the population pharmacokinetic model. No trends with age where identified. A total of 303 subjects were included in studies 001, 002, 003, 009, 010, 011, 012, 013, 014, 015, 016, and 018 with age distribution as shown in the Table below.

	Age <65	Age 65-74	Age 75-84	Age 85+
overall	293 (97%)	10 (3%)	0 (0%)	0 (0%)

No subjects were included in these studies with an age above 70. In study 007, submitted later in the procedure, patients ranged from 19 to 83 years. Mavacamten is indicated for subjects of 18 years and older in this procedure. Therefore, no clinical PK studies are needed in paediatric subjects.

Body weight

The exposure was 1.6-fold increased at a body weight of 45 kg compared to the reference body weight of 84 kg. The initial starting dose of 5 mg is not expected to translate in a significant safety risk in adult patients with a CYP2C19 intermediate to ultra-rapid phenotype as a consequence of increased mavacamten exposure due to low body weight. The exposure was 0.68-fold in subjects with CYP2C19 intermediate to normal phenotype with a body weight of 140 kg compared to the reference body weight of 84 kg. CYP2C19 ultra-rapid metabolisers with a high body weight (>140 kg) may have a decreased exposure such that the efficacy may be reduced in these subjects. Furthermore, patients with a low body weight (<50 kg) and CYP2C19 poor metabolisers may have increased safety issues, especially at dosages of 5 mg once daily or higher.

Gender

No significant effect of gender (n = 261 males and n = 200 females) was identified in the population pharmacokinetic model after correcting for differences in body weight.

Race

In CYP2C19 normal metabolisers, no differences in the pharmacokinetics were observed between Japanese and Caucasian subjects following a single oral dose of 25 mg mavacamten. However, the ethnic prevalence of the CYP2C19 phenotypes is different, with a high frequency of the poor metabolising phenotype in Asians. Thus, a difference in PK due to race can be expected independent on the effect of body weight.

Pharmacokinetic interaction studies

Mavacamten as victim

Based on *in vitro* data, mavacamten appears to be mainly metabolised by CYP2C19 and can also be metabolised by CYP3A4 and 3A5. *In vivo*, the elimination half-life of mavacamten ranged from 72 h to 533 h, depending on the CYP2C19 phenotype. Therefore, the effect of other medicinal products on the PK of mavacamten will depend on the CYP2C19 phenotype. CYP2C19 inhibitors may have a significant effect on the PK of mavacamten in CYP2C19 intermediate to ultra-rapid metabolisers but no effect in CYP2C19 poor metabolisers. CYP3A4/5 inhibitors may have a limited effect on the PK of mavacamten in CYP2C19 intermediate to ultra-rapid metabolisers but a significant effect in CYP2C19 poor metabolisers. Clinical DDI studies were conducted in CYP2C19 normal metabolisers to assess the clinical impact of the combination of mavacamten with omeprazole (proton pump inhibitor and weak CYP2C19 inhibitor) and with verapamil (moderate CYP3A4 inhibitor).

Co-administration of mavacamten with a moderate to weakCYP2C19 inhibitor (omeprazole) resulted in a 58% increase in AUC and no effect on the C_{max}. The observed effect of omeprazole was not due to increased gastric pH since the solubility was similar over the pH range of 1-6. The effect of a strong CYP2C19 inhibitor on the PK of mavacamten was not investigated in a clinical DDI study but will be similar to the effect of poor CYP2C19 metabolising status. Therefore, the dose should be reduced from 15 mg to 5 mg and from 10 mg and 5 mg to 2.5 mg or pause treatment if on 2.5 mg when starting with a CYP2C19 strong inhibitor in CYP2C19-intermediate to ultra-rapid metabolisers in patients that are CYP2C19 non-poor metabolisers.

Co-administration of mavacamten with a moderate CYP3A4 inhibitor (verapamil) resulted in a ~15% increase in AUC in CYP2C19 normal metabolisers, which is not considered clinically significant. C_{max} after this single dose was ~50% higher. No dose adjustment is required when mavacamten is co-administered with verapamil or other moderate CYP3A4 inhibitors in CYP2C19 intermediate to ultra-rapid metabolisers. The effect of a strong CYP3A4 inhibitor on the PK of mavacamten was not investigated and may result in a significant increase in the C_{max}, especially in CYP2C19-poor metabolisers. The effect of a CYP3A inhibitor in CYP2C19 poor metabolisers remains therefore unknown, but based on the elimination pathway, may be so significant that CYP3A4 strong inhibitors are contra-indicated.

Mavacamten as perpetrator

Mavacamten is not an *in vitro* inhibitor of CYP3A, glycoprotein and BCRP at maximal intestinal concentrations. Furthermore, mavacamten is not an inhibitor of OCT1, OATP1B1 and OATP1B3 at maximal portal vein concentrations. In addition, mavacamten is not an inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19 and 2D6 and of the transporters OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE2-K and BSEP at maximal systemic concentration. Furthermore, mavacamten is not a time-dependent CYP inhibitor at clinically relevant concentrations. However, mavacamten is an inhibitor of MATE1 at maximal systemic concentrations and an inducer of CYPs and transporters via CAR and PXR at clinically relevant concentrations.

Clinical DDI studies were conducted in CYP2C19 normal metabolisers to assess the clinical impact of the combination of mavacamten as a CYP3 inducer with midazolam (CYP3A substrate) and with oral contraceptives. Co-administration of mavacamten for 15 to 28 days (maximal induction was obtained) did not affect the exposure to midazolam (CYP3A substrate) and of the biomarker 4-β hydroxycholesterol (indicator of PXR induction). C_{max} of midazolam was 7% lower, and the AUC was 24% lower. No change in 4-β hydroxycholesterol levels were observed. 4-β hydroxycholesterol is an acceptable biomarker to investigate the induction potential of CYP3A (Leil et al., 2014; Diczfalusy et al., 2011; Diczfalusy et al.,2008; Bjorkhem-Bergman et al., 2013). Furthermore, no effect was observed on the exposure to ethinyl oestradiol + norethindrone in oral contraceptives. Overall, this indicates that mavacamten is not an inducer of CYP3A via PXR in CYP2C19 normal metabolisers dosed up to 15 mg and in CYP2C19 poor metabolisers dosed up to 5 mg.

The effect of mavacamten on the pharmacokinetics of a MATE1 substrate was not investigated, but it cannot be excluded that mavacamten is a clinically relevant inhibitor of MATE1 following repeated dosing.

2.5.2.1. Pharmacodynamics

Mechanism of action

Mavacamten is a selective, allosteric, and reversible cardiac myosin inhibitor and represents a first in class of therapeutic agent, the first medical therapy developed specifically for oHCM that targets the pathophysiology of the disease.

Mavacamten modulates the number of myosin heads that can enter “on actin” power-generating states, thus reducing (or in HCM normalizing) the probability of force-producing (systolic) and residual (diastolic) cross-bridge formation. Mavacamten also shifts the overall myosin population towards an energy-sparing, but recruitable, super-relaxed state. Excess cross-bridge formation and dysregulation of the super-relaxed state of myosin are mechanistic hallmarks of HCM, which can result in hyper-contractility, impaired relaxation, excess energy consumption, and myocardial wall stress. In HCM

patients, cardiac myosin inhibition with mavacamten normalises contractility, reduces dynamic left ventricular outflow tract (LVOT) obstruction, and improves cardiac filling pressures.

Primary pharmacology

The pharmacodynamic effects of mavacamten were evaluated after single and multiple-dose administrations in healthy subjects (Table 3).

Study MYK-461-002 was a randomized, double-blind, placebo-controlled sequential-group single ascending-dose phase I study to investigate the safety and tolerability of mavacamten after single oral doses of 1, 2, 6, 12, 24 or 48 mg or placebo in 48 healthy subjects. Six cohorts of 8 adults were randomized 6:2, mavacamten to placebo. Doses 6 mg and higher were administered in 8 aliquots 15 minutes apart. Secondary and exploratory objectives of this study were to investigate the pharmacokinetics and pharmacodynamics, respectively.

Transthoracic echocardiography showed dose-dependent reductions in left ventricular ejection fraction (LVEF)(max mean decrease of 5.9% with 48 mg; Figure 2), left ventricular outflow trac velocity time integral (LVOT-VTI)(max mean decrease of 16.71% with 48 mg; Figure 3), left ventricular fractional shortening (LVFS)(max mean decrease of 22.46% with 48 mg; Figure 4) and stroke volume (SV) (max mean decrease of 18.55% with 48 mg; Figure 5) after a single administration of mavacamten doses ≥12 mg. Additionally, there was an inverse relationship between mavacamten plasma concentration and effects on LVEF ($p=0.0126$), LVOT-VTI ($p<0.0001$), LVFS ($p<0.0001$) and SV ($p<0.001$). No consistent, dose-dependent changes were evident in left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV) and isovolumetric relaxation time.

Figure 2. Mean percent change from baseline in LVEF versus time by mavacamten dose level, linear scale

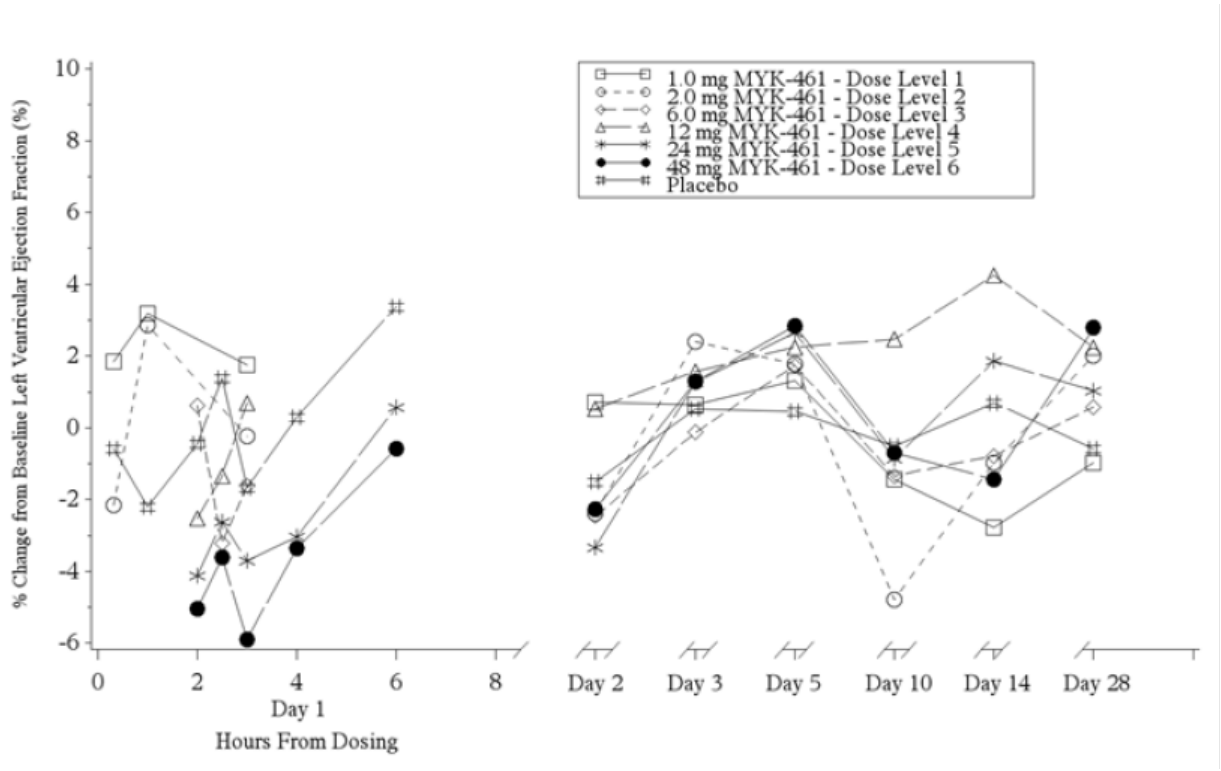


Figure 3. Mean percent change from baseline in LVOT-VTI versus time by mavacamten dose level, linear scale

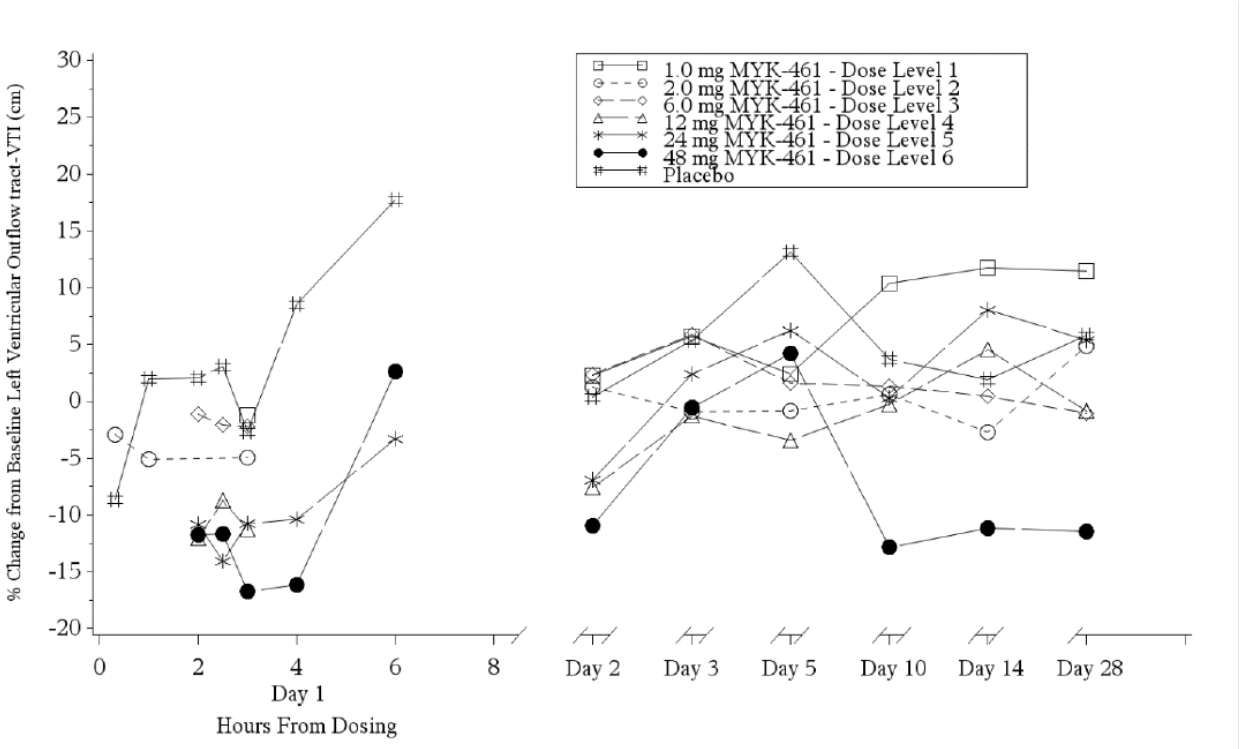


Figure 4. Mean percent change from baseline in LVFS versus time by mavacamten dose level, linear scale

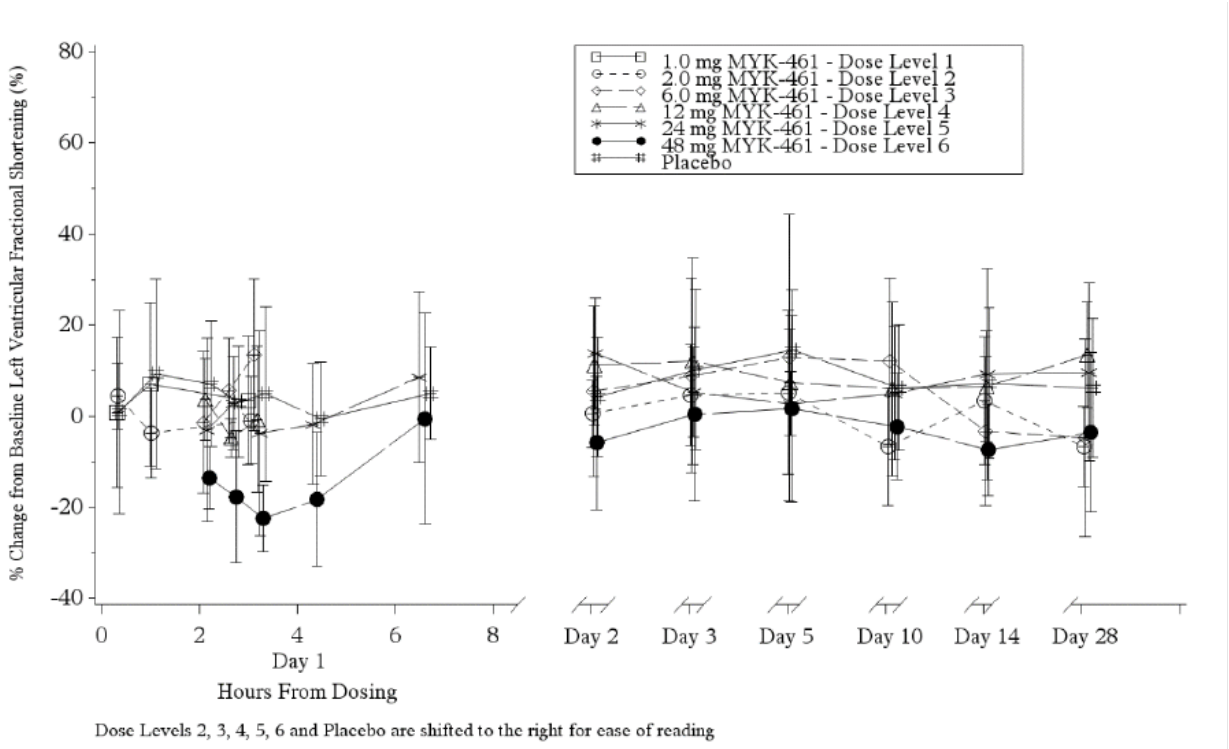
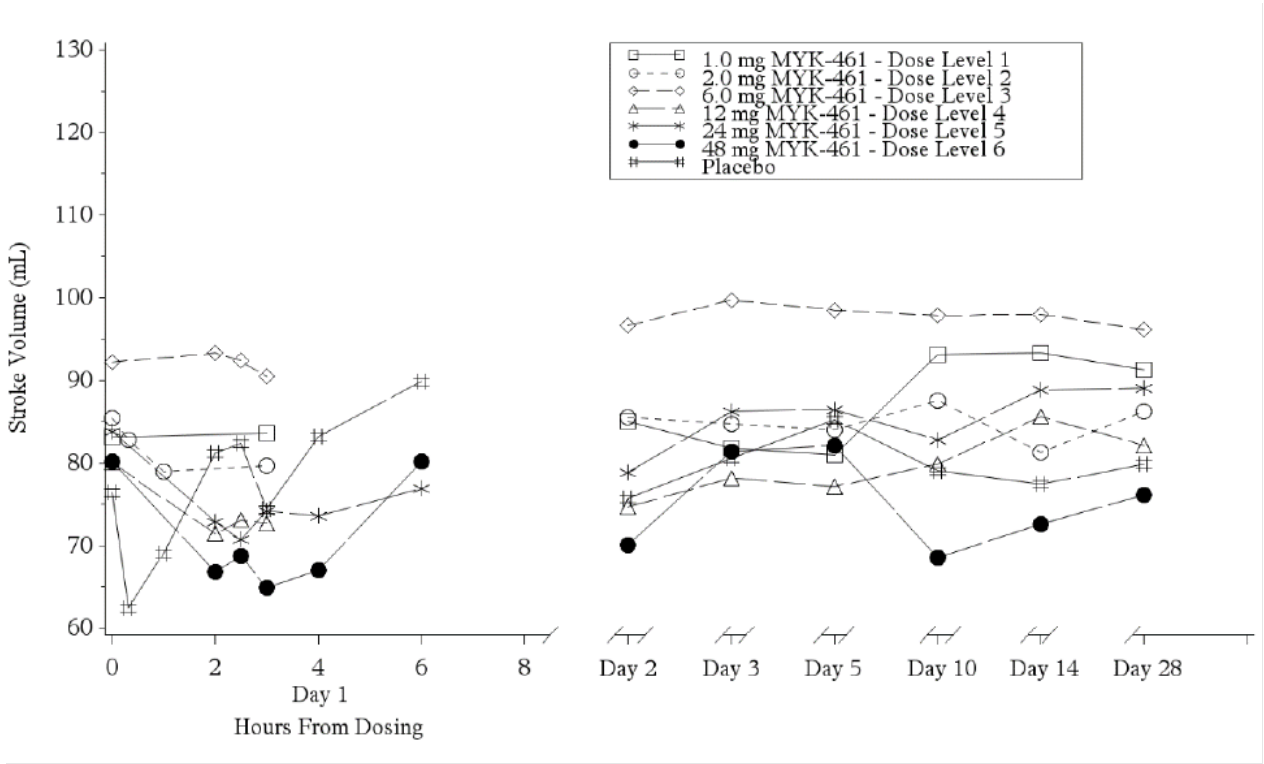


Figure 5. Mean percent change from baseline in SV versus time



Study MYK-461-001 was a sequential group, single-ascending oral dose phase I study to investigate the safety and tolerability of mavacamten after single oral doses of 48, 96 and 144 mg (in 8 aliquots every 15 minutes) in 15 NYHA class I, II, or III hypertrophic cardiomyopathy subjects.

Transthoracic echocardiography showed dose-dependent reductions in LVEF (Figure 6), LVOT-VTI (Figure 7), LVFS (Figure 8), and stroke volume (Figure 9) and dose-dependent increases in LVEDV (Figure 10) and LVESV (Figure 11). Generally, values returned to near baseline levels by 6 hours post-dose or by Day 2 in the lower dose groups. LVEF, LVOT-VTI, and LVFS remained slightly decreased on Day 2 in the 144 mg group but returned to near baseline by Day 14. Additionally, there was an inverse relationship between mavacamten plasma concentration and effects on LVEF ($p<0.0001$), LVOT-VTI ($p<0.0001$)), and LVFS ($p=0.00167$). The changes in resting LVEF, LVOT-VTI, and GLS returned to baseline values during the follow-up visits after discontinuation of the study drug. However, with respect to resting LVEDV, LVEDD, LVESD, and LVFS values did not fully return to baseline by D63 in the higher groups of 18.5 mg and 25 mg QD mavacamten but were returned to baseline after 100 to 200 days post-dose.

Figure 6. Mean (SD) LVEF (2D) versus time by cohort (linear scale; PD population)

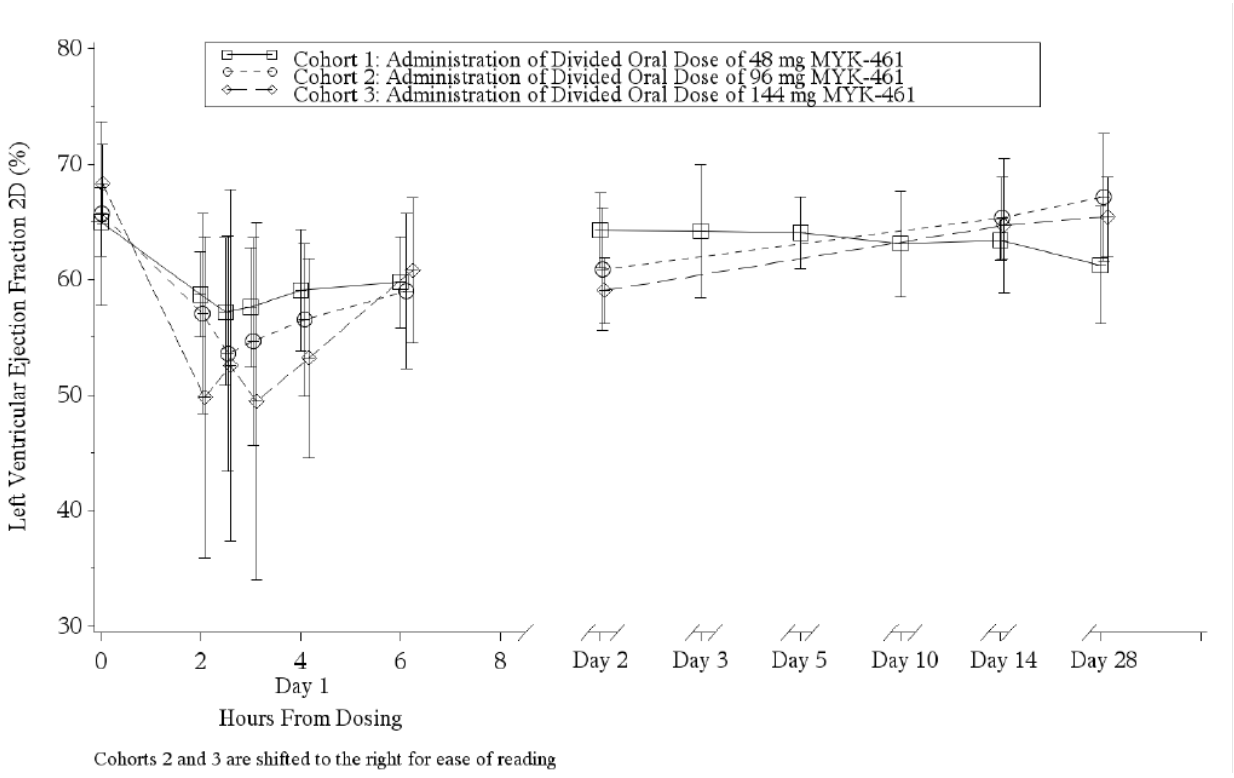


Figure 7. Mean (SD) LVOT-VTI versus time by cohort (linear scale; PD population)

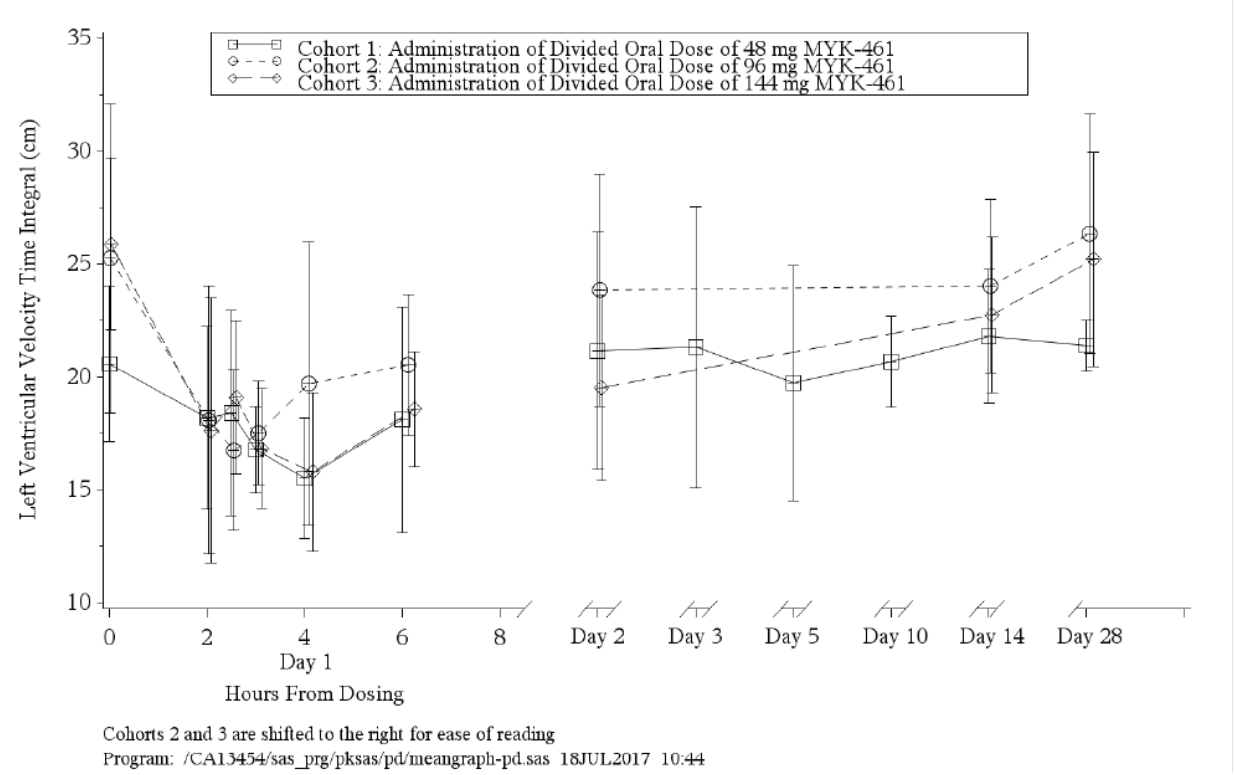


Figure 8. Mean (SD) LVFS versus time by cohort (linear scale; PD population)

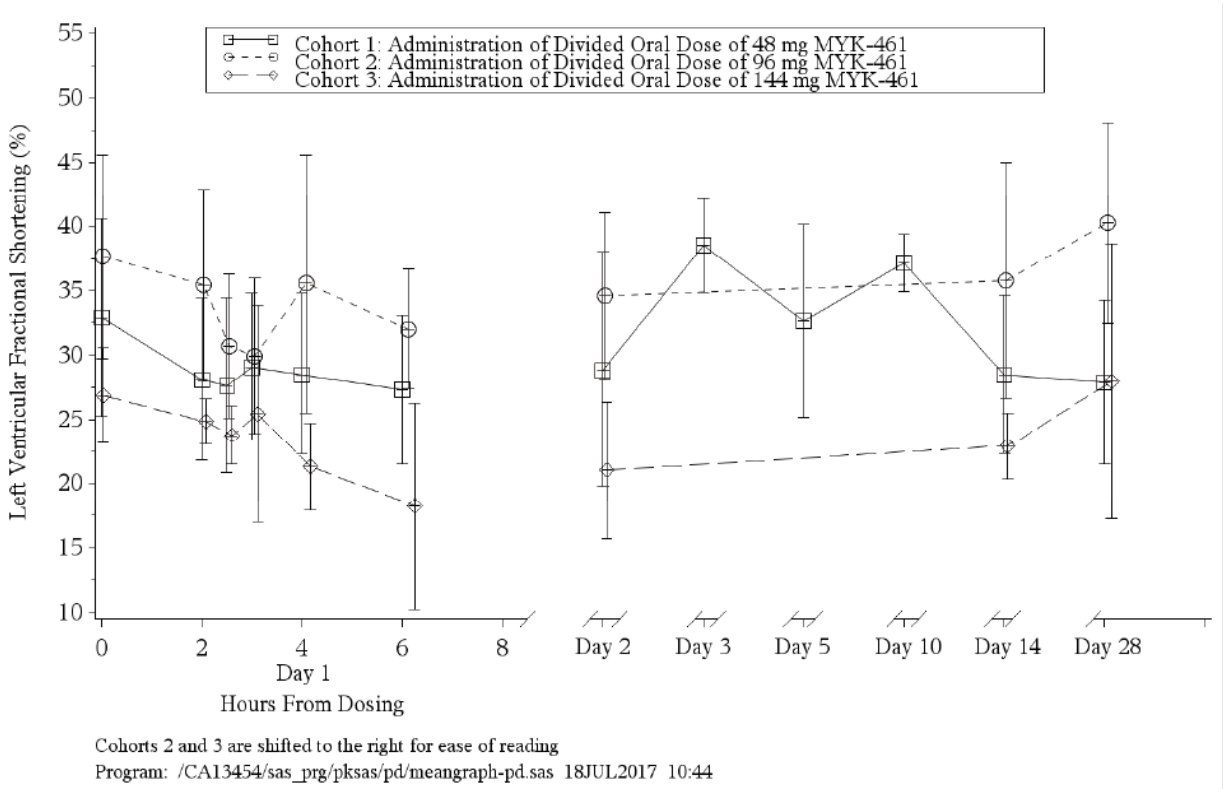


Figure 9. Mean (SD) left ventricular SV versus time by cohort (linear scale; PD population)

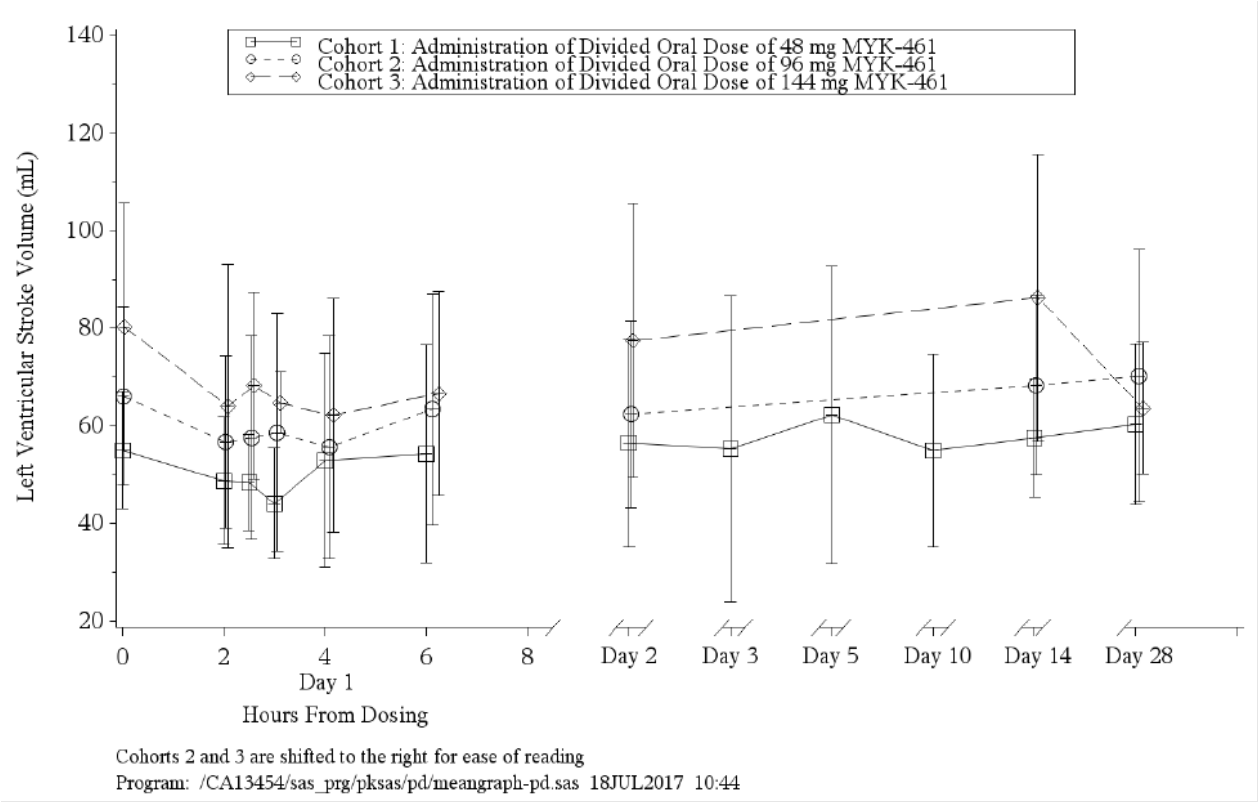
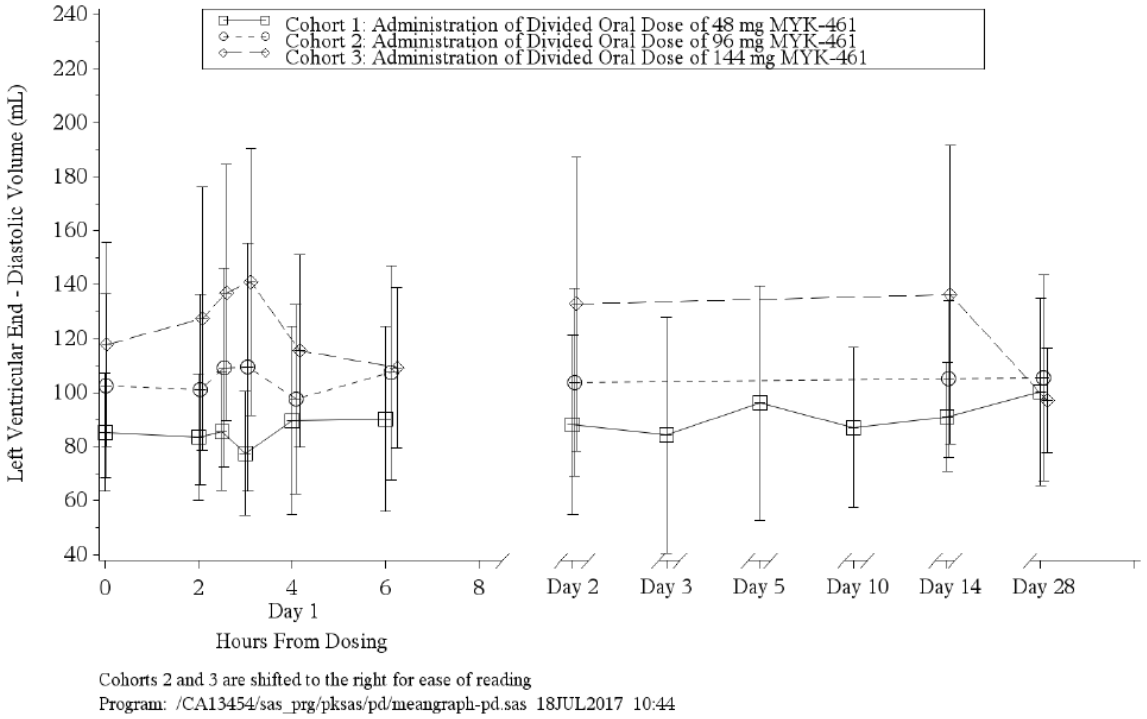
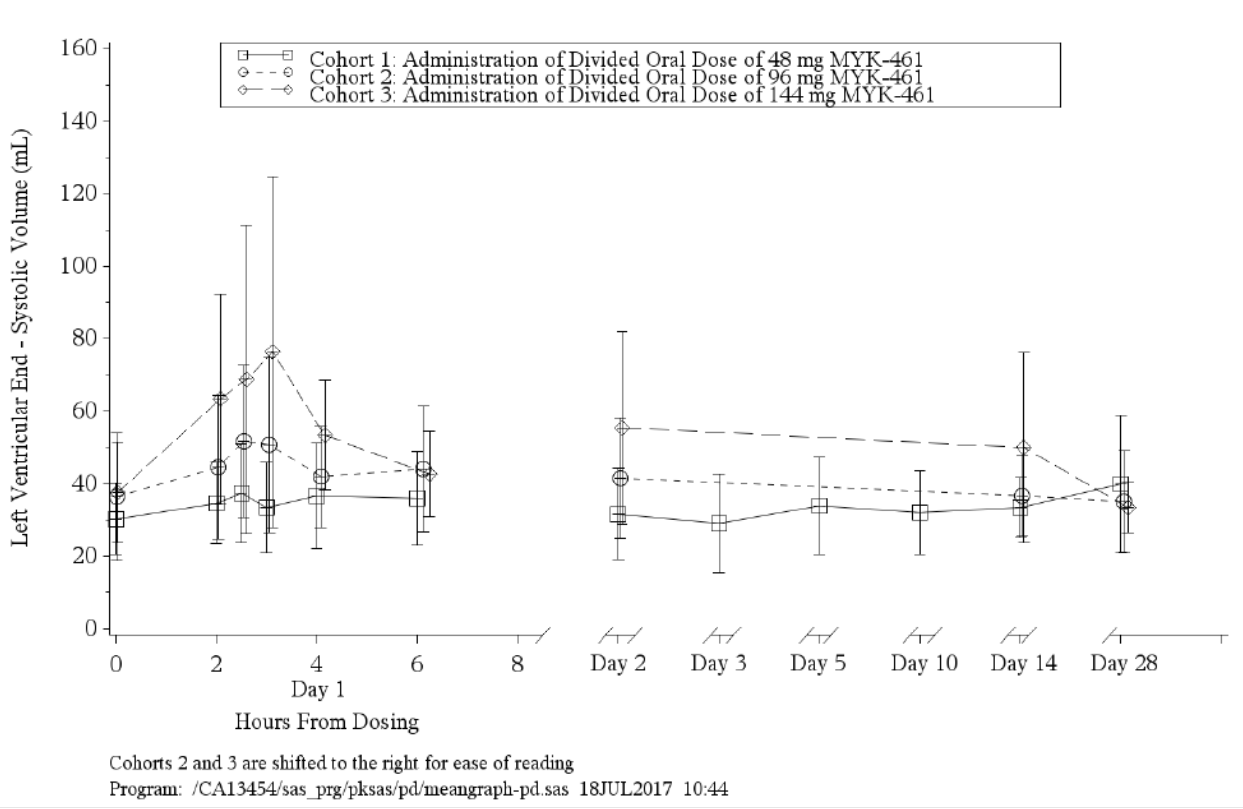


Figure 10. Mean (SD) LVEDV versus time by cohort (linear scale; PD population)



Source: Figure 14.2.6.7.1.
Abbreviations: PD = pharmacodynamic, SD = standard deviation.

Figure 11. Mean (SD) LVESV versus time by cohort (linear scale; PD population)



Study MYK-461-003 was a double-blind, randomized, placebo-controlled, sequential-group, multiple-ascending phase I study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of mavacamten after oral dosing of 1 mg BID, 3 mg BID, 12.5 mg QD, 18.5 mg QD, and 25 mg QD for 28 days in 60 healthy subjects.

Resting transthoracic echocardiography

Resting transthoracic echocardiography showed dose-dependent reductions in LVEF (max mean decrease of 11.25% with 25 mg QD; Figure 12 and Figure 13), LVOT-VTI (max mean decrease of 5.35 cm with 18.5 mg QD; Figure 14), and LVFS (max mean decrease of 11.11 % with 25 mg QD) and dose-dependent increases in GLS (max mean increase of 3.61 % with 18.5 mg QD) and LVEDV (max mean increase of 9.70 ml with 18.5 mg QD using 3D analysis), left ventricular end-diastolic diameter (LVEDD) (max mean increase of 0.41 cm with 25 mg QD), and left ventricular end-systolic diameter (LVESD) (max mean increase of 0.85 cm with 25 mg QD). Additionally, there were inverse relationships between mavacamten plasma concentration and effects on LVEF, LVOT-VTI, LVFS and positive relationships between mavacamten plasma concentration and effects on GLS, LVEDV, LVEDD, and LVESD.

Figure 12. Resting LVEF (%; 2DE) (TTE analysis population)

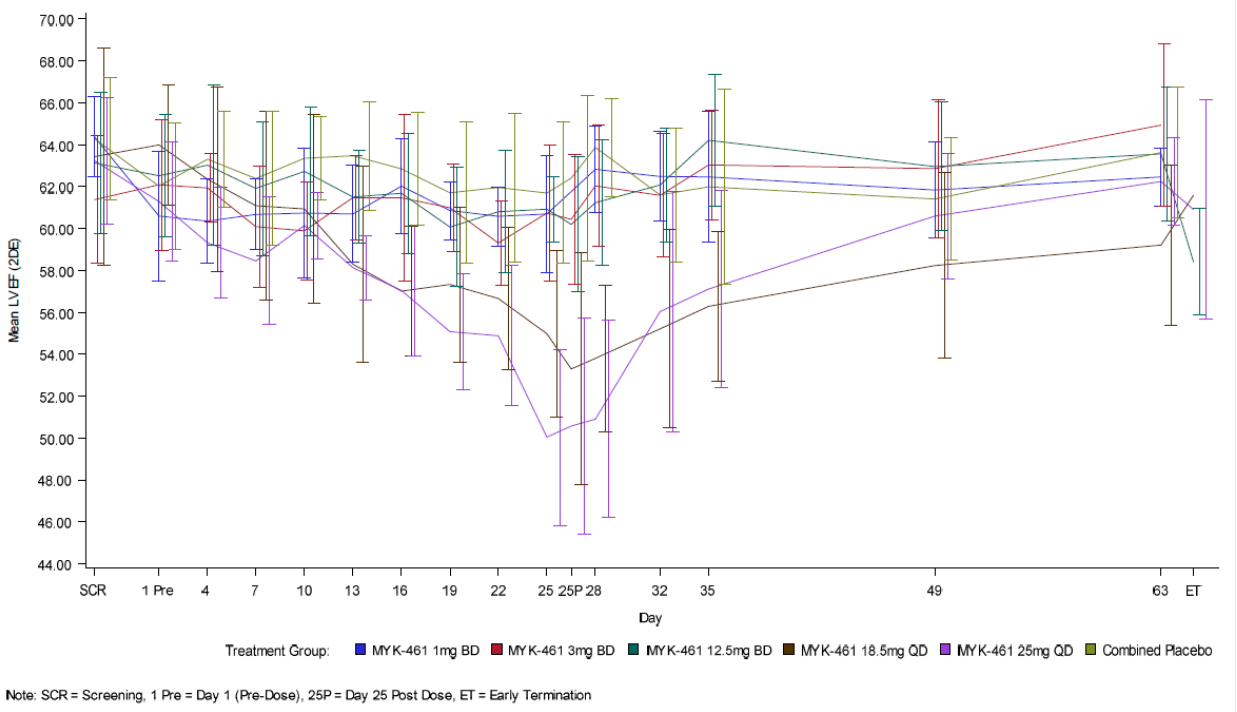


Figure 13. Change from baseline in resting LVEF (2DE) versus plasma concentrations of mavacamten (PK analysis population)

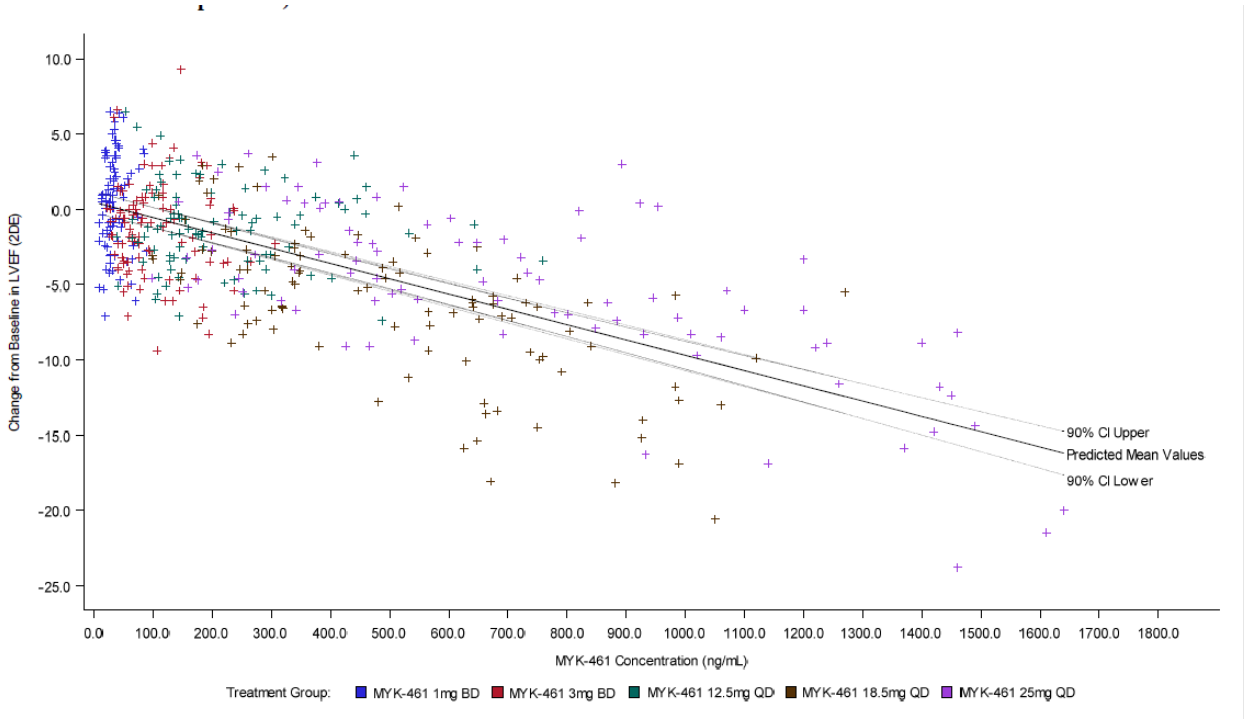
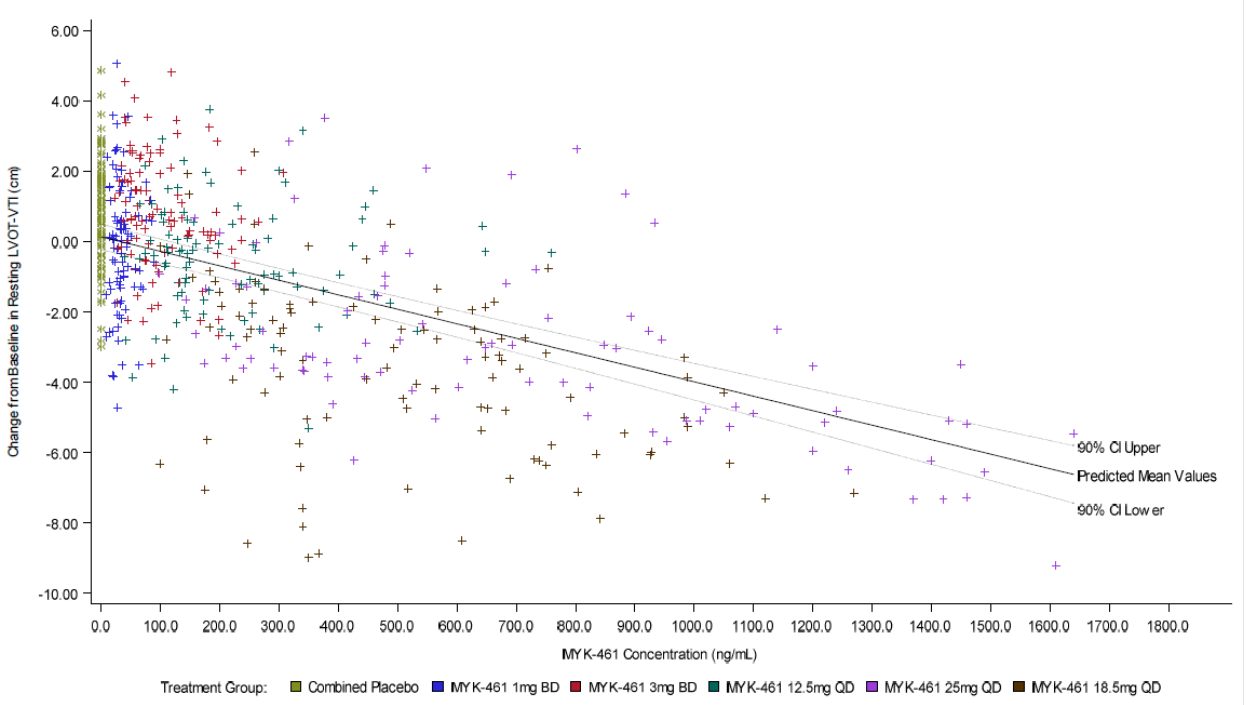


Figure 14. Change from baseline in resting LVOT-VTI (cm) versus plasma concentrations of mavacamten (ng/mL)



Post-exercise transthoracic echocardiography

Post-exercise transthoracic echocardiography showed similar results compared with resting transthoracic echocardiography with dose-dependent reductions in LVEF (max mean decrease of 14.24 % with 18.5 mg QD), LVOT-VTI (max mean decrease of 4.29 cm with 18.5 mg QD), and LVFS (max mean decrease of 11.25 % with 25 mg QD) and dose-dependent increases in LVEDV (max mean increase of 22.15 ml with 25 mg QD), LVEDD (max mean increase of 0.36 cm with 25 mg QD), and left ventricular end-systolic diameter (LVESD) (max mean increase of 0.79 cm with 25 mg QD).

Secondary pharmacology

Effect on cardiac electrophysiology

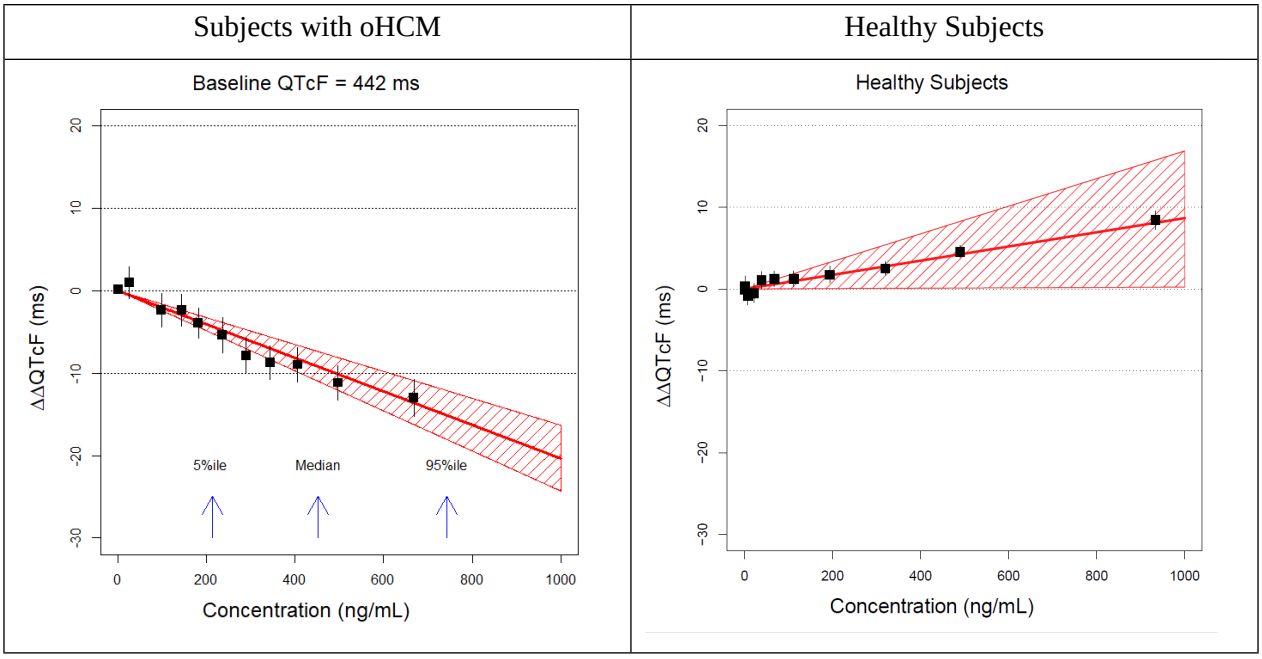
The concentration-response for the QTcF interval was analyzed and modelled. Data from 9 clinical studies were the basis for these analyses, including MYK-461-002, MYK-461-003, MYK-461-004, MYK-461-005, MYK-461-006, MYK-461-007 (data per cut-off date 27May2020), MYK-461-008 (data per cutoff date 22Jan2020), MYK-461-010, and MYK-461-014.

No evidence of QTc prolongation was noted in healthy subjects receiving single doses of mavacamten. However, prolonged exposure to supratherapeutic mavacamten plasma concentrations in healthy subjects was associated with a modest concentration-dependent increase in QTcF. A median concentration <1152 ng/mL would be expected to maintain the mean ΔΔQTcF <10 ms in healthy subjects (Figure 15). A median concentration <593 ng/mL would be expected to maintain the upper 90% CI of mean ΔΔQTcF <10 ms.

In oHCM subjects, there was no indication for any increase in QTcF in subjects with HCM receiving mavacamten; in fact, a slight exposure-dependent shortening was observed which averaged -8.7 ms (upper and lower limit of the 90% CI 6.7 ms and 10.8 ms, respectively) at the median steady-state C_{max} of 452 ng/ml (Figure 15). Despite this decrease, the values remained within the normal range.

Several key differences exist between these 2 populations of healthy subjects and oHCM subjects. Average baseline QTcF was considerably higher in oHCM subjects (442 ms) versus healthy subjects (399 ms). Exposure to mavacamten decreases normal contractility in healthy hearts, whereas it normalizes hypercontractility in oHCM. Thus, prolonged exposure to mavacamten is deleterious to healthy individuals but beneficial to oHCM patients. These results suggest not only the lack of QTc prolongation in the target population but a slight QTc shortening that may be partly mediated by inhibition of INaL, which is upregulated in HCM.

Figure 15. Exposure-response relationship of ΔΔQTcF in subjects with oHCM and healthy subjects



oHCM = obstructive hypertrophic cardiomyopathy; QTcF = QT interval with Fridericia correction
The red line represents the model-predicted mean values of ΔΔQTcF versus mavacamten concentration, and the shaded area indicates 90% CIs. Simulation was done for median baseline QTcF of subjects with oHCM (442 ms, left panel) and healthy subjects (399 ms, right panel). Squares are the means of observed ΔΔQTcF in subjects with oHCM (left panel) or healthy subjects (right panel) binned by plasma concentrations of mavacamten, and the error bars represent 90% CIs. Blue vertical arrows (left panel) indicate the 5th, 50th, and 95th percentiles of steady-

state Cmax (2 h post dose) observed at Week 30 in Study MYK-461-005 treated with a titrated dose of mavacamten once daily.

Isometric handgrip strength

Isometric handgrip strength was also assessed as a measure of skeletal muscle activity. In the single ascending dose study in healthy subjects (Study MYK-461-002), no clinically significant findings or trends were observed in handgrip strength. Mean changes from baseline tended to be negative for both the mavacamten and placebo groups.

Also, in the single ascending dose study in oHCM subjects (Study MYK-461-001), no clinically significant findings or trends were observed in handgrip strength. Mean changes from Baseline tended to be negative for all groups, with larger general decreases observed in the higher dose mavacamten groups; however, overall trends in handgrip strength are difficult to discern due to the small sample size.

In the multiple ascending dose study in healthy subjects (Study MYK-461-003), handgrip strength generally increased slightly over time in the placebo group, while there were no apparent trends across time or dose in the mavacamten groups.

Pharmacodynamic interactions with other medicinal products or substances

Calcium channel blockers (CCB) of the nondihydropyridine variety such as verapamil and diltiazem act directly on the myocardium to reduce contractility and heart rate. These features can have the salutary effects of decreasing LVOT obstruction and allowing the left ventricle more time to fill in diastole. However, CCB are not felt to be as potent or effective as beta adrenergic receptor blockers (BB) in the treatment of obstructive HCM. Thus, background therapy with CCB was not as prevalent in MYK-461-005 (EXPLORER-HCM) as BB.

Beta-adrenergic receptor blockers (BB) are very effective in reducing contractility and heart rate and have been used to treat obstructive HCM since the 1960s. In EXPLORER-HCM, reduction in LVOT gradient on mavacamten treatment was similar in subjects on background BB therapy versus those who were not (-37.5 mmHg vs -42.2 mmHg at rest, -50.0 mmHg vs -46.3 mmHg Valsalva). There was a slightly greater reduction in LVOT gradient at rest and with Valsalva manoeuvre in subjects who were not on background BB. Disopyramide and ranolazine are other agents which may also decrease contractile force, albeit via different mechanisms. Other than heart rate with regard to BB, there were no significant differences in parameters of LVEF or blood pressure between placebo and mavacamten and no excess of AEs related to heart failure regardless of background therapy for HCM.

Despite both BB and CCB both acting to decrease myocardial contractility, combination therapy is sometimes necessary at the decision of the treating physician and thus is not uncommon in the treatment of obstructive HCM with BB-disopyramide and CCB-disopyramide being most frequently seen. Disopyramide was excluded in EXPLORER-HCM and this is discussed in greater detail in the response. While combination therapy was excluded in EXPLORER-HCM, in MYK-461-017 (VALOR-HCM) trial where all combinations were allowed, clinically prescribed combinations of BB-CCB (14%) and even triple therapy with BB-CCB-disopyramide (2.7%) were seen (refer to data in the response to Question 85). No excess of AEs have been seen in VALOR-HCM data.

As such, mavacamten has been evaluated extensively in the setting of accepted background therapies of BB and CCB and more recently with combination therapies including those agents as well as other negative inotropes. This has resulted in no discernible signal for excessive decreases in cardiac function or risk for heart failure.

Genetic differences in PD response

Overall, 75.7% of subjects had HCM genotype assaying in the EXPLORER-HCM study (73.2% in the mavacamten group and 78.1% in the placebo group). The proportion of subjects with at least 1 pathogenic or likely pathogenic mutation was 31.1% in the mavacamten group and 22.0% in the placebo group. Four subjects (4.4%) in the mavacamten group with current HCM genotype testing had > 1 pathogenic or likely pathogenic mutation identified. No subjects in the placebo group had > 1 pathogenic or likely pathogenic mutation identified. Consistent with the results from the published literature, the most common genes affected were MYBPC3 (12.2% of mavacamten subjects and 13.0% of placebo subjects) and MYH7 (7.8% of mavacamten subjects and 3.0% of placebo subjects).

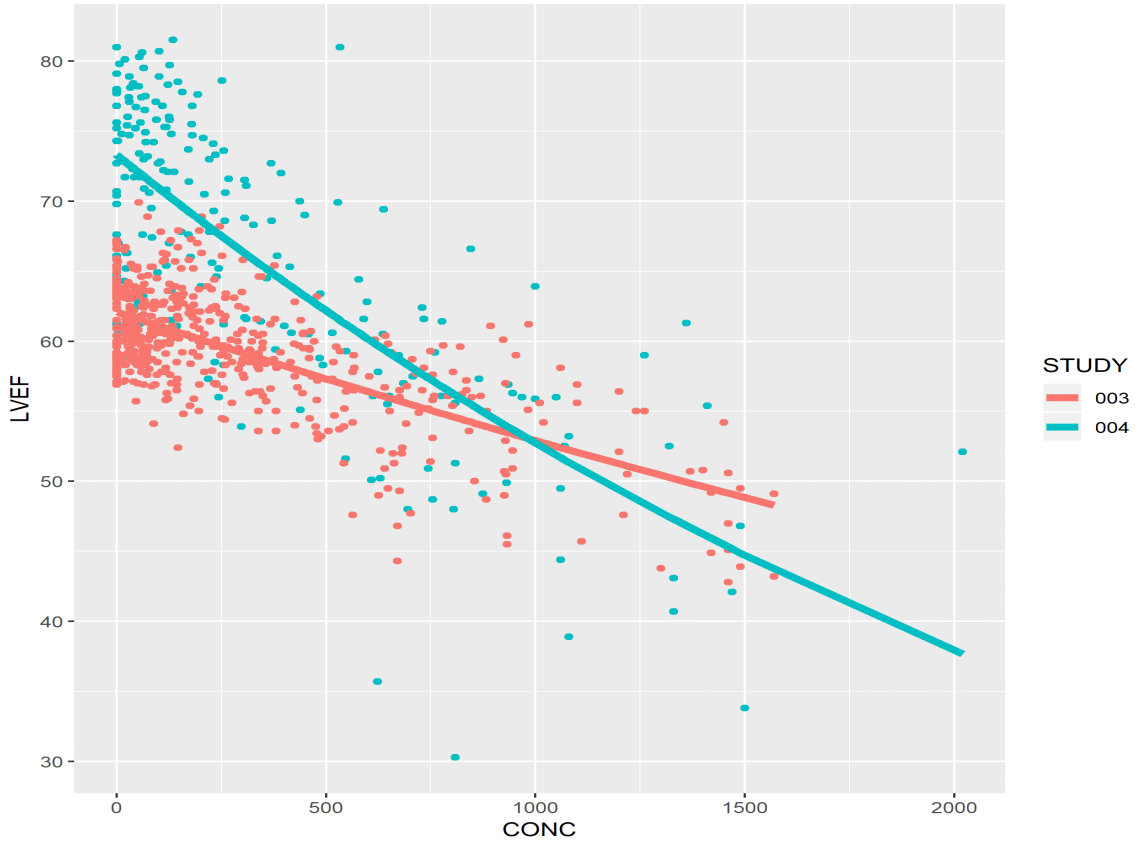
Subjects with any HCM pathogenic or likely pathogenic mutation were included in a subgroup analyses of efficacy endpoints. Overall, there was no consistent relationship between the primary composite endpoint or the secondary endpoints response (including pVO2) and the genetic subgroups; the CI for the treatment effects were generally overlapping between subgroups (see outcomes and estimation).

Relationship between plasma concentration and effect

Exposure-response of LVEF in healthy subjects vs subjects with oHCM

Mavacamten therapy results in concentration-dependent reductions of LVEF. Baseline left ventricular ejection fraction (LVEF) is higher in oHCM subjects, consistent with their generally hypercontractile state, compared with healthy subjects. Furthermore, the slope of the concentration-dependent reduction in LVEF is steeper in oHCM with what appears to be a normalization of LVEF, compared with healthy subjects (Figure 16). Given the differences in response between healthy subjects and the target populations, only patient data were considered to further explore the ER relationships described below.

Figure 16. LVEF versus mavacamten plasma concentration in subjects with oHCM in Study MYK-461-004 and healthy subjects in Study MYK-461-003



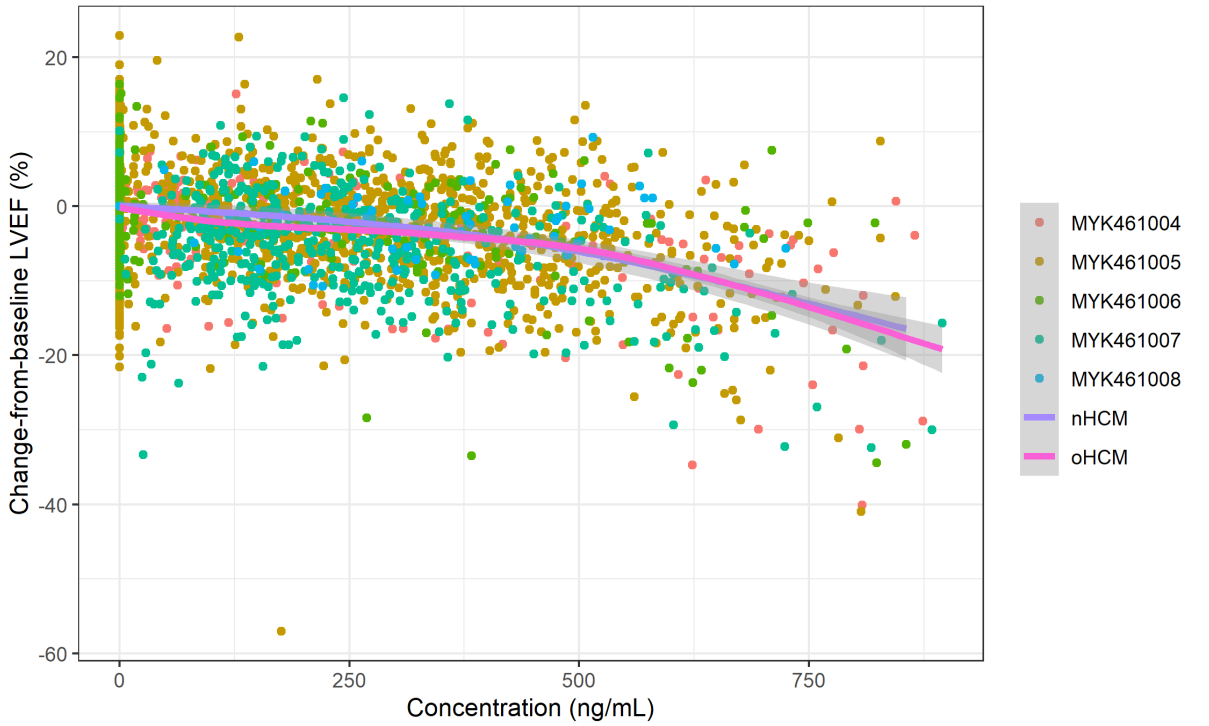
CONC = mavacamten plasma concentration (ng/mL); LVEF = left ventricular ejection fraction. Green (004)= oHCM and red (003)= healthy subjects. Points are visit-matched predose concentration and LVEF.

Exposure-response of LVEF in oHCM vs nHCM subjects

Nonobstructive HCM subjects had lower baseline LVEF than oHCM subjects; however, the data suggests once a lower baseline LVEF in nHCM is accounted for, the inverse (possibly sigmoidal-shape) relationship between exposure and LVEF does not differ by study population (nHCM versus oHCM)(Figure 17).

The evaluation of the impact of covariates on the mavacamten ER models focused on the most clinically relevant covariates. In the end, 5 continuous (LVEF, Valsalva LVOT gradient, NT-pro-BNP, lateral E/e`, and hsTroponin-I) and 6 categorical covariates (beta-blocker use (y/n), verapamil, diltiazem use (y/n), sex, NYHA BL (2/3), pacemaker use (y/n), population (oHCM/nHCM)) were tested in this ER analysis. The only 2 dependencies between covariate pairs were that nHCM subjects had lower baseline LVEF than oHCM subjects and that women had higher baseline LVEF than men.

Figure 17. Absolute change from baseline in LVEF versus observed plasma mavacamten concentrations ≤ 900 ng/mL in subjects with nHCM and oHCM

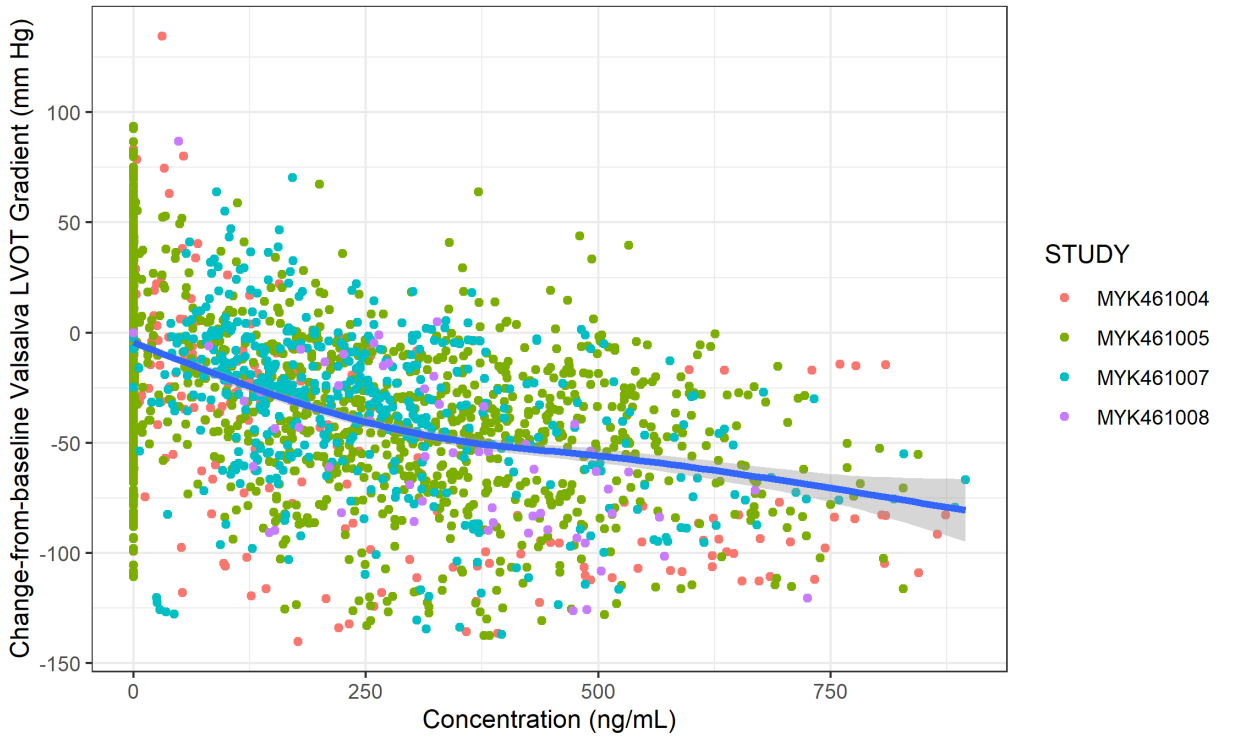


LVEF = left ventricular ejection fraction; nHCM = nonobstructive hypertrophic cardiomyopathy; oHCM = obstructive hypertrophic cardiomyopathy. Change-from-baseline computed as baseline LVEF – LVEF (absolute change in LVEF).

Exposure-response of LVOT gradient

Mavacamten therapy results in a decaying exponential pattern with a marked beneficial effect LVOT gradient reduction during Valsalva in many subjects at mavacamten plasma concentrations as low as 200 ng/mL with additional gradient reductions through 750 ng/mL in subjects with oHCM (Figure 18). The scatter plot also illustrates that some subjects require higher exposures to achieve a clinically relevant improvement in LVOT obstruction, supporting an individualized dose-titration strategy that is guided by directly measured LVEF and LVOT gradient by echocardiogram.

Figure 18. Change from baseline in Valsalva LVOT gradient versus observed mavacamten plasma concentrations ≤ 900 ng/mL

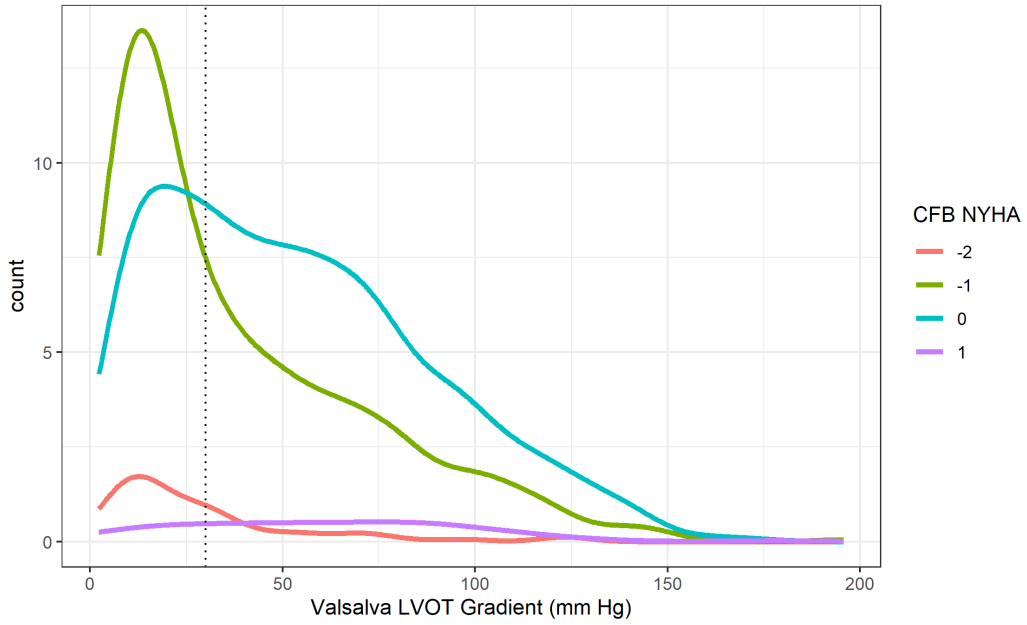


LVOT = left ventricular outflow tract

NYHA Class versus LVOT gradient

Figure 19 illustrates the frequency distribution of the Valsalva LVOT gradient for Week ⩾12 by change from baseline in NYHA class. Data suggest that the best outcomes, consisting of an improvement by 1 to 2 levels in the NYHA class, occur at Valsalva LVOT gradients below approximately 30 mmHg, a value which is generally used as the clinical threshold for diagnosing obstructive disease.

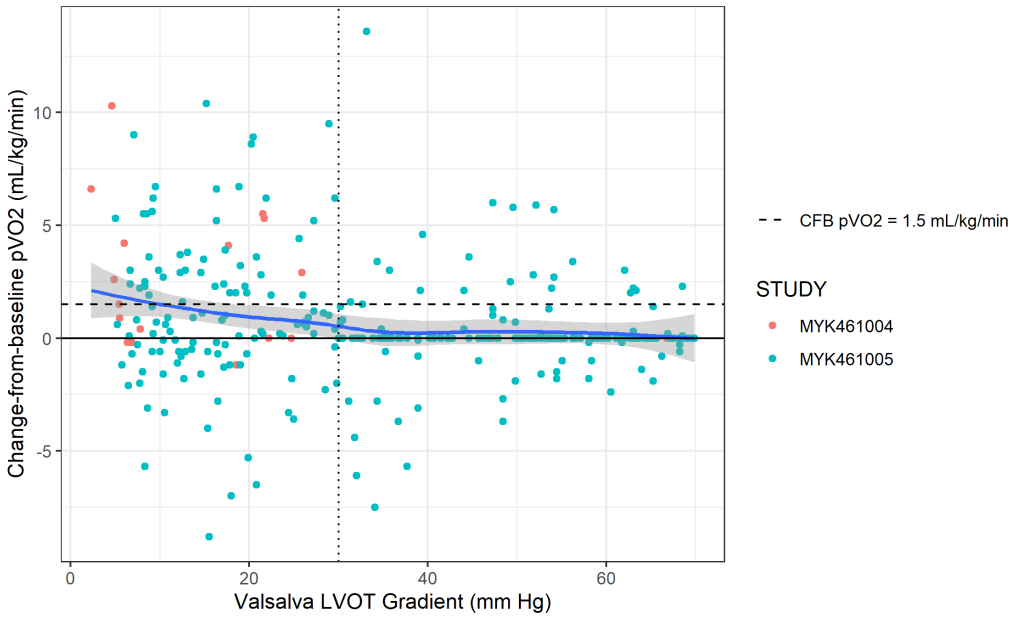
Figure 19. Frequency distribution of valsalva LVOT gradient by change from baseline in NYHA Class (Week ≥12)



pVO_2max versus LVOT gradient

Figure 20 demonstrates the change from baseline in pVO_2max versus Valsalva LVOT gradient at Week ⩾12 and truncated for gradients ⩽ 70 mmHg to highlight the relationship for lower gradient values. Similar to the findings for NYHA class, the figure suggests that the largest improvement in pVO_2max occurs at gradients below approximately 30 mmHg.

Figure 20. Change from baseline in pVO_2max versus Valsalva LVOT gradient ≤ 70 mmHg



Valsalva LVOT gradient versus baseline LVEF

There was no significant correlation observed between baseline LVOT gradient and LVEF in either mavacamten or placebo groups, as there was a wide distribution of baseline LVOT gradient and LVEF across both treatment groups (Figure 21). Furthermore, there was a slight trend for a greater decrease in LVEF with a greater LVOT gradient reduction from baseline in both treatment groups with a slightly stronger trend observed in the mavacamten treatment group (

Figure *22*).

Figure 21. Scatter Plot of Baseline Valsalva LVOT Gradient (mmHg) versus Baseline Resting LVEF (%) (ITT Analysis Set, EXPLORER-HCM Study)

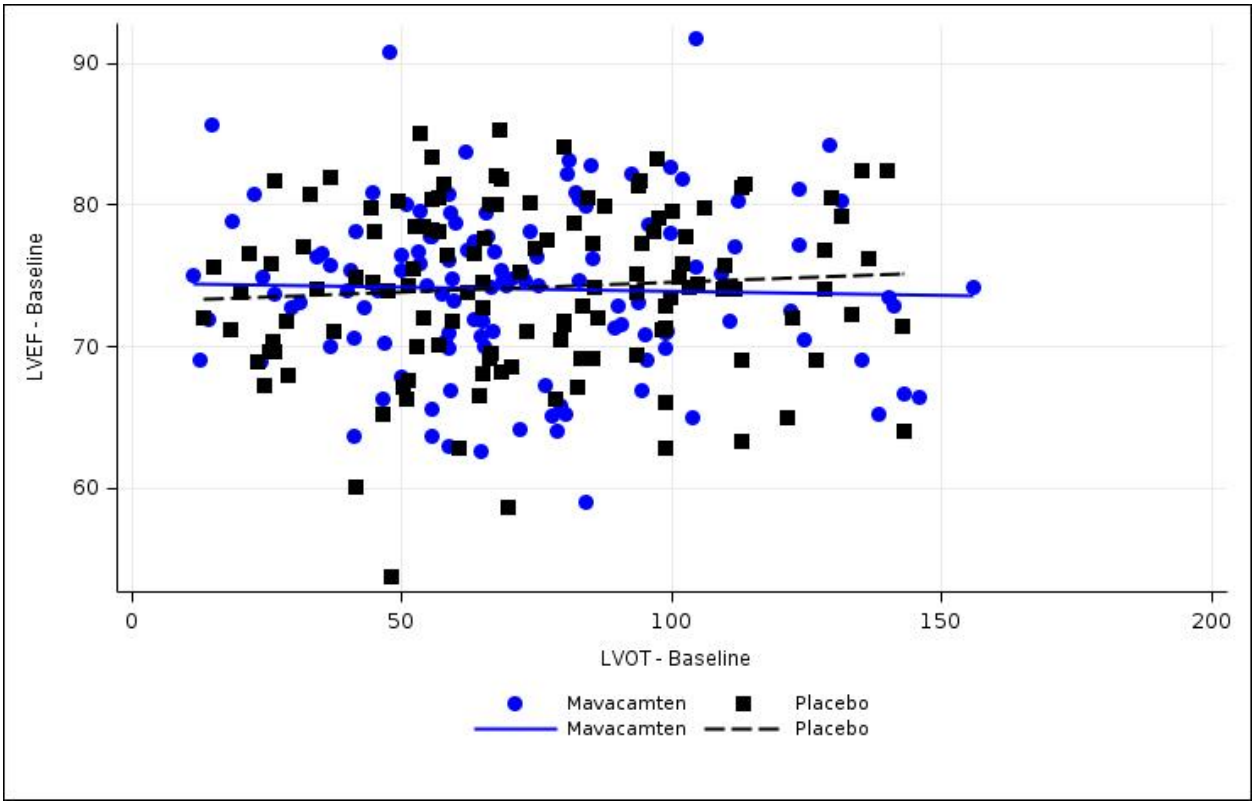
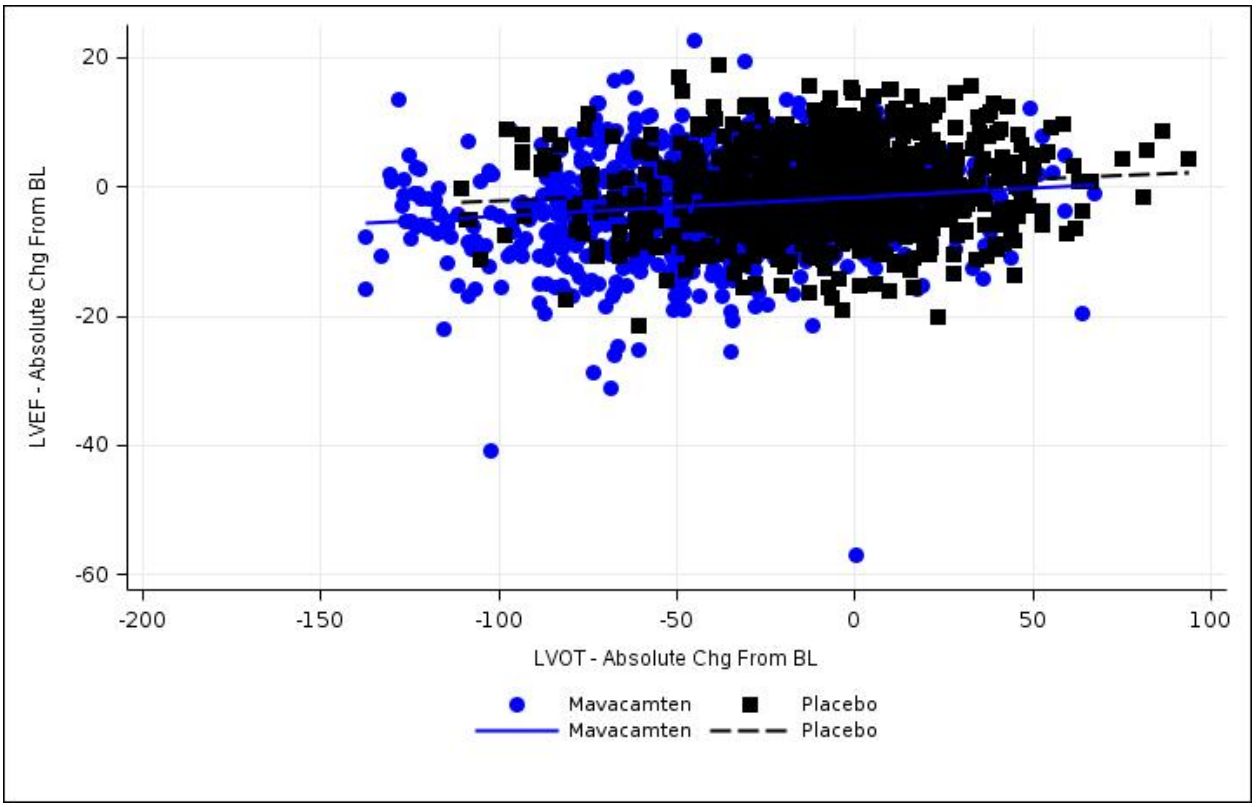


Figure 22. Scatter Plot of Absolute Change from Baseline to All Post-Baseline Visits in Valsalva LVOT Gradient (mmHg) versus Absolute Change from Baseline to All Post-baseline Visits in Resting LVEF (%) (ITT Analysis Set, EXPLORER-HCM Study)



2.5.3. Discussion on clinical pharmacology

Pharmacokinetics

The pharmacokinetics of mavacamten have been investigated in 12 dedicated clinical PK studies (11 studies in healthy volunteers and 1 study in patients) in plasma. In addition, sparse blood samples were obtained in 5 clinical studies in which the efficacy and safety of mavacamten was investigated in patients with obstructive hypertrophic cardiomyopathy. Due to the significant effect of CYP2C19 phenotype on the PK, the starting dose is 2.5 mg with a maximum dose of 5 mg in CYP2C19 poor metabolisers and the starting dose is 5 mg with a maximum dose of 15 mg in CYP2C19 non-poor metabolisers.

Pharmacodynamics

Mavacamten is a first-in-class cardiac myosin inhibitor representing the first medical therapy targeting the pathophysiology of obstructive hypertrophic cardiomyopathy (oHCM). Mechanistic hallmarks of oHCM include excess cross-bridge formation and dysregulation of the super-relaxed state of myosin resulting in hypercontractility, impaired relaxation, excess energy consumption, and myocardial wall stress. Myosin inhibition by mavacamten reduces (or in HCM normalises) cardiac myosin cross-bridge formation, which normalises contractility, reduces dynamic LVOT obstruction, and improves diastolic dysfunction and biomarkers of cardiac stress, improving symptoms and exercise capacity.

The pharmacodynamic effects of mavacamten were evaluated after single and multiple-dose administrations in healthy subjects (Study MYK-461-002 and Study MYK-461-003) and subjects with HCM (Study MYK-461-001). In Study MYK-461-002, a single dose of mavacamten 12, 24, and 48 mg resulted in dose-dependent decreases in left ventricular ejection fraction (LVEF), left ventricular outflow tract velocity integral (LVOT-VTI), left ventricular fractional shortening (LVFS), and stroke volume (SV) in healthy volunteers. Additionally, a dose-proportional relationship between mavacamten plasma concentration and PD effects (LVEF, LVOT-VTI, LVFS and SV) was observed. No consistent, dose-dependent changes were evident in biplane 2- and 4-chamber left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV) and isovolumetric relaxation time. In Study MYK-461-003, multiple dosing of mavacamten resulted in dose-dependent decreases in LVEF, LVOT-VTI, and LVFS both in resting and post-exercise transthoracic echocardiography in healthy subjects. Additionally, multiple dosing of mavacamten resulted in dose-dependent increases in global longitudinal strain (GLS), LVEDV, left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD). Generally, the largest effects were observed in the higher dose groups, i.e. 18.5 mg and 25 mg QD mavacamten. The effects caused by mavacamten were reversible as LVEF, LVOT-VTI, and GLS values returned toward baseline during the follow-up visits (up to Day 63) after discontinuation of the study drug. However, resting LVEDV, LVEDD, LVESD and LVFS values did not fully return to baseline by Day 63 in the higher groups of 18.5 mg and 25 mg QD mavacamten but were returned to baseline after 100 to 200 days post-dose. In patients with HCM (Study MYK-461-001), a single dose of 48, 96, and 144 mg mavacamten resulted in dose-dependent decreases in LVEF, LVOT-VTI, LVFS, and stroke volume. Additionally, a single dose of 96 mg and 144 mg mavacamten resulted in dose-dependent increases in LVEDV and LVESV.

Prolonged exposure with mavacamten in healthy subjects resulted in a concentration-dependent increase in QTcF. In oHCM subjects, treatment with mavacamten resulted in a slight concentration-dependent QTcF shortening that may be partly mediated by inhibition of INaL, which is upregulated in HCM. Despite the slight QTcF shortening observed in oHCM subjects, the absolute values remained well within normal limits and represents a degree of normalization of the interval in this population, whose baseline QTc tends to be higher than that in healthy subjects (442 ms vs 399 ms, respectively). The totality of data suggests that mavacamten does not result in torsade de pointes in subjects with oHCM. Nevertheless, since a modest concentration-dependent QTcF prolongation in healthy subjects was found, ECG evaluation has been performed in subsequent clinical studies, which is considered a conservative and therefore acceptable approach.

No important effects on handgrip strength were observed, indicating that mavacamten specifically affects cardiac muscle activity, but not skeletal muscle activity, which is reassuring.

There are no pharmacodynamic interactions with accepted background therapies of beta-blockers and calcium channel blockers. Furthermore, there was no consistent relationship between pVO_2max and HCM genotype.

Exposure-response analysis demonstrated a clear inverse relationship between mavacamten plasma concentrations versus LVEF and LVOT gradient. Nevertheless, a high interindividual PD variability (in addition to PK variability) has been observed, which underscores the need for an individualized dose-titration strategy, as currently proposed by the applicant (see section “Dose-response studies”). Furthermore, relationship analysis of LVOT gradient versus NYHA class and pVO_2max indicates that the largest improvements in NYHA class and pVO_2max occur at LVOT gradients ≤ 30 mmHg. The baseline Valsalva LVOT gradient versus baseline LVEF by treatment group scatter plot showed no correlation in either mavacamten or placebo group. However, the absolute change from baseline in Valsalva LVOT gradient versus absolute change in LVEF showed a slight trend for a greater decrease in LVEF with a greater decrease in LVOT gradient.

2.5.4. Conclusions on clinical pharmacology

The pharmacokinetics of mavacamten have been investigated in 12 dedicated clinical PK studies (11 studies in healthy volunteers and 1 study in patients) in plasma and via sparse sampling in 5 clinical efficacy and safety studies in patients with obstructive hypertrophic cardiomyopathy. There were concerns regarding effect of CYP2C19 phenotype on the PK and posology of mavacamten. A revised posology was agreed for patients that are CYP2C19 poor metaboliser. If treatment initiation occurs prior to determination of CYP2C19 phenotype, patients should follow dosing instructions for poor metabolisers until CYP2C19 phenotype is determined.

Generally, the pharmacokinetics and pharmacodynamics of mavacamten have been sufficiently evaluated.

2.5.5. Clinical efficacy

This application is based on efficacy data obtained from the following studies:

- Phase II dose-ranging study: PIONEER-HCM (Study MYK-461-004)
- Phase III study: EXPLORER-HCM (Study MYK-461-005)
- Phase III study: VALOR-HCM (Study MYK-461-017) (RCT complete and LTE ongoing)

Supportive data are obtained from the ongoing long term extension studies MAVA-LTE (Study MYK-461-007) and PIONEER-OLE (Study MYK-461-008).

The Phase II study MAVERICK-HCM (MYK-461-006) is conducted in patients with nonobstructive hypertrophic cardiomyopathy (nHCM) and does not contribute to the efficacy analysis presented in this application.

An overview of the Phase II and Phase III clinical development program is provided in the table below.

Table 4. Overview of Phase II and Phase III mavacamten clinical development program

Study/Phase/Status	Population / Key inclusion criteria	Design	Endpoints	Test Drugs, Dose, Treatment Duration	Number of Subjects Treated
Pivotal Study					
MYK-461-005 Phase 3 Completed FPFV: 30-May-2018 LPLV: 06-May-2020 (EXPLORER-HCM)	Adults with symptomatic oHCM defined by LV wall hypertrophy, with significant LVOT gradient, one measurement ≥50 mmHg at rest, during Valsalva, or after exercise and 30 mmHg at screening and symptoms (NYHA Class II or III). Treatment with beta-blocker or non-dihydropyridine calcium channel blocker was allowed as monotherapy	A Phase 3, double-blind, randomized, placebo-controlled, multicenter, international, parallel-group study. Randomization was stratified by NYHA class (II or III), current treatment with a beta-blocker (yes or no), planned type of ergometer used during the study (treadmill or exercise bicycle), and consent for the CMR substudy (yes or no).	**Primary composite:** • Functional and symptomatic response (pVO2 + NYHA class) **Secondary:** • Post-exercise LVOT peak gradient • pVO_2 • NYHA class • KCCQ-23 CSS • HCMSQ SoB domain score **Key Exploratory:** • Cardiac biomarkers (NT-proBNP and cardiac troponin) • LVOT gradient • Cardiac structure and systolic and diastolic function by TTE and CMR	Mavacamten 2.5, 5, 10, or 15 mg or placebo once daily. Starting mavacamten dose: 5 mg; up-titration at Week 8 and 14. Treatment duration: 30 weeks. Post-treatment follow-up period: 8 weeks.	Mavacamten: 123 Placebo: 128
MYK-461-017 Phase 3 Completed: placebo-controlled dosing	Adults with symptomatic oHCM† who are SRT-eligible†† and	A Phase 3 a multicenter, randomized, double-blind, placebo-controlled	**Primary composite:** 1. Decision to proceed with SRT prior to or at Week 16	**Placebo-controlled Period** *randomization to Week 16*	**Placbo-controlled dosing Period:** Mavacamten: 56

Study/Phase/Status	Population / Key inclusion criteria	Design	Endpoints	Test Drugs, Dose, Treatment Duration	Number of Subjects Treated
period and Primary Analysis at Week 16. Ongoing: active-controlled dosing period (Week 16 to Week 32) and long-term extension period (Week 32 to Week 128) FPFV: 29-Jul-2020 Interim data cut-off date: 07-Feb-2022 (VALOR-HCM)	referred (or under active consideration) for SRT within 12 months prior to screening. Treatment with SoC monotherapy or combination was allowed. † symptomatic oHCM defined by LV wall hypertrophy with LVOT gradient ≥50 mmHg (at rest, during Valsalva, or after exercise) and NYHA Class III functional symptoms or NYHA Class II with history exertional syncope †† 2011 ACCF/AHA HCM guideline18 criteria for SRT eligibility	study with 3 dosing periods. Randomization was stratified by - type of SRT procedure recommended (myectomy or ASA) - NYHA functional class.	2. SRT guideline eligible at Week 16 based on the 2011 ACCF/AHA HCM guideline **Secondary endpoints:** • Post-exercise LVOT gradient • Improvement ≥1 NYHA Class • KCCQ-CSS • NT-proBNP • Troponin	Starting regimen: mava 5 mg QD or matched placebo Up-titration evaluation at Weeks 8 and 12 based on the LVEF and Valsalva LVOT gradient measured by ECHO (max dose: 15 mg) Down-titration evaluation at Week 4 for early efficacy (VLVOT <30 mmHg). Dose interruption at any visit for LVEF <50% followed by down-titration. In LTE dose adjustment allowed if discussed with medical monitor. **Active-controlled Period** *Week 16 to 32* Placebo arm crosses over to mava at Week 16 with the same 5 mg starting dose and equivalent adjustment schedule (up-titration at 8 and 12 weeks of exposure; possible down-titration at 4 weeks of exposure) as the mava group during the Placebo-controlled Period During the Active-controlled Period, patients who started on mava at Day 1 remain on mava	Placebo: 56 **Active-controlled Period / LTE Period** Mava: 106 (54 former mava, 52 former placebo)

Study/Phase/Status	Population / Key inclusion criteria	Design	Endpoints	Test Drugs, Dose, Treatment Duration	Number of Subjects Treated
				therapy with no scheduled dose changes. **LTE Period** *Week 32 to 128* All patients remain on mava with potential dose titration based on site-read ECHO parameters	
Supportive Study					
MYK-461-004 Phase 2 Completed FPFV: 07-Oct-2016 LPLV: 17-Nov-2017 (PIONEER-HCM)	Adults with symptomatic oHCM; significant LVOT obstruction and NYHA II-III.	A phase 2 open-label study.	**Primary:** Post-exercise LVOT gradient **Secondary:** • Resting LVOT gradient • Valsalva LVOT gradient • Resting LVEF • pVO_2 • VE/VCO_2 slope • Dyspnea score	Mavacamten 2, 5, 10, 15, or 20 mg once daily. Treatment duration: 12 weeks. Post-treatment follow-up period: 4 weeks. **Part A:** Starting dose of 10 mg for subjects who weigh ≤ 60 kg and 15 mg for subjects who weigh > 60 kg. No HCM background therapy allowed. **Part B**: Starting dose 2 mg with maximal titration to 5 mg. Background therapy with beta-blockers allowed. Parts A and B had dose adjustments at the end of Week 4 (Part A based on change in LVEF and Part B based on change in LVOT gradient).	Part A:11 Part B: 10
Long-term Extension Studies					

Study/Phase/Status	Population / Key inclusion criteria	Design	Endpoints	Test Drugs, Dose, Treatment Duration	Number of Subjects Treated
MYK-461-007[a] (EXPLORER-LTE) Phase 2/3 Ongoing FPFV: 05-Oct-2018 (MAVERICK-LTE cohort) FPFV: 18-Mar-2019 (EXPLORER-LTE) LPLV: not occurred, study is ongoing; interim data cutoff 31 Aug 2021	Adults with symptomatic oHCM that participated and completed the parent study MYK-461-005.	A Phase 2/3, long-term treatment (5 years) extension study.	**Primary:** Safety **Secondary:** • Valsalva LVOT gradient • NYHA class • NT-proBNP • Cardiac structure and systolic (LVEF) and Diastolic function • Frequency of septal reduction therapy in the study cohort	Mavacamten 2.5, 5, 10, or 15 mg once daily up to 5 years. Starting mavacamten dose: 5 mg; clinically guided dose adjustments starting Week 4. Treatment duration of up to five years (ongoing). Exposure as of 31 Aug 2021 cutoff: 224 subjects completed 12 week dose titration phase. 221 subjects completed 24 weeks treatment. 205 subjects completed 48 weeks (1 year) treatment. 34 subjects completed 96 weeks (2 years) treatment	EXPLORER-LTE Cohort: 231
MYK-461-008 Phase 2 LTE Ongoing FPFV: 26-Apr-2018 LPLV: not occurred, study is ongoing; interim data cutoff 31 Aug 2021.	Adults with symptomatic oHCM, that participated and completed the parent study MYK-461-004.	A Phase 2, open-label, long-term treatment (5 years) extension study.	**Primary:** Safety **Secondary:** • LVOT gradient • NYHA class • KCCQ-23 CSS • NT-proBNP • Cardiac structure and systolic (LVEF) and diastolic function • Frequency of septal reduction therapy in the study cohort	Mavacamten 5, 10, or 15 mg capsule once daily up to 5 years. Starting mavacamten dose: 5 mg; with dose adjustment at Week 6. Treatment duration of up to five years (ongoing). Exposure as of 31 Aug 2021 cutoff: Median duration of exposure was 162 weeks (~3 years)	13

Abbreviations: ACCF/AHA = American College of Cardiology Foundation/American Heart Association; ASA = alcohol septal ablation; CSS = clinical summary score; ECHO = echocardiogram; FPFV = first patient first visit; HCM = hypertrophic cardiomyopathy; oHCM = obstructive HCM; KCCQ-23 = Kansas City Cardiomyopathy Questionnaire 23-item version; LPLV = last patient last visit; LTE = long-term extension; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; pVO2 = peak oxygen uptake; SoB = shortness of breath; nHCM = nonobstructive HCM; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; m = mava; OSS = overall summary score; QD = taken once daily; SoC = standard-of-care; SRT = septal reduction therapy; VE/VCO2 = volume expired/carbon dioxide production slope.

[a] Study MYK-461-007 enrolled subjects from the parent Phase 2 MYK-461-006 (nHCM population) study and Phase 3 MYK-461-005 (oHCM population); in this summary of efficacy, data from study MYK-461-007 is presented only for oHCM subjects enrolled from the parent Phase 3 MYK-461-005 (referred to as the EXPLORER-LTE cohort).

2.5.5.1. Dose response studies

The 5 mg starting dose and individualized echocardiogram-guided dose adjustments for the proposed posology are recommended based on the findings in the dose-ranging Phase 2 PIONEER-HCM study (MYK-461-004), the pivotal Phase 3 study EXPLORER-HCM (MYK-461-005) and the EXPLORER-LTE cohort in the ongoing extension study of long-term safety and efficacy of mavacamten (MAVA-LTE; MYK-461-007). The data from these studies and the clinical pharmacological knowledge of mavacamten have been integrated through modelling and simulation, namely population PK and PK/PD (E-R).

PIONEER-HCM

In the open-label dose-ranging PIONEER-HCM study, a wide exposure-response range was evaluated to identify the range of mavacamten plasma concentrations associated with therapeutic benefit and minimal risk in subjects with symptomatic HCM and LVOT obstruction. The study consisted of two-part (Part A (n=13)) and Part B (n=12)) and had a 12-week treatment phase followed by a 4-week washout phase. In Part A, which was designed to provide dose ranging information on mavacamten and PK/PD characterization at lower drug concentrations, the starting dose was 10mg for subjects who weighed ≤ 60 and 15 mg for subjects who weighed > 60 kg. In Part B, which was designed to characterize dose-response and to define the minimum inhibitory dose, the starting dose was 2 mg. Both Parts A and B had dose adjustments (based on percent decrease from baseline in LVEF (Part A) or LVOT gradient (Part B) at week 4. In total, 13 subjects were enrolled in Part A and 9 (69.2%) subjects completed the study. Four subjects discontinued the study due to failed screening (n=2) and withdrawn consent (n=2). In Part B, 12 subjects enrolled; 10 (83.3%) subjects completed the study while 2 failed Screening. The primary efficacy endpoint, change in post-exercise peak LVOT gradient from baseline to week 12, showed a significant 82% mean reduction from 103 ± 50 mmHg at baseline to 19 ± 13 mmHg at Week 12 (p = 0.008) in Part A and a significant 27% mean reduction from 86 ± 43 to 63 ± 26 mmHg (p = 0.020) in Part B (Table 5). The primary efficacy endpoints were further supported by improvements in the secondary efficacy endpoints, dyspnea scores, exercise capacity (pVO_2max) and NYHA FC for both Part A and Part B and systolic anterior motion (SAM) for Part A only. The observed effect is reversible considering that the LVOT gradient values returned toward baseline at week 16, i.e. 4 weeks after discontinuing mavacamten. Exposure-responses analyses showed a relationship between mavacamten plasma concentration and Valsalva LVOT gradient (Figure 23 and Figure 24) and LVEF (Figure 25 and Figure 26). Overall, results from this dose-ranging PIONEER-HCM study provided the rationale for the individualized dosing algorithm based on PD and concentration targets used in the pivotal phase III study EXPLORER-HCM, i.e., a starting dose of mavacamten 5 mg and a provisional target therapeutic range of mavacamten plasma trough concentration between 350 and 1000 ng/mL.

Table 5. Left ventricular outflow tract gradient, efficacy set

	Part A			Part B		
	Baseline (N)	**Week 12 (N)**	**Mean Change (p-value)**	**Baseline (N)**	**Week 12 (N)**	**Mean Change (p-value)**
Post-exercise peak LVOT Gradient (mmHg)	103 ± 50 (9)	19 ± 13 (10)	-90 ± 58 (p = 0.008)	86 ± 43 (9)	63 ± 26 (10)	-25 ±29 (p = 0.020)
Resting LVOT Gradient (mmHg)	60 ± 28 (11)	14 ± 25 (10)	-48 ± 34 (p = 0.006)	86 ± 63 (10)	38 ± 31 (10)	-48 ± 48 (p = 0.004)
Valsalva LVOT Gradient (mmHg)	97 ± 32 (11)	16 ± 28 (10)	-85 ± 41 (p = 0.002)	100 ± 65 (10)	53 ± 36 (10)	-47 ± 49 (p = 0.002)

Source: t_11_2_grad_rest A and B, t_11_3_grad_ex A and B, t_11_9_grad V A and B.

Abbreviation: LVOT = left ventricular outflow tract.

Note: The p-values are from Wilcoxon Signed-Rank tests evaluating the distribution of within-subject 12-week changes from baseline around a null of zero.

Figure 23. Resting LVOT gradient vs mavacamten plasma concentration, Part A, Efficacy Set

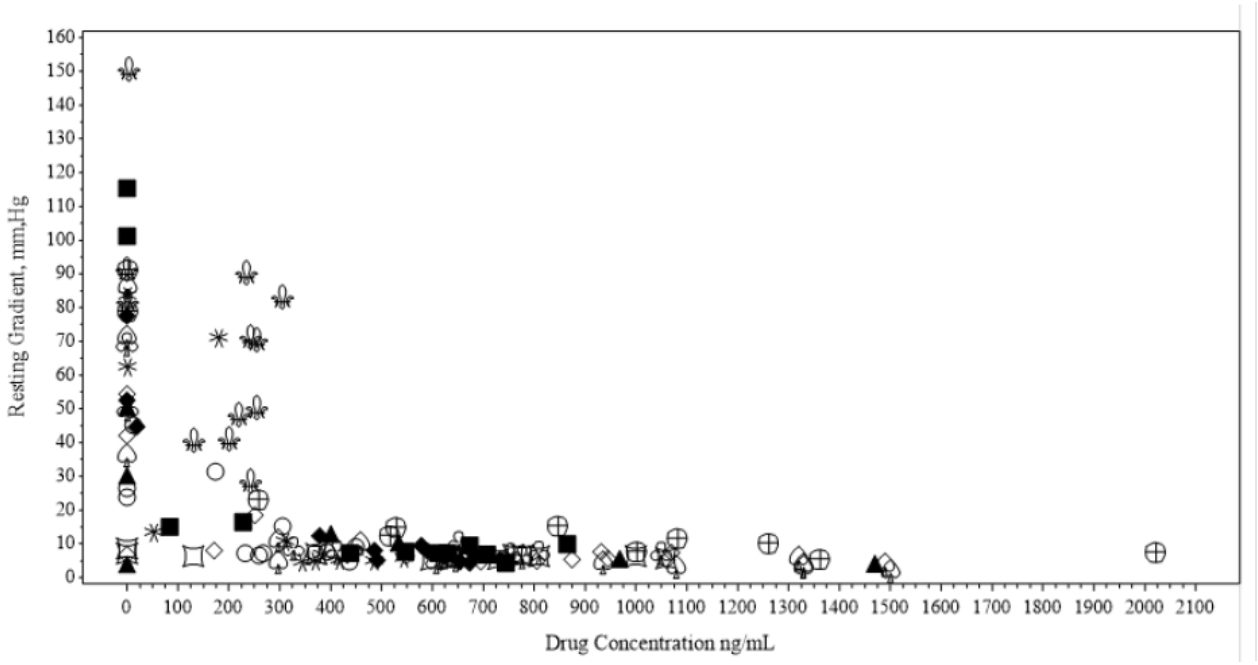


Figure 24. Resting LVOT gradient vs mavacamten plasma concentration, Part B, Efficacy Set

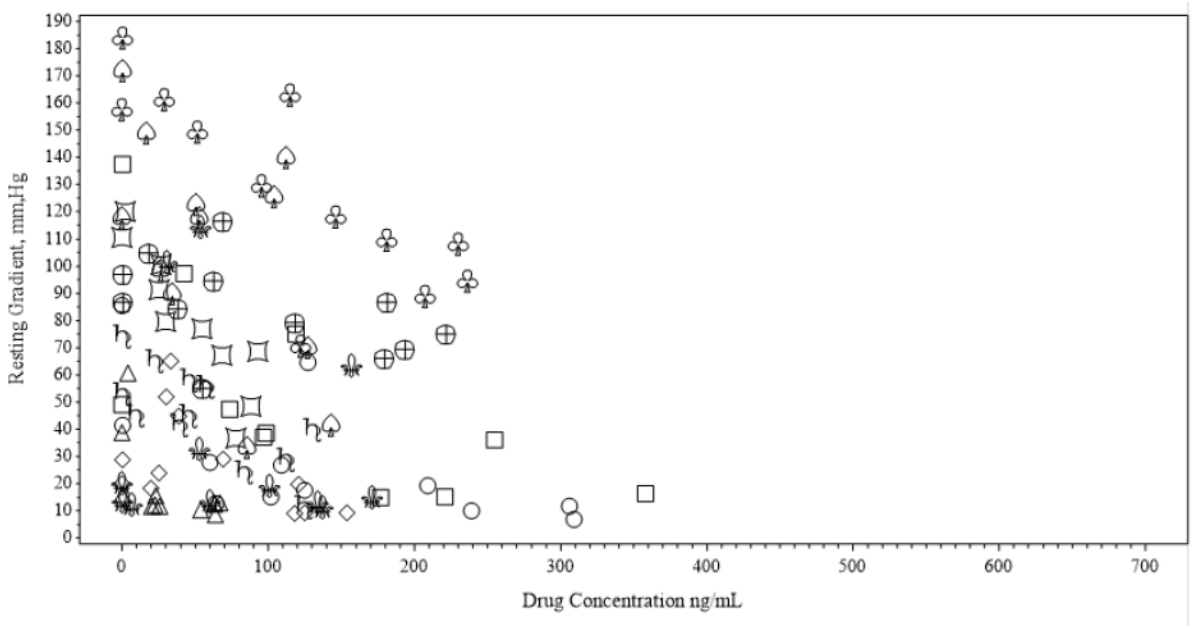


Figure 25. Resting LVEF versus Mavacamten plasma concentrations, Part A, Efficacy Set

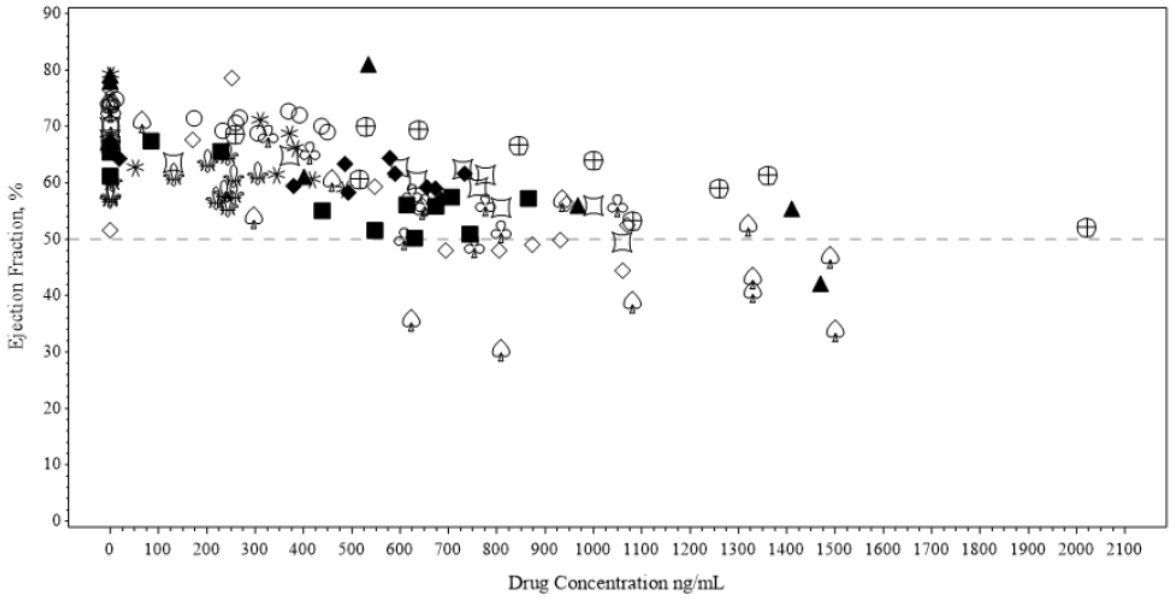
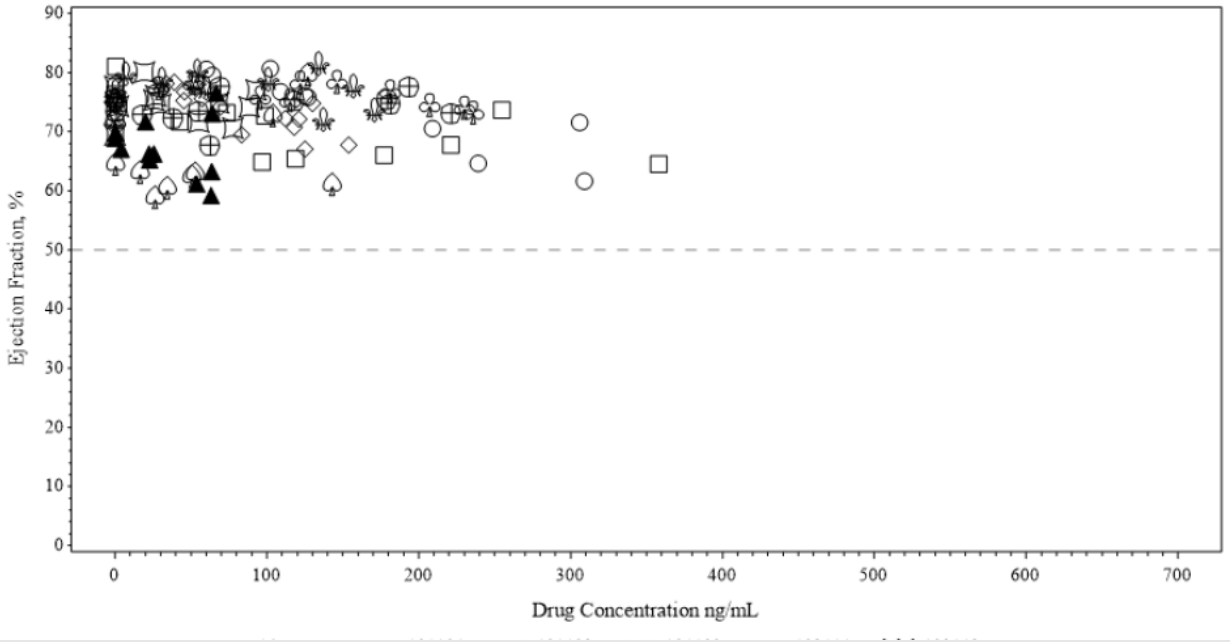


Figure 26. Resting LVEF versus Mavacamten plasma concentrations, Part B, Efficacy Set



Rationale for dose selection and titration regimen

Additional changes to the pivotal study EXPLORER-HCM titration scheme beyond echocardiogram-guided dosing have been implemented in the proposed posology (Table 6). Of particular importance is the use of a more stringent down titration cut-off value (Valsalva LVOT gradient <20 mmHg vs <30 mmHg); a minimum of 12 weeks and LVEF ≥55% prior to dose up-titration and a follow-up visit at 4 weeks after any up-titration. The rationale for the dose selection and titration regimen, including these changes, are presented below.

Table 6. Key titration regimen criteria in Study MYK-461-005, Study MYK-461-007, and the proposed PI

	MYK-461-005 (EXPLORER-HCM)	**MYK-461-007 (EXPLORER-LTE Cohort)**	**Proposed PI**
Starting dose	5 mg	5 mg	5 mg
Early down-titration	As early as Week 6 if Conc 700 to 1000 ng/mL (based on Week 4 PK)	Week 4 if VLVOT gradient <30 mmHg	Weeks 4 and 8 if VLVOT gradient <20 mmHg
Up-titration	As early as Week 8 if LVEF ≥50% and Conc <350 ng/mL and VLVOT gradient ≥30 mmHg	As early as Week 8 if LVEF ≥50% and VLVOT gradient ≥30 mmHg	As early as Week 12 if LVEF ≥55% and VLVOT gradient ≥30 mmHg (minimum 12 weeks between up-titrations)
Down-titration	Conc 700 to 1000 ng/mL at any visit	n/a	n/a
Temporary Interruption	LVEF <50% or Conc ≥1000 ng/mL	LVEF <50% or Conc ≥1000 ng/mL	LVEF <50%

Mavacamten starting dose

The results of the phase II dose-ranging PIONEER-HCM study in combination with phase I studies were included in the PK/PD modelling and provided the data to justify the 5 mg starting dose, the 15 mg maximum dose, and the dose-adjustment algorithms used in the pivotal EXPLORER-HCM study and in the EXPLORER-LTE cohort of the long-term extension study MAVE-LTE.

In the pivotal phase III study EXPLORER-HCM, the 5-mg starting dose was shown to be safe with the initial down titration capturing those subjects who required a dose reduction to 2.5 mg and no subject experienced a drop in LVEF <50% at the early-down titration point. By the end of the study, over 90% of subjects received either a 5, 10 or 15 mg dose, and only 4.9% received 2.5 mg. As in the pivotal study EXPLORER-HCM, the starting dose for subjects in the ongoing extension MAVE-LTE study (EXPLORER-LTE cohort) was 5 mg. In this study, the direct measurement of an early PD response (Valsalva LVOT gradient <30 mmHg), rather than plasma mavacamten concentrations, was used as the criterion for down-titration to 2.5 mg at Week 4. Based on the interim analysis in this study, no subjects reported an LVEF <50% at Week 4 and were down titrated due to meeting the early efficacy criteria of Valsalva LVOT gradient <30 mmHg.

According to the applicant, the starting dose of 5 mg is considered suitable for all patients, regardless of age, sex, body weight, CYP2C19 metabolizer status, mild or moderate hepatic or renal impairment, and concomitant medication. Although an increase in exposure is anticipated with certain patient factors, namely CYP2C19 poor metabolizer status (PMs) and lower body weight, the monitoring intervals prespecified in the dosing recommendations and described below are designed to effectively identify patients that may need dose adjustment in a timely manner.

Echocardiogram-guided dosing

The clinical experience and modelling, and simulation work support the use of clinically guided dosing using echocardiogram over the measurement of mavacamten plasma concentration. Both the pharmacologic effect of mavacamten on cardiac contractility, LVEF, and the attendant efficacy measure, LVOT gradient, can be readily measured on echocardiography. Additionally, due to the significant interindividual PK variability, monitoring of concentrations does not accurately predict LVEF.

When study EXPLORER-HCM was initiated, limited exposure-response data were available. Consequently, blinded dose adjustment for individual subjects was based on a combination of clinical response (Valsalva LVOT gradient) and tolerability/safety (LVEF) together with mavacamten plasma concentrations aimed at maintaining concentrations between 350 to 700 ng/mL. Mavacamten plasma trough concentrations ≥1000 ng/mL or LVEF <50% triggered temporary treatment discontinuation. Study EXPLORER-HCM demonstrated that a starting dose of 5 mg with gradual adjustment and individualized up- or down-titration to doses of 2.5 to 15 mg based on echocardiography and plasma concentrations was safe and effective, and no excursions of plasma concentrations >1000 ng/mL occurred. Based on the results from study EXPLORER-HCM and PK/PD modelling, it was determined that echocardiographic monitoring of PD parameters (LVEF and LVOT gradient) could be utilized as a means to guide dose titration on an individual basis while monitoring disease status and clinical response after treatment initiation and at follow-up visits for up- or down-titration. The safety of dose adjustment based on clinically guided dose titration proposed for use in clinical practice is supported by data from the ongoing EXPLORER-LTE cohort and VALOR-HCM study in which titration was only based on monitoring of the PD parameters LVOT gradient and LVEF to manage individual patient dosing directly.

Dose-titration

The proposed mavacamten starting dose for all patients of 5 mg is followed by echocardiogram-guided dose adjustment. The rationale for the proposed mavacamten dose-adjustment regimen is to ensure

that the optimal dose for each individual is reached in a safe and effective manner. Careful titration and monitoring of the key response parameters, LVOT gradient and LVEF, are used to guide dose adjustment during mavacamten therapy to ensure the subject safety (i.e. few to no subjects experiencing LVEF <50, which is the lower limit of the normal range) and to attain the target efficacy criteria (Valsalva LVOT gradient <30 mm Hg).

An initial follow-up visit is proposed at 4 and 8 weeks after treatment initiation to assess for an early efficacy response (e.g., evidence of minimal residual obstruction [Valsalva LVOT gradient <20 mmHg]), in which case dose reduction to 2.5 mg is recommended. The strategy for this approach at the initial visit window and the specified level of LVOT gradient reduction is to allow the opportunity to detect an early clinical response and assess tolerability (eg, maintenance of a normal LVEF and assessment of patient symptom status). It also ensures that the optimal dose is achieved in every patient at the earliest possible time point while avoiding excessive decreases in LVEF, as supported by PK/PD modelling. In the product information, a lower LVOT gradient threshold of <20 mmHg compared with <30 mmHg used in the EXPLORER-LTE cohort is proposed for down-titration due to the observation that many patients in the EXPLORER-LTE cohort were down titrated to 2.5 mg for an early response and later required up-titration back to 5 mg. The rationale for this change was supported by modelling and simulation to ensure patients achieved their individualized dose without any compromise to safety. In the EXPLORER-LTE cohort, 80 subjects who were down titrated to 2.5 mg at Week 4 (for LVOT gradient <30 mmHg) had a Week 12 Visit performed. At week 4, 52 (65.0%) of the 80 subjects had LVOT gradients <20 mmHg. Among these 52 subjects, 32.7% subsequently had LVOT gradient > 30 mmHg at the Week 12 visit and therefore would have been considered for re-up-titration to 5 mg if the protocol had allowed. The other 28 (35.0%) subjects of the 80 who were down titrated to 2.5 mg at Week 4 had an LVOT gradient between 20 to 30 mmHg. Of these 28 subjects, 20 (71.4%) had an LVOT gradient > 30 mmHg at Week 12 and would have been re-up-titrated to 5 mg if the protocol had allowed it. Therefore, the more stringent threshold will minimize unnecessary dose fluctuations.

An increase in mavacamten dose may be considered 12 weeks after treatment initiation or after at least 12 weeks on a stable dose if symptoms of oHCM persist, i.e. Valsalva LVOT gradient is > 30 mmHg, and LVEF is > 55%. A higher criterion of LVEF > 55% than the LVEF> 50% used in the clinical studies is proposed to ensure that a dose increase will be tolerated and provides an additional buffer for the expected effect on contractility with an increased dose.

If LVEF is <50% at any visit, dosing with mavacamten should be interrupted and the patient should be re-assessed until LVEF is ≥50% at which point dosing at the same or lower dose can be resumed.

Monitoring intervals

Monitoring intervals in the proposed PI were modified from those used in the clinical studies based on modelling and simulation analysis. Based on the totality of data, the patient should be assessed for an early clinical response 4 and 8 weeks after treatment initiation. Patients who have not had their treatment paused, and who have a LVEF ≥55% and a LVOT gradient with Valsalva manoeuvre ≥30 mmHg may have their dose increased by one level (e.g., 2.5 to 5 mg; 5 to 10 mg; 10 to 15mg; 15 mg is the maximum daily dose) followed by a 4-week follow-up visit. This more conservative approach to dose increase is predicted to reduce the proportion of patients who experience an event of LVEF <50% compared with the schedule of potential dose increases used in the EXPLORER-LTE cohort (ie, at Weeks 4, 8, and 12). Once an individualised maintenance dose is achieved, patients should be assessed every 12 weeks. If at any visit the patient's LVEF is <50%, the treatment with mavacamten should be interrupted for 4 weeks and until LVEF returns to ≥50%. Thereafter, the treatment may resume on the next lower dose level. The modelling and simulation work demonstrates that this approach for monitoring intervals ensures appropriate benefit/risk, which is supported through the evaluation of the time-course of mavacamten plasma concentrations, LVOT gradients, and LVEF, which

remain stable through 2 years of treatment and supported by available data in the ongoing study MYK-461-007. This is consistent with observations in the ongoing study MYK-461-008, in which decreases in LVEF to <50% have not been observed with mavacamten treatment for up to a mean of 112.7 weeks.

The projected distribution of doses is highly similar between the proposed dosing regimen and both the simulated and observed distribution of doses using the MYK-461-005 titration regimen, providing additional support for the utility of the proposed dosing recommendations to achieve comparable efficacy to that achieved in the pivotal Phase 3 study MYK-461-005.

Proposed posology

Based on the collective knowledge from the clinical studies and modelling and simulation results, the following dosing recommendation is proposed in this study:

- Starting dose of 5 mg QD in all subjects
- Down-titrate to 2.5 mg at 4 and 8 weeks based on Valsalva LVOT gradient <20 mmHg after treatment initiation
- Consider step-wise dose increases (5, 10, up to a maximum of 15 mg) at Week 12, or after at least 12 weeks on a stable dose if
    - Valsalva LVOT gradient ≥30 mmHg, and
    - LVEF ≥55%
- Evaluate LVEF and LVOT gradient 4 weeks after each dose increase
- Discontinue dosing for 4 weeks any time LVEF is <50% and resume dosing at lower dose as indicated by clinical circumstances

2.5.5.2. Main studies

Study EXPLORER-HCM (MYK-461-005)) and study VALOR-HCM (MYK-461-017) are the phase 3 pivotal studies to support the proposed indication.

Study MYK-461-005

Study MYK-461-005 - A Randomized, Double-Blind, Placebo-Controlled Clinical Study to Evaluate Mavacamten (MYK-461) in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy (EXPLORER-HCM)

Methods

MYK-461-005 was a Phase 3, double-blind, randomized, placebo-controlled, multicenter, international, parallel-group study to evaluate the efficacy, safety, and tolerability of mavacamten compared with placebo in subjects with symptomatic oHCM.

Study Participants

The main inclusion/exclusion criteria are provided in Table 7 below.

Table 7. Key inclusion/exclusion criteria of EXPLORER-HCM

Study MYK-461-005
Inclusion Criteria
a) At least 18 years old at screening
b) Body weight > 45 kg at screening
c) Adequate acoustic windows to enable accurate transthoracic echocardiography (TTEs)
- Diagnosed with oHCM consistent with current AACF/AMA and ESC guidelines (ie, satisfied both criteria below [criteria documented by the echocardiography core laboratory]): a. Unexplained LV hypertrophy with nondilated ventricular chambers in the absence of other cardiac (eg, hypertension, aortic stenosis) or systemic disease and with maximal LV wall thickness ≥15 mm (or ≥13 mm with positive family history of HCM) as determined by core laboratory interpretation, and b. LVOT peak gradient ≥50 mmHg during screening as assessed by echocardiography at rest, after Valsalva manoeuvre, or post exercise (confirmed by echocardiography core laboratory interpretation)
- Documented LVEF ≥55% at rest by echocardiography core laboratory read of screening TTE
- LVOT gradient with Valsalva manoeuvre at screening TTE ≥30 mmHg determined be echocardiography core laboratory
d) NYHA Class II or III symptoms at screening
e) Documented oxygen saturation at rest ≥90% at screening
- Able to perform upright CPET and respiratory exchange ratio (RER) ≥1.0 at screening per central reading; if the RER was between 0.91 and 1.0, the prospective subject may have been enrolled only if it was determined by the central CPET laboratory that peak exercise was achieved by the prospective subject (the only permitted reasons for subpeak performance were [1] a decrease in systolic blood pressure or [2] severe angina as described in the CPET Laboratory Manual).
Exclusion Criteria
- Previously participated in a clinical study with mavacamten
- Hypersensitivity to any of the components of the mavacamten formulation
- Participated in a clinical trial in which the subject received any investigational drug (or was currently using an investigational device) within 30 days prior to screening or 5 times the respective elimination half-life (whichever was longer)
- Known infiltrative or storage disorder causing cardiac hypertrophy that mimicked oHCM, such as Fabry disease, amyloidosis, or Noonan syndrome with LV hypertrophy
- Any medical condition that precluded upright exercise stress testing
- History of syncope within 6 months prior to screening or history of sustained ventricular tachyarrhythmia with exercise within 6 months prior to screening
- History of resuscitated sudden cardiac arrest (at any time) or known history of appropriate ICD discharge/shock for life-threatening ventricular arrhythmia within 6 months prior to screening. (Note: history of anti-tachycardia pacing within 6 months or ever was allowed.)
- Paroxysmal, intermittent atrial fibrillation with atrial fibrillation present per the investigator's evaluation of the subject's ECG at screening
- Persistent or permanent atrial fibrillation not on anticoagulation for at least 4 weeks prior to screening and/or not adequately rate controlled within 6 months of screening. (Note: subjects with persistent or permanent atrial fibrillation who were anticoagulated and adequately rate controlled were allowed.)
- Current treatment (within 14 days prior to screening) or planned treatment during the study with disopyramide or ranolazine
- Current treatment (within 14 days prior to screening) or planned treatment during the study with a combination of beta-blockers and verapamil or a combination of beta-blockers and diltiazem
- For individuals on beta-blockers, verapamil, or diltiazem, any dose adjustment of that medication within 14 days prior to screening or an anticipated change in treatment regimen using those medications during the study
- Successfully treated with invasive septal reduction (surgical myectomy or percutaneous alcohol septal ablation (ASA)) within 6 months prior to screening or planned to have either of these treatments during the study (Note: individuals with myectomy or percutaneous ASA performed > 6 months prior to screening may have been enrolled if study eligibility criteria for LVOT gradient criteria were met.)
- ICD placement or pulse generator change within 2 months prior to screening or planned new ICD placement during the study (pulse generator changes, if needed during the study, were allowed)
- QTcF > 500 ms at screening or any other ECG abnormality considered by the investigator to pose a risk to subject safety (eg, second-degree atrioventricular block type II)
- Documented obstructive coronary artery disease (> 70% stenosis in 1 or more epicardial coronary arteries) or history of myocardial infarction (MI)
- Known moderate or severe (as per investigator's judgment) aortic valve stenosis at screening

Eligibility for the CMR substudy

At selected sites, subjects who provided additional, specific consent may have participated in the CMR substudy. To be eligible for participation in the substudy, subjects must not have had 1) an ICD or pacemaker or 2) Atrial fibrillation at screening (subjects who were in atrial fibrillation at the time of

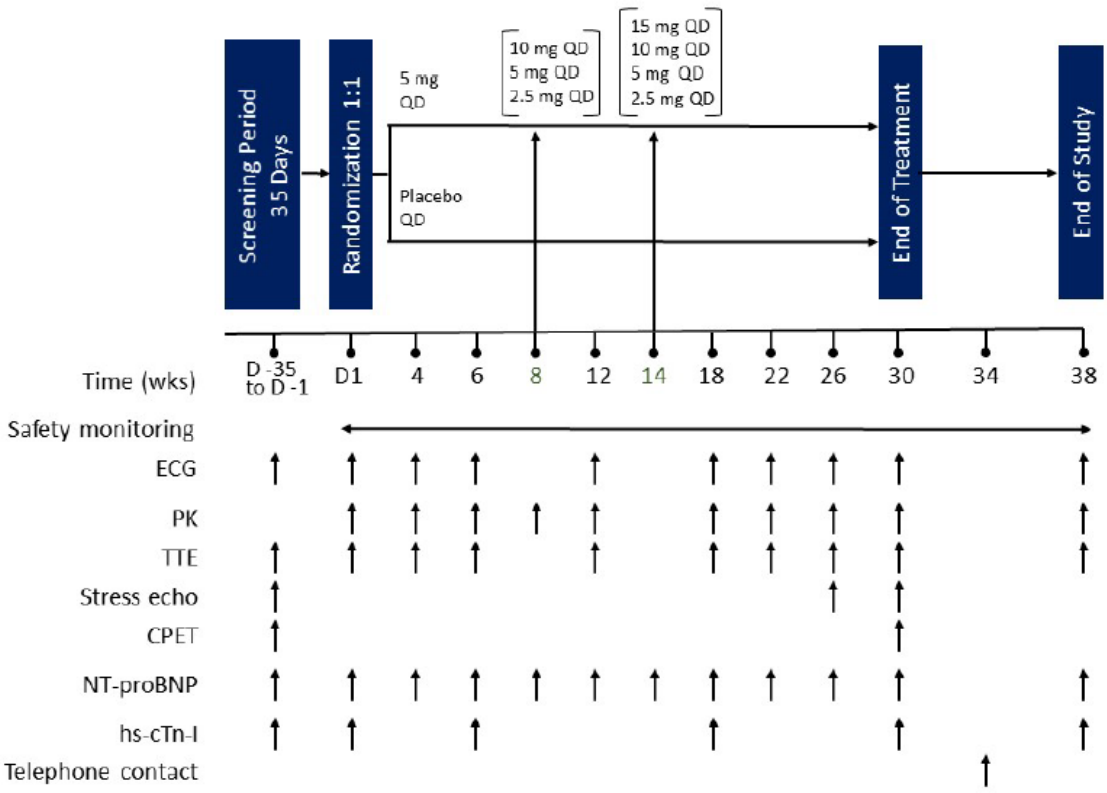
imaging were asked to return for reassessment within 1 month, and if the subject was still in atrial fibrillation, they were disqualified from enrolling in the CMR substudy).

Treatments

The design of the study included a screening period of up to 35 days, a double-blind treatment period of 30 days in which subjects received 2.5, 5, 10 or 15 mg mavacamten or matching placebo once daily (1:1) , and a follow-up period of 8 weeks (or 20 weeks for subjects who chose not to roll over or were not eligible to roll over into MAVA-LTE) (Figure 27).

In the double-blind treatment period, eligible patients started with 5 mg mavacamten or a matching placebo. At Week 6, the mavacamten dose could be down-titrated based on mavacamten plasma concentration and echocardiography responses on week 4, i.e. assessment for an early response (Table 8). At Week 8 and 14 the dose could be up-titrated, down-titrated, or remained unchanged based on mavacamten plasma concentration and echocardiography responses on Week 6 and 12 (Table 8 and Table 9). After the second dose adjustment at Week 14, no additional up-titrations were permitted. If at any subsequent on-treatment study visit (ie, Weeks 18, 22 or 26) PK and/or PD criteria were met for a decrease in dose, an unscheduled visit was arranged for 2 weeks later to reduce the mavacamten dose as outlined in Table 8. If the mavacamten dose was decreased at any time during the study, the subject was to continue on the reduced dose through Week 30/end of treatment unless safety or tolerability concerns required further dose reduction or discontinuation of study drug.

Figure 27. EXPLORER-HCM Study Schema



CPET = cardiopulmonary exercise testing; hs-cTn-I = high-sensitivity cardiac troponin-I; D = day; ECG = electrocardiogram; NT-proBNP = N-terminal pro b-type natriuretic peptide; PK = pharmacokinetics; QD = once daily; stress echo = postexercise stress echocardiogram; TTE = transthoracic echocardiography; wks = weeks

Table 8. EXPLORER-HCM: Criteria for Down-Titration of Mavacamten Dose

Time of Assessment	Resting LVEF[a, b] (%)	Mavacamten Plasma Trough Concentration (ng/mL)[b]	Time and Dose Reduction[c]
Week 4	≥ 50	> 700 to < 1000	Week 6: Reduce from 5 mg to 2.5 mg
Week 6			Week 8: Reduce to next lower dose • 5 mg to 2.5 mg • 2.5 mg to placebo
Week 8[c]			2 Weeks later[d]: Reduce to next lower dose • 10 mg to 5 mg • 5 mg to 2.5 mg • 2.5 mg to placebo
Week 12			Week 14: Reduce to next lower dose • 10 mg to 5 mg • 5 mg to 2.5 mg • 2.5 mg to placebo
Weeks 18, 22, and 26			2 Weeks later: Reduce to next lower dose • 15 mg to 10 mg • 10 mg to 5 mg • 5 mg to 2.5 mg • 2.5 mg to placebo

LVEF = left ventricular ejection fraction

[a] Resting LVEF < 50% triggered temporary discontinuation of study drug.

[b] LVEF and trough PK were communicated directly to the interactive response system from the core laboratories so that the investigator, study site personnel, and sponsor remained blinded.

[c] Dose reduction applied if PK criterion was met.

[d] Transthoracic echocardiography was not performed at the Week 8 assessment. Therefore, dose reduction was based solely on plasma concentration value at that time.

Table 9. EXPLORER-HCM: Criteria for Up-Titration or No Change in Mavacamten Dose at Week 8 and Week 14

Mavacamten Plasma Concentration and Valsalva Gradient at Week 6 or Week 12	Resting LVEF (%)[a]	Dose Titration[b]	At Week 8	At Week 14
PK < 350 ng/mL and Valsalva gradient ≥ 30 mmHg	≥ 50	Increase	5 mg to 10 mg	Increase from prior dose: • 5 mg to 10 mg • 10 mg to 15 mg
PK < 350 ng/mL and Valsalva gradient < 30 mmHg		No change	Continue prior dose: 2.5 mg or 5 mg	Continue prior dose: 2.5 mg, 5 mg, or 10 mg
PK ≥ 350 ng/mL and ≤ 700 ng/mL (regardless of Valsalva gradient)		No change	Continue prior dose: 2.5 mg or 5 mg	Continue prior dose: 2.5 mg, 5 mg, or 10 mg

LVEF = left ventricular ejection fraction; PK = pharmacokinetics (mavacamten plasma trough concentration)

[a] Resting LVEF < 50% triggered temporary discontinuation of study drug.

[b] Dose adjustments were communicated directly to the interactive response system based on Week 6 and Week 12 assessments, including measures of peak Valsalva gradient reported by the core laboratory so that blinding was maintained.

Cardiac Magnetic Resonance (CMR) substudy

In addition to the primary schedule of study assessments, subjects who participated in the CMR substudy underwent CMR on Day 1 and at Week 30.

Objectives

The primary objective of this study was as follows:

- To compare the effect of a 30-week course of mavacamten with placebo on clinical response comprising of exercise capacity and clinical symptoms in subjects with symptomatic oHCM

The secondary objectives of this study were as follows:

- To compare the effect of a 30-week course of mavacamten with placebo on symptoms and LVOT obstruction as determined by Doppler echocardiography
- To compare the effect of a 30-week course of mavacamten with placebo on exercise capacity, clinical symptoms, and patient-reported outcomes (PROs)
- To assess the safety and tolerability of mavacamten
- To assess the pharmacokinetic (PK) characteristics of mavacamten

The exploratory objective of this study was as follows:

- To assess the effect of a 30-week course of mavacamten on LVOT obstruction; disease biomarkers; symptoms, health-related quality of life (QoL), and work activity as assessed by PROs; cardiac rhythm patterns as assessed by continuous cardiac rhythm monitoring; functional capacity as assessed by accelerometer; and risk for SCD as assessed by the HCM risk prediction model.

The objective of the cardiac magnetic resonance imaging (CMR) substudy was as follows:

- To assess the effect of mavacamten on cardiac mass and structure as evaluated by CMR.

Outcomes/endpoints

The primary efficacy endpoint was composite functional response at Week 30, defined as achieving:

1. An improvement of ≥1.5 mL/kg/min in pVO_2max as determined by CPET and a reduction of ≥1 NYHA class or
2. An improvement of ≥3.0 mL/kg/min in pVO_2max with no worsening in NYHA class.

The applicant argued that the combined interrogation of these two parameters provides complementary assessments of the impact of treatment on myocardial function (pVO_2max) and symptomatic burden (NYHA class) and requiring an NYHA class improvement at the lower pVO_2max threshold provided an increased level of stringency to support clinical relevance. In addition, this design was also intended to attenuate a potential placebo response rate if assessing NYHA class alone (up to ≈30%). Therefore, NYHA class was assessed as a component of the primary composite endpoint and a secondary endpoint. According to the applicant, the combination as a composite endpoint is supported by the fact that both measures are independent prognostic variables in HCM and allows an integrated assessment of both benefits on the functional and symptomatic limitations of oHCM patients.

The secondary efficacy endpoints, which were tested sequentially, were:

- Change from baseline to Week 30 in postexercise LVOT peak gradient
- Change from baseline to Week 30 in pVO_2max as determined by cardiopulmonary exercise testing (CPET)
- Proportion of subjects who had at least 1 class of improvement from baseline in NYHA class at Week 30
- Change from baseline to Week 30 in subject-reported health status as assessed by the KCCQ-23 CSS
- Change from baseline to Week 30 in subject-reported severity of HCM symptoms as assessed by the HCMSQ SoB domain score

The exploratory endpoints included absolute values and changes from baseline in multiple CPET and echocardiography parameters, PRO, and cardiac biomarkers.

The primary efficacy endpoint of the CMR substudy was change from baseline to Week 30 in left ventricular mass index (LVMI). Exploratory endpoints included changes in left atrial (LA) volume and LV wall thickness, volume, and function, as well as myocardial fibrosis assessed by extracellular volume fraction and late gadolinium enhancement (LGE).

Sample size

The planned sample size of 220 subjects (1:1 ratio or 110 subjects per treatment group) was chosen to provide up to 96% power to detect superiority of MYK-461 in improving pVO_2max and NYHA functional class relative to placebo with a type I error (overall 2-sided alpha) of 0.05. The power calculation was derived assuming a 25% difference between MYK-461 and placebo in clinical response. The clinical response rate for the mavacamten group was assumed to be 50% based on MYK-461-004 and for placebo at 25%. Participants who terminate early or cannot be assessed for the clinical response at the end of the 30-week dosing period will be considered as non-responders. The sample size calculation was based on a 2-sided Cochran-Mantel-Haenszel (CMH) test for stratified categorical data.

The study did not include sample-size re-estimation based on interim analysis.

Randomisation and blinding (masking)

Randomization was stratified by NYHA class (II or III), current treatment with a beta-blocker (yes or no), planned type of ergometer used during the study (treadmill or exercise bicycle), and consent for the CMR substudy (yes or no).

The study drug was administered in a double-blind manner via the IXRS, such that subjects, investigators and study site staff, including the pharmacist, did not know what study drugs and doses were administered. In addition, the sponsor, the central and core laboratories, and clinical site monitors were blinded to assigned treatment.

Subjects randomized to the placebo group took 1 placebo capsule by mouth once daily for 30 weeks. To maintain the study blind, subjects in the placebo group had the same titration assessments as subjects in the mavacamten group but remained on blinded placebo. To avoid bias, the IXRS randomly selected subjects from the placebo group to undergo unscheduled follow-up visits.

Members of the pharmacovigilance team were unblinded for suspected unexpected serious adverse reaction (SUSAR) reporting. The independent data monitoring committee (IDMC) was provided unblinded safety and efficacy data for periodic review.

Statistical methods

All efficacy analyses were based on the Intent-to-Treat (ITT) Population unless otherwise noted, defined as all randomized subjects, regardless of whether or not they received study drug, with analyses conducted according to randomized treatment assignment. The composite functional endpoint rate was summarized by the treatment group using descriptive statistics to analyse and report the results. The estimates of treatment group differences and 95% confidence intervals (CIs) based on normal approximation were provided.

The primary efficacy endpoint was a composite functional analysis designed to capture the treatment effect of mavacamten relative to placebo on both symptoms and functional capacity. This primary composite endpoint at Week 30, was defined as achieving:

1) An improvement of ≥1.5mL/kg/min in pVO_2max as determined by CPET and a reduction of ≥1 NYHA class or

2) An improvement of ≥3.0mL/kg/min in pVO_2max with no worsening in NYHA class

For the primary efficacy analysis, a Cochran-Mantel-Haenszel (CMH) test for categorical data was used to test the statistical significance of the difference in the composite functional endpoint rate between the mavacamten and placebo groups. An unstratified Chi-square test was performed as a sensitivity analysis.

The analysis of the primary efficacy endpoint was stratified for NYHA class (II or III), current treatment with β-blocker (yes or no) and type of ergometer (treadmill or exercise bicycle). Consent for the CMR substudy, which was used as a stratification factor in the randomization procedure, was not included as a stratification factor for the primary efficacy analysis.

No interim analysis was performed.

Missing data of pVO_2max at week 30 were not imputed, and the participant was considered as a non-responder. In the case that pVO2 at week 30 was available but NYHA class at week 30 was missing, the NYHA class at week 30 was imputed with the latest available record of NYHA class at week 26. Participants with missing response status at week 30 were classified as non-responders.

The secondary endpoints were each tested sequentially in the following order at a 2-sided alpha level of 0.05):

- Change from baseline to Week 30 in postexercise LVOT peak gradient
- Change from baseline to Week 30 in pVO_2max as determined by CPET
- Proportion of subjects who had at least 1 class of improvement from baseline in NYHA class at Week 30
- Change from baseline to Week 30 in subject-reported health status as assessed by the Kansas City Cardiomyopathy Questionnaire (23 item version) (KCCQ-23 CSS)

- Change from baseline to Week 30 in subject-reported severity of HCM symptoms as assessed by the Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ) shortness of breath (SoB) domain score

The CMH test was used to assess the categorical secondary endpoint (proportion of subjects who had at least 1 class of improvement from baseline in NYHA class) between the mavacamten and placebo groups. Between-group comparisons of the continuous secondary endpoints were based on analysis of covariance (ANCOVA) for LVOT gradient and pVO_2max and based on a mixed model for repeated measures (MMRM) for KCCQ-23 CSS and HCMSQ SoB domain score. The estimates of treatment group differences and the 95% confidence intervals (CIs) were provided.

Exploratory endpoints were summarized, and between-group comparisons were performed, as described above for secondary endpoints. The p-values generated from exploratory analyses were not adjusted for multiplicity and are considered descriptive.

The family wise error rate was controlled by applying a hierarchical test strategy for the primary and secondary endpoints.

Missing NYHA values will be handled the same way as for the primary endpoint.

Results

Participant flow

In this study, 429 potential subjects were screened, and 251 subjects (123 subjects to mavacamten and 128 subjects to placebo) were randomized, which all received at least 1 dose of study drug (Table 10). The percentage of subjects who completed treatment was 97.2%, with 96.7% in the mavacamten group and 97.7% in the placebo group. A total of 67 subjects (26.7%) who had their Week 38/end of study visit via telephone communication rather than on site due to the COVID-19 pandemic were characterized as having discontinued the study due to “Other”. Consequently, the percentage of subjects who completed the study was 71.9% (71.5% and 70.3% in the mavacamten and placebo group, respectively). In addition to the 5 subjects who discontinued study treatment/study (2 due to AEs, 1 due to death, 2 subject withdrawals), 1 additional subject was lost to follow-up and did not complete the study, for a total of 6 subjects who discontinued the study.

Table 10. EXPLORER-HCM: Subject disposition (ITT population)

	Mavacamten (N = 123)	Placebo (N = 128)	Overall (N = 251)
Total Number of Subjects, n (%)			
Randomized	123 (100.0)	128 (100.0)	251 (100.0)
Treated	123 (100.0)	128 (100.0)	251 (100.0)
Completed Treatment	119 (96.7)	125 (97.7)	244 (97.2)
Completed Study	88 (71.5)	90 (70.3)	178 (70.9)
Discontinued Treatment[a]	4 (3.3)	3 (2.3)	7 (2.8)
Adverse Event	2 (1.6)	0	2 (0.8)
Death	0	1 (0.8)	1 (0.4)
Other	1 (0.8)	1 (0.8)	2 (0.8)
Withdrawal by Subject	1 (0.8)	1 (0.8)	2 (0.8)
Discontinued Study	35 (28.5)	38 (29.7)	73 (29.1)
Adverse Event	2 (1.6)	0	2 (0.8)
Death	0	1 (0.8)	1 (0.4)
Lost to Follow-Up	1 (0.8)	0	1 (0.4)
Other[b]	31 (25.2)	36 (28.1)	67 (26.7)
Withdrawal by Subject	1 (0.8)	1 (0.8)	2 (0.8)
ITT Population[c]	123 (100.0)	128 (100.0)	251 (100.0)
Safety Population[d]	123 (100.0)	128 (100.0)	251 (100.0)
PK Population[e]	123 (100.0)	0	123 (49.0)
CMR Substudy Population[f]	17 (13.8)	18 (14.1)	35 (13.9)
Randomization Stratification (per IXRS)[g]			
NYHA Functional Classification			
Class II	93 (75.6)	98 (76.6)	191 (76.1)
Class III	30 (24.4)	30 (23.4)	60 (23.9)

	Mavacamten (N = 123)	Placebo (N = 128)	Overall (N = 251)
Beta-Blocker			
Yes	94 (76.4)	94 (73.4)	188 (74.9)
No	29 (23.6)	34 (26.6)	63 (25.1)
Type of Ergometer			
Exercise Bicycle	55 (44.7)	58 (45.3)	113 (45.0)
Treadmill	68 (55.3)	70 (54.7)	138 (55.0)
Consent for the CMR Substudy			
Yes	19 (15.4)	24 (18.8)	43 (17.1)
No	104 (84.6)	104 (81.3)	208 (82.9)

Percentages are based on the number of subjects in the ITT Population.
CMR = cardiac magnetic resonance imaging; ITT = intent to treat; NYHA = New York Heart Association; PK = pharmacokinetics

[a] Subjects may have discontinued treatment and remain on study.
[b] In the contex of COVID-19, 67subjects who completed telephone visits at Week 38 rather than onsite visits were categorized as "Other" but did complete the study, for a total of 178 + 67 = 245 subjects who completed the study (97.6%).
[c] The ITT Population is defined as all randomized subjects regardless of whether they receive study drug or not. Subjects are analyzed by randomized treatment assignment.
[d] The Safety Population is defined as all randomized subjects who received at least 1 dose of study drug (mavacamten or placebo). Subjects are analyzed by actual treatment received.
[e] The PK Population is defined as all randomized subjects who receive at least 1 dose of mavacamten and have at least 1 detectable mavacamten plasma concentration.
[f] The CMR Substudy Population is defined as all subjects who consent to participate in the CMR substudy and have CMR scans available at both Day 1 and Week 30. Subjects are analyzed by randomized treatment assignment.
[g] Stratification per IXRS is considered "assigned". Stratification was also sorted based on eCRF and was considered "actual". The primary and secondary endpoints were analyzed based on the assigned values.

Dose titration and modification

Temporary treatment discontinuation

As an additional safety precaution, dosing was temporarily discontinued if a subject met any of the following criteria: mavacamten plasma concentration ≥1000 ng/mL, resting LVEF <50%, or QTcF prolongation, based on blinded assessments at each study visit.

No subjects met the temporary treatment discontinuation criterion of mavacamten plasma concentration ≥1000 ng/mL

Resting LVEF <50%

A total of 9 subjects (3.6%) had LVEF <50% (median 48%, range 35-49%) while on treatment, including 7 subjects in the mavacamten group (5.7%) and 2 subjects (1.6%) in the placebo group. Three of the 7 mavacamten subjects met the LVEF temporary discontinuation criterion at Week 6 (n = 1) or Week 18 (n = 2). Per protocol, these subjects discontinued the study drug for a short period of time and subsequently resumed dosing and completed the study. For 4 mavacamten subjects, LVEF <50% occurred at the Week 30 visit, and no dose adjustments were made, as treatment ended at that visit. None of these subjects with LVEF <50% had any TEAEs of heart failure or systolic dysfunction coincident with LVEF reduction.

QTcF prolongation

Six subjects (2.4%) met the temporary discontinuation criterion of QTcF prolongation at least once during 30 weeks of treatment, including 3 subjects (2.4%) in the mavacamten group and 3 subjects (2.3%) in the placebo group. All 6 subjects underwent temporary treatment discontinuation and subsequently resumed dosing and completed treatment.

Dose reduction due to mavacamten plasma concentration ≥700 ng/mL to <1000 ng/mL

Across visits, 17 subjects had a total of 20 excursions of mavacamten plasma concentrations between 700 and 1000 ng/mL (range: 703 to 844 ng/mL). For 3 of the 17 subjects, increased mavacamten concentrations were measured simultaneously with LVEF <50% (1 at Week 18, triggering temporary discontinuation of dosing and 2 at Week 30/end of treatment, with no dose reduction). A total of 13 subjects (10.6%) receiving mavacamten had dose reductions following increases in mavacamten plasma concentration ≥700 ng/mL, including 8 subjects with dose reductions from 10 mg to 5 mg and 5 subjects with dose reductions from 5 mg to 2.5 mg (Table 11). One subject with consecutive concentration values ≥700 ng/mL had 2 dose reductions: from 5 mg to 2.5 mg and from 2.5 mg to placebo. In all cases, mavacamten plasma concentrations decreased to <700 ng/mL following dose reduction.

Table 11. Mavacamten Dose Reductions Resulting from Mavacamten

Subject ID	Study Visit (Week)	C_{trough} (ng/mL)	Mavacamten Dose Reduction 2Weeks Later (mg)
118-507	6	739	5 → 2.5
101-502	12	750	10 → 5
203-510	12	704	10 → 5
701-504[a]	12	721	10 → 5
799-501	12	703	5 → 2.5
117-502	18	768	10 → 5
138-501	18	707	5 → 2.5
202-516	18	724	10 → 5
203-516	18	803	5 → 2.5
	22	844	2.5 → Placebo
397-502	18	768	5 → 2.5
796-517	18	775	10 → 5
	22	828	Dose not reduced[b]
797-502	22	828	10 → 5
507-501	22	722	10 → 5
	26	715	Dose not reduced[b]
702-503	26	720	Dose not reduced[b]

C_{trough} = mavacamten plasma trough concentration

[a] Subject 701-504 took study drug prior to PK assessment. Therefore, mavacamten plasma concentration was considered a postdose value, and the subject was excluded from Table 33.

[b] Mavacamten dose was not reduced due to unscheduled follow-up visits not being registered in the IXRS system.

Dose increases

Approximately 50% of subjects remained on mavacamten 5 mg throughout the treatment period (Table 12). Forty subjects (32.5%) had a dose increase from 5 to 10 mg at Weeks 8 or 14 and remained on 10 mg for the remainder of the treatment period; 13 subjects (10.6%) had a dose

increase from 5 to 10 mg at Week 8 and a further dose increase from 10 to 15 mg at Week 14 and remained on 15 mg for the remainder of the treatment period.

Table 12. Mavacamten Dose Increases During 30 Weeks of Treatment

Mavacamten Daily Dose	Day 1	Mavacamten (N = 123)							
		Study Week							
		4	6	8	12	14	18	22	26
5 mg	123 (100.0)	121 (98.4)	117 (95.1)	70 (56.9)	70 (56.9)	56 (45.5)	56 (45.5)	56 (45.5)	60 (48.8)
10 mg	0	0	0	49 (39.8)	49 (39.8)	47 (38.2)	47 (38.2)	40 (32.5)	40 (32.5)
15 mg	0	0	0	0	0	14 (11.4)	14 (11.4)	13 (10.6)	13 (10.6)
Missing	0	2 (1.6)	6 (4.9)	2 (1.6)	2 (1.6)	4 (3.3)	2 (1.6)	7 (5.7)	3 (2.4)

Only doses at scheduled visits are summarized.
Missing dose data were due to early treatment termination, drug interruption, no study drug dispensed on the scheduled visit, or pill counts indicated no pills had been taken from the bottle.

Protocol deviations

Important protocol deviations (IPD) were categorized depending on whether or not they were considered related to the COVID-19 pandemic. The proportion of subjects with IPDs not related to COVID-19 and with IPDs related to COVID-19 was approximately similar for the mavacamten and placebo groups (16.3% vs 13.3 % and 25.2% vs 28.9%, respectively) (Table 13).

Table 13. EXPLORER-HCM: Important Protocol Deviations (ITT Population)

	Mavacamten (N = 123) n (%)	Placebo (N = 128) n (%)	Overall (N = 251) n (%)
Total Number of IPDs	70	71	141
Not related to COVID-19	26	20	46
Related to COVID-19	41	48	89
Treatment Compliance < 80%	3	3	6
Total number of subjects with IPDs	49 (39.8)	50 (39.1)	99 (39.4)
Treatment Compliance < 80%	3 (2.4)	3 (2.3)	6 (2.4)
Not related to COVID-19	20 (16.3)	17 (13.3)	37 (14.7)
Exclusion Criteria	6 (4.9)	4 (3.1)	10 (4.0)
Inclusion Criteria	1 (0.8)	0	1 (0.4)
Safety Reporting (eCRF)	4 (3.3)	2 (1.6)	6 (2.4)
Missing Endpoint Assessments	0	1 (0.8)	1 (0.4)
Study Treatment Randomization	12 (9.8)	12 (9.4)	24 (9.6)
Related to COVID-19	31 (25.2)	37 (28.9)	68 (27.1)[a]
Missing Endpoint Assessments	6 (4.9)	5 (3.9)	11 (4.4)

eCRF = electronic case report form; IPD = important protocol deviation
Subjects may have had more than 1 IPD. In a given category, a subject was counted only once if there was more than 1 deviation.
Compliance < 80% was determined by cumulative dose for mavacamten-treated subjects and by cumulative pill count for placebo-treated subjects.
[a] Subject 398-505 had an onsite visit at Week 38 but was unable to complete the second day of the visit due to COVID-19 and did not complete echocardiography assessments.

Recruitment

This study was conducted at 68 centres, including 31 sites in the European Union, 29 sites in the United States, 6 sites in Israel, and 2 sites in the United Kingdom. Approximately half of the participants (n=128) were from European countries (Belgium, Czechia, Germany, Denmark, Spain, France, United Kingdom, Italy, Netherlands, Poland, and Portugal). The number of subjects enrolled from the European sites was equally distributed between the mavacamten and placebo groups, 64/123 (52%) and 64/128 (50%) respectively. Other non-European countries participating in the study were United States (US) (43.0% subjects treated) and Israel (6.0% subjects treated).

The first patient screened was on 30 May 2018, and the last patient observation for this report was on 6 May 2020.

Conduct of the study

The original protocol for study MYK-461-005 was dated 14-Jul-2017. A total of 5 global amendments were issued. The first patient was enrolled on 25-Jun-2018 under protocol amendment 3 (21-Mar-2018), and two amendments, 4 and 5, occurred during the conduct of the study.

Key efficacy changes are as follows: the primary efficacy endpoint in the original protocol initially assessed the improvement in pVO_2max alone and was first modified with protocol amendment 2, dated 25 Jan 2018, to a composite functional endpoint to add NYHA. The composite endpoint was defined as an improvement of ≥1.5 mL/kg/min in pVO_2max as determined by CPET and a reduction ≥1 NYHA class. The primary endpoint was subsequently modified with protocol amendment 4, dated 13-Nov-2018, in response to US health authority recommendation to include a second definition in the composite endpoint as follows: 1) An improvement of ≥1.5 mL/kg/min in pVO_2max as determined by CPET and a reduction ≥1 NYHA class OR 2) An improvement of 3.0 mL/kg/min or more in pVO_2max with no worsening in NYHA class.

Secondary endpoints were also amended during the conduct of the study. The Kansas City Cardiomyopathy Questionnaire 23-item version (KCCQ-23) was changed from an exploratory to a secondary endpoint with protocol amendment 5. The endpoints of the proportion of subjects with post-exercise LVOT peak gradient <30mmHg and <50mmHg at Week 30 were changed from secondary to exploratory endpoints under Amendment 5, dated 04-Oct-2019.

These changes in primary and secondary endpoints were implemented at least 6 months before performing the primary analysis (triggered when all subjects completed 30 weeks of treatment) and the subsequent final database lock; the primary endpoint was updated approximately 1.5 years before primary data analysis. These changes therefore had no impact on the operations of data collection nor on the integrity of the efficacy results.

Baseline data

Subject demographics and baseline characteristics were generally similar for the mavacamten and placebo groups. The majority of subjects were male (59.4%) (with a greater proportion of females in the mavacamten group compared with the placebo group [46.3% vs. 35.2%]), white (91.2%), and not Hispanic or Latino (92.8%) (Table 14). The mean age of subjects was 58.5 years (range 18 to 82 years). Mean baseline BMI was 29.4 kg/m2 (range 15.9 to 51.9 kg/m2). At baseline, the majority of subjects were NYHA Class II (72.9% overall), with the remainder NYHA Class III. Most subjects were using beta-blockers (75.3%), 16.7% were using non-dihydropyridine calcium channel blockers (verapamil or diltiazem), and 8.0% were using neither beta-blockers nor calcium channel blockers. Left ventricles were hypertrophic (mean LV maximum wall thickness 20 mm), and function was hypercontractile (mean LVEF 74%), with progressive obstruction from rest to provocation (mean resting LVOT gradients approximately 50 mmHg and increasing to approximately 85 mmHg after exercise)(Table 15). There was a high prevalence of SAM, mitral regurgitation, and LA enlargement.

Table 14. EXPLORER-HCM: Subject Demographics and Baseline Characteristics (ITT population)

Demographics and Baseline Characteristics	Mavacamten (N = 123)	Placebo (N = 128)	Overall (N = 251)
Age (Years)			
Mean (SD)	58.5 (12.17)	58.5 (11.75)	58.5 (11.93)
Min,	26, 82	18, 81	18, 82
Age, n (%)			
<= 49	27 (22.0)	25 (19.5)	52 (20.7)
50 - 64	51 (41.5)	63 (49.2)	114 (45.4)
>= 65	45 (36.6)	40 (31.3)	85 (33.9)
Sex, n (%)			
Male	66 (53.7)	83 (64.8)	149 (59.4)
Female	57 (46.3)	45 (35.2)	102 (40.6)

Demographics and Baseline Characteristics	Mavacamten (N = 123)	Placebo (N = 128)	Overall (N = 251)
Region, n (%)			
US	53 (43.1)	55 (43.0)	108 (43.0)
ex-US	70 (56.9)	73 (57.0)	143 (57.0)
Race, n (%)			
White	115 (93.5)	114 (89.1)	229 (91.2)
Black or African American	1 (0.8)	5 (3.9)	6 (2.4)
American Indian or Alaska Native	0	1 (0.8)	1 (0.4)
Asian	4 (3.3)	2 (1.6)	6 (2.4)
Unknown	3 (2.4)	6 (4.7)	9 (3.6)
Ethnicity, n (%)			
Hispanic or Latino	8 (6.5)	4 (3.1)	12 (4.8)
Not Hispanic or Latino	114 (92.7)	119 (93.0)	233 (92.8)
Not Reported	1 (0.8)	5 (3.9)	6 (2.4)
BMI (kg/m^2)			
Mean (SD)	29.7 (4.85)	29.2 (5.61)	29.4 (5.25)
Range	20.8, 51.9	15.9, 50.1	15.9, 51.9
BSA (m^2)			
Mean (SD)	1.96 (0.23)	1.97 (0.24)	1.97 (0.23)
Range	1.49, 2.67	1.37, 2.74	1.37, 2.74
Heart Rate (beats/min)			
Mean (SD)	63 (10.1)	62 (10.6)	63 (10.3)
Min, Max	41, 108	41, 90	41, 108
Mean (SD) Blood Pressure (mmHg)			
Systolic	128.4 (16.18)	128.4 (14.57)	128.4 (15.35)
Diastolic	75.5 (10.76)	76.1 (9.87)	75.8 (10.30)
CYP2C19 Metabolizer Phenotype, n (%)			
Normal	48 (39.0)	44 (34.4)	92 (36.7)
Rapid	27 (22.0)	32 (25.0)	59 (23.5)
Ultrarapid	4 (3.3)	3 (2.3)	7 (2.8)
Intermediate	31 (25.2)	33 (25.8)	64 (25.5)
Poor	2 (1.6)	3 (2.3)	5 (2.0)
Not Poor	3 (2.4)	1 (0.8)	4 (1.6)
Missing	8 (6.5)	12 (9.4)	20 (8.0)

Demographics and Baseline Characteristics	Mavacamten (N = 123)	Placebo (N = 128)	Overall (N = 251)
Duration of oHCM (Years)			
Mean (SD)	7 (7.2)	7 (6.6)	7.7 (6.9)
Range	0.2, 49.3	0.2, 34.4	0.2, 49.3
NYHA class			
II	88 (71.5)	95 (74.2)	183 (72.9)
III	35 (28.5)	33 (25.8)	68 (27.1)
Background HCM Therapy			
Beta-Blocker	94 (76.4)	95 (74.2)	189 (75.3)
Calcium Channel Blocker[a]	25 (20.3)	17 (13.3)	42 (16.7)
Neither Beta-Blocker nor Calcium Channel Blocker	4 (3.3)	16 (12.5)	20 (8.0)
Baseline NT-proBNP (ng/L)			
N	120	126	246
Geometric Mean (%CV)	777 (136.4)	616 (108.4)	nc
Mean (SD)	1516 (2066.4)	1050 (1138.7)	1277 (1670.3)
Median	784	648	710
Q1, Q3	373.0, 1759.5	354.0, 1360.0	366.0, 1610.0
Min; Max	52; 11,420	18; 6067	18; 11,420
Baseline hs-cTn-I (ng/L)			
N	120	119	
Geometric Mean (%CV)	12.5 (207.8)	12.5 (372.8)	nc
Mean (SD)	25.2 (52.3)	45.8 (170.6)	nc
Median	10.6	10.0	nc
Q1, Q3	5.0, 23.6	5.0, 22.0	nc
Min; Max	5.0, 463.9	5.0, 1395.0	nc

%CV = percent coefficient of variation; BMI = body mass index; BSA = body surface area; HCM = hypertrophic cardiomyopathy; hs-cTn-I = high-sensitivity cardiac troponin-I; min, max = minimum, maximum; nc = value not calculated; NT-proBNP = N-terminal pro b-type natriuretic peptide; NYHA = New York Heart Association; Q1, Q3 = first quartile, third quartile; SD = standard deviation

BMI = (body weight in kilograms)/(square of height in meters).

BSA = 0.007184 * Height(cm)**0.725 * Weight(kg)**0.425.

Baseline is defined as the last nonmissing measurement prior to the first dose.

n is the number of subjects with nonmissing data

[a] Includes verapamil, verapamil hydrochloride, diltiazem, and dilitiazem hydrochloride

Table 15. EXPLORER-HCM: Baseline Peak Oxygen Consumption and Key Echocardiography Parameters (ITT Population)

Parameter	Mavacamten (N = 123)		Placebo (N = 128)	
	n	Mean (SD)	n	Mean (SD)
pVO_2 (mL/kg/min)	123	18.9 (4.9)	128	19.9 (4.9)
ECHO Parameters				
Resting LVEF (%)	123	74 (5.8)	128	74 (5.9)
LVOT Gradient (mmHg)				
Resting	123	52 (29.4)	128	51 (31.9)
Valsalva	123	72 (31.7)	128	74 (32.0)
Postexercise	122	86 (34.3)	127	84 (35.7)
LV Wall Thickness (mm)				
Septal	121	17 (2.5)	127	17 (2.8)
Posterior	118	12 (2.4)	124	11 (2.4)
Maximum	123	20 (3.7)	128	20 (3.3)
LV Mass Index (g/m^2)	117	112 (27.2)	123)	110 (26.1)
LAVI (mL/m^2)	122	40 (12.1)	128	41 (13.8)
SAM of Mitral Valve (yes), n (%)	119	97 (81.5)	126	102 (81.0)
MR (yes), n (%)	120	117 (97.5)	125	124 (99.2)

ECHO = echocardiogram; pVO_2 = peak oxygen consumption; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; MR = mitral regurgitation; SAM = systolic anterior motion

HCM genotype

Overall, 75.7% of subjects had HCM genotype assayed in this study, including 73.2% (90 of 123 subjects) in the mavacamten group and 78.1% (100 of 128 subjects) in the placebo group. The proportion of subjects with at least 1 pathogenic or likely pathogenic mutation was 31.1% in the mavacamten group and 22.0% in the placebo group. Four subjects (4.4%) in the mavacamten group with current HCM genotype testing had > 1 pathogenic or likely pathogenic mutation identified. No subjects in the placebo group had > 1 pathogenic or likely pathogenic mutation identified.

For both treatment groups, the most common mutations identified were in the MYBPC3 (12.2% of mavacamten subjects and 13.0% of placebo subjects) and MYH7 (7.8% of mavacamten subjects and 3.0% of placebo subjects) genes.

A total of 58.9% of mavacamten subjects and 52.0% of placebo subjects had at least 1 variant of uncertain significance (VUS). The most common VUSs identified were contained within the following genes:

• Mavacamten: FLNC (7.8%), MYH7 (5.6%), and MYBPC3 (4.4%)

• Placebo: MYBPC3 (7.0%), MYH6 (5.0%), FLNC (4.0%), and TPM1 (4.0%)

HCM-related medical history

HCM-related medical history was similar for the mavacamten and placebo groups, and for the majority of subjects, HCM symptoms were ongoing at baseline (Table 16).

Of note, fewer subjects in the mavacamten group compared with the placebo group had a history of atrial fibrillation (9.8% vs 18.0%, respectively). The proportion of subjects with a history of nonsustained ventricular tachycardia (NSVT), an important complication of HCM, was slightly higher for the mavacamten group compared with the placebo group (17.1% vs 12.5%, respectively). The overall history of septal reduction therapy (SRT) (myectomy or ASA) was 8.9% for the mavacamten group and 6.3% for the placebo group.

Table 16. MYK-461-005: Hypertrophic Cardiomyopathy-Related History (Safety Population)

	Mavacamten (N = 123) n (%)	Placebo (N = 128) n (%)	Overall (N = 251) n (%)
Subjects with family history of HCM	33 (26.8)	36 (28.1)	69 (27.5)
Subjects with family history of sudden cardiac death in persons < 50 years of age	15 (12.2)	13 (10.2)	28 (11.2)
Subjects who experienced any of the following symptoms within the past 12 months	118 (95.9)	121 (94.5)	239 (95.2)
Chest Pain	53 (43.1)	61 (47.7)	114 (45.4)
Ongoing	44 (35.8)	49 (38.3)	93 (37.1)
Fatigue	82 (66.7)	94 (73.4)	176 (70.1)
Ongoing	73 (59.3)	86 (67.2)	159 (63.3)
Palpitations	55 (44.7)	59 (46.1)	114 (45.4)
Ongoing	43 (35.0)	40 (31.3)	83 (33.1)
Shortness of Breath	114 (92.7)	113 (88.3)	227 (90.4)
Ongoing	104 (84.6)	106 (82.8)	210 (83.7)
Subjects who experienced any of the following cardiac rhythm events in the past	35 (28.5)	37 (28.9)	72 (28.7)
Atrial Fibrillation	12 (9.8)	23 (18.0)	35 (13.9)
NSVT	21 (17.1)	16 (12.5)	37 (14.7)
Sustained VT	5 (4.1)	5 (3.9)	10 (4.0)
Subjects with a history of any of the following surgeries or procedures	35 (28.5)	34 (26.6)	69 (27.5)
SRT	11 (8.9)	8 (6.3)	19 (7.6)
ASA	10 (8.1)	6 (4.7)	16 (6.4)
Myectomy	1 (0.8)	2 (1.6)	3 (1.2)
ICD and/or Pacemaker	27 (22.0)	29 (22.7)	56 (22.3)

ASA = alcohol septal ablation; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; NSVT = nonsustained ventricular tachycardia; SRT = septal reduction therapy; VT = ventricular tachycardia

Concomitant medication

All subjects in the mavacamten group and 98.4% of subjects in the placebo group were taking at least 1 concomitant medication. Across treatment groups, the 3 most common Anatomical

Therapeutic Chemical (ATC) classes of concomitant medications were as follows:

- Beta blocking agents (78.9% in the mavacamten group and 75.0% in the placebo group)
- Lipid modifying agents (46.3% in the mavacamten group and 47.7% in the placebo group)
- Antithrombotic agents (35.0% in the mavacamten group and 43.8% in the placebo group)

Calcium channel blocker use (verapamil or diltiazem) was reported for 20.3% of subjects in the mavacamten group and 13.3% of subjects in the placebo group (Table 14).

Other concomitant medications used by > 25.0% of subjects in either treatment group included analgesics, vitamins, diuretics, drugs for acid-related disorders, anti-inflammatory and anti-rheumatic products, and systemic antibacterials

Numbers analysed

A total of 251 subjects were randomized into the study and received at least 1 dose of the study drug and were included in the ITT and safety populations (Table 17). All 123 subjects in the mavacamten group had at least 1 detectable mavacamten plasma concentration and were included in the PK Population.

Table 17. EXPLORER-HCM: Analysis Populations (ITT Population)

Analysis Population	Mavacamten (N = 123)	Placebo (N = 128)	Overall (N = 251)
ITT Population	123 (100.0)	128 (100.0)	251 (100.0)
Safety Population	123 (100.0)	128 (100.0)	251 (100.0)
PK Population	123 (100.0)	0	123 (49.0)
CMR Substudy Population	17 (13.8)	18 (14.1)	35 (13.9)

CMR = cardiac magnetic resonance imaging; ITT = intention to treat; PK = pharmacokinetics

Outcomes and estimation

Primary endpoint

A greater proportion of subjects in the mavacamten group compared with the placebo group achieved the composite primary endpoint defined as achieving: 1. an improvement of ≥1.5 mL/kg/min in pVO_2max as determined by CPET and a reduction of ≥1 NYHA class or 2. an improvement of ≥3.0 mL/kg/min in pVO_2max with no worsening in NYHA class (36.6% vs 17.2%, respectively). The between-group difference was 19.4% (95% CI: 8.67, 30.13; p=0.0005) (Table 18). In addition, the proportion of subjects who achieved both an increase of ≥3 mL/kg/min in pVO_2max and an improvement of ≥1 NYHA class (ie, the more stringent criteria for each component of the composite primary endpoint) was greater for the mavacamten group compared with the placebo group (20.3% vs 7.8%, respectively). The between-group difference was 12.5% (95% CI: 4.02, 21.01).

There was no clear apparent concentration-response relationship within the range of concentrations achieved in the study.

Table 18. EXPLORER-HCM: Composite functional endpoint at Week 30 (ITT population)(adapted by assessor)

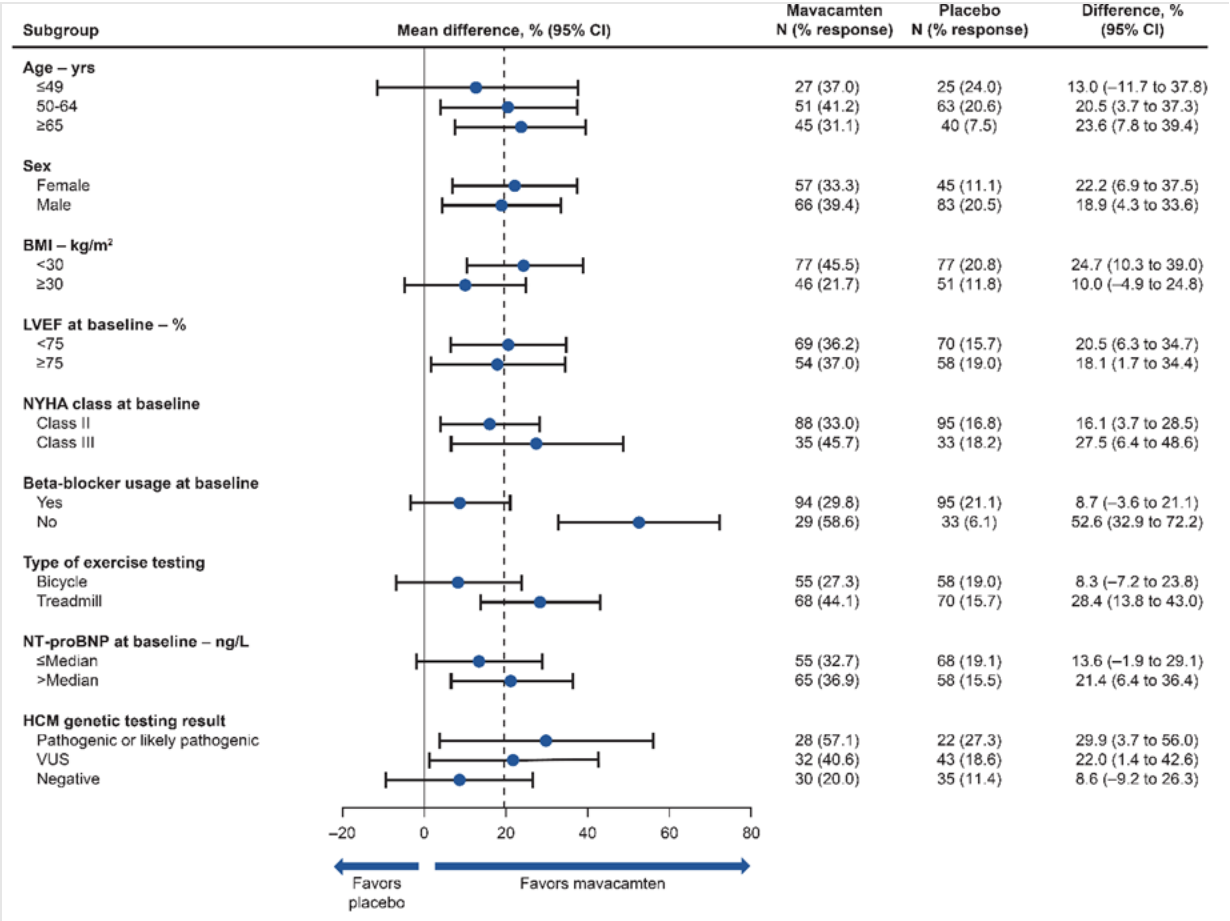
	Mavacamten N = 123	**Placebo N = 128**
Patients achieving composite primary endpoint at Week 30, n (%)	45 (36.6%)	22 (17.2%)
Treatment difference (95% CI)	19.4 (8.67, 30.13)	
p-value	0.0005	
Patients with change from baseline in pVO_2max ≥1.5 mL/kg/min and improvement in NYHA class ≥1 at Week 30, n (%)	41 (33%)	18 (14%)
Treatment difference (95% CI)	19 (8.99, 29.55)	
Patients with change from baseline in pVO_2max ≥3.0 mL/kg/min and no worsening in NYHA class at Week 30, n (%)	29 (24%)	14 (11%)
Treatment difference (95% CI)	13 (3.39, 21.89)	
Patients with change from baseline in pVO_2max ≥3.0 mL/kg/min and improvement in NYHA class ≥1 at Week 30, n (%)	25 (20.3%)	10 (7.8%)
Treatment difference (95% CI)	12.5 (4.02, 21.01)	

Subgroup analysis of the primary endpoint

Mavacamten showed consistent benefit for the primary composite functional endpoint and all secondary endpoints across a diverse range of subjects with respect to demographic characteristics, including age, sex, and BMI (Figure 28). The therapeutic effects of mavacamten were also observed across baseline disease characteristics, which included LVEF, NYHA class, NT proBNP levels, and HCM genotype.

However, the magnitude of the treatment effect for the primary composite functional endpoint was greater for subjects who were not using beta-blockers (between-group difference 52.6%; 95% CI: 32.9, 72.2) compared with those who were using beta-blockers (between-group difference 8.7%; 95% CI: -3.6, 21.1]). As expected, the mean peak heart rate with exercise was lower for subjects using beta-blockers compared with those not using beta-blockers (118 beats/min vs 138 beats/min, respectively at baseline). Similarly, mean baseline pVO_2max by CPET tended to be lower for the beta-blocker subgroup compared with the non-beta-blocker subgroup and mean (SD) change from baseline at Week 30 in pVO_2max, a component of the composite functional endpoint, was lower for subjects using beta-blockers compared with those who were not using beta-blockers (1.1 [3.11] versus 2.2 [3.04] mL/kg/min). This reflects the well-established blunting effect of beta-blockers on CPET performance. Furthermore, additional analyses were conducted to assess between-group differences by beta-blocker use (yes or no) in changes from baseline in measures of patient symptoms (NYHA class), health status (KCCQ-23 CSS), CPET parameters (pVO_2max and VE/VCO_2 slope), cardiac function and structure (LVOT gradient, LVEF, LAVI, and LVMI), and biomarkers of cardiac stress and injury (NT-proBNP and cTnI). These analyses show similar effects favouring mavacamten with overlapping CIs (Figure 29 and Table 19). Notably, the heart rate-independent parameter of CPET, VE/VCO2 slope (ventilatory efficiency) showed comparable improvements with mavacamten treatment compared with placebo regardless of beta-blocker use.

Figure 28. EXPLORER-HCM: Subgroup Analysis of the Primary Composite Functional Endpoint (ITT Population)



BMI = body mass index; HCM = hypertrophic cardiomyopathy; LVEF = left ventricular ejection fraction; NT proBNP = N terminal pro B type natriuretic peptide; NYHA = New York Heart Association; VUS = variant of uncertain significance

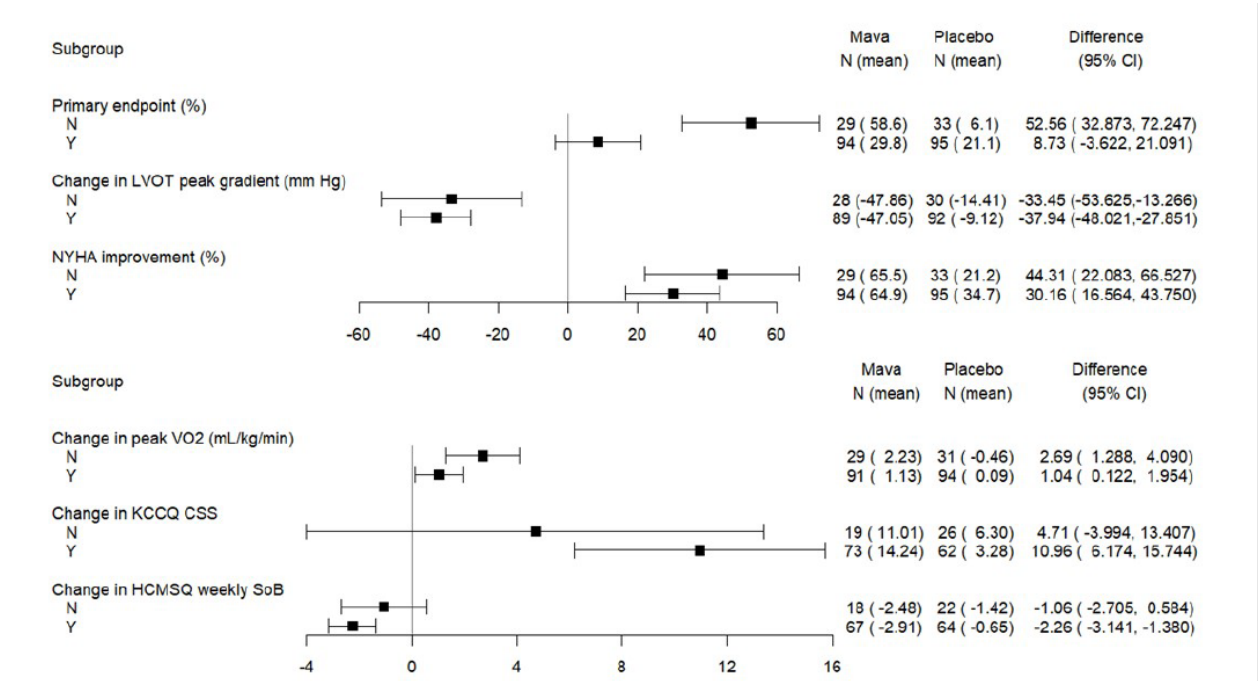
The dashed vertical lines (overall effect) represent the between-treatment group difference in the overall study cohort, and the solid vertical lines (no effect) indicate no difference between treatment groups.

Missing NYHA class at Week 30 was imputed using available NYHA class at Week 26. After the imputation, the subjects whose response status at Week 30 was still missing were classified as nonresponders.

The 95% CIs of the response differences between mavacamten and placebo groups are based on normal approximation.

The subgroups by stratification factors were determined using data in the electronic case report form.

Figure 29. Differences in Key Efficacy Outcomes by Beta-Blocker Use



CSS = clinical summary score; HCMSQ = Hypertrophic Cardiomyopathy Symptom Questionnaire; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVOT = left ventricular outflow tract; N = subgroup not using beta-blockers; NYHA = New York Heart Association; SoB = shortness of breath; VO_2 = oxygen consumption; Y = subgroup using beta-blockers
95% CIs are based on normal approximation.

Table 19. EXPLORER-HCM: Clinical Response Between Treatment Groups at Week 30 Across Beta-Blocker Subgroups

	Beta Blocker Use - Yes			**Beta Blocker Use - No**		
	Mavacamten Change W30 to Baseline N = 94	**Placebo Change W30 to Baseline N = 95**	**Difference (95% CI)**	**Mavacamten Change W30 to Baseline N = 29**	**Placebo Change W30 to Baseline N = 33**	**Difference (95% CI)**
Function						
Peak pVO_2max mL/kg/min	1.1 (3.1)	0.1 (3.2)	1.0 (0.1, 2.0)	2.2 (3.0)	-0.5 (2.4)	2.7 (1.3, 4.1)
VE/VCO2 slope	-2.4 (4.5)	0.6 (4.1)	-2.9 (-4.1, -1.7)	-2.7 (4.9)	-0.1 (4.4)	-2.6 (-5.0, -0.2)
Echocardiogram						
LVEF (%), mean	-3.6 (7.7)	0.4 (7.1)	-4.0 (-6.2, -1.8)	-5.0 (7.6)	-1.3 (5.8)	-3.7 (-7.3, -0.05)
LVOT Resting gradient, mmHg	-37.5 (30.1)	-5.1 (27.5)	-32.4 (-40.9, -24.0)	-42.2 (27.9)	-6.8 (29.7)	-35.4 (-50.4, -20.3)
LVOT Valsalva, mmHg	-50.0 (36.8)	-10.4 (30.3)	-39.6 (-49.4, -29.7)	-46.3 (25.6)	-17.3 (32.8)	-29.0 (-44.4, -13.5)
Post-exercise LVOT gradient, mm Hg	-47.1 (37.9)	-9.1 (30.6)	-37.9 (-48.0, -27.9)	-47.9 (47.9)	-14.4 (26.4)	-33.5 (-53.6, -13.3)
LAVI, mL/m²	-7.4 (7.6)	0.4 (8.8)	-7.8 (-10.2, -5.4)	-7.9 (8.5)	-1.5 (8.3)	-6.4 (-10.8, -2.0)
LVMI, g/m²	-6.1 (16.5)	8.3 (15.8)	-14.4 (-19.4, -9.5)	-11.4 (21.4)	10.4 (13.6)	-21.8 (-31.6, -11.9)
Biomarkers	**Ratio W30 to Baseline, GM**	**Ratio W30 to Baseline, GM**	**GM ratio (95% CI)**	**Ratio W30 to**	**Ratio W30 to**	**GM ratio (95% CI)**

	Beta Blocker Use - Yes			Beta Blocker Use - No		
				Baseline, GM	Baseline, GM	
NT-proBNP, ng/L	0.2 (283.6)	1.0 (50.4)	0.2 (0.2, 0.3)	0.2 (115.2)	1.0 (69.8)	0.2 (0.1, 0.3)
Hs-cTnl, ng/L	0.6 (46.9)	1.0 (161.3)	0.6 (0.5, 0.8)	0.5 (57.5)	1.1 (60.8)	0.4 (0.3, 0.6)

Secondary endpoints

Mavacamten-treated subjects demonstrated significant improvements compared with placebo for all secondary endpoints, including postexercise LVOT peak gradient, pVO_2max, NYHA Class, KCCQ-23 CSS, and HCMSQ SoB domain score (p-values $\leqslant$ 0.0006 for stratified and unstratified analyses)(Table 20 and Table 21).

Table 20. EXPLORER-HCM: Between-Group Comparisons in Changes from Baseline in Continuous Secondary Endpoints (ITT Population)

Endpoint	Mavacamten (N = 123)	Placebo (N = 128)
Change from Baseline to Week 30 in Postexercise LVOT Peak Gradient (mmHg)	n = 117	n =122
Mean (SD)	-47 (40.3)	-10 (29.6)
LS Mean Difference Mavacamten vs Placebo (95% CI)[a]	-35 (-43.2, -28.1)	
P-value	< 0.0001	
Baseline	n = 122	n = 127
Mean (SD)	86 (34.3)	84 (35.7)
Week 30	n = 118	n = 123
Mean (SD)	38 (32.1)	73 (34.9)
Change from Baseline to Week 30 in pVO_2 (mL/kg/min)	n = 120	n = 125
Mean (SD)	1.4 (3.12)	-0.05 (3.02)
LS Mean Difference Mavacamten vs Placebo (95% CI)	1.4 (0.59, 2.12)	
P-value[a]	0.0006	
Baseline	n = 123	n = 128
Mean (SD)	18.9 (4.86)	19.9 (4.91)
Week 30	n = 120	n = 125
Mean (SD)	20.4 (5.36)	19.9 (5.40)
Change from Baseline to Week 30 in KCCQ-23 CSS	n = 92	n = 88
Mean (SD)	13.6 (14.42)	4.2 (13.68)
LS Mean Difference Mavacamten vs Placebo (95% CI)	9.1 (5.46, 12.66)	
P-value[b]	< 0.0001	

Endpoint	Mavacamten (N = 123)	Placebo (N = 128)
Baseline	n = 99	n = 97
Mean (SD)	71.1 (16.33)	70.6 (19.08)
Week 30	n = 108	n = 113
Mean (SD)	82.0 (16.45)	73.0 (20.25)
Change from Baseline to Week 30 in HCMSQ SoB Domain Score	n = 85	n = 86
Mean (SD)	-2.8 (2.68)	-0.9 (2.41)
LS Mean Difference Mavacamten vs Placebo (95% CI)	-1.8 (-2.40, -1.20)	
P-value[b]	< 0.0001	
Baseline	n = 108	n = 109
Mean (SD)	4.9 (2.48)	4.5 (3.24)
Week 30	n = 92	n = 97
Mean (SD)	2.0 (2.60)	3.7 (3.02)

KCCQ-23 CSS = Kansas City Cardiomyopathy Questionnaire (23-item version) clinical summary score; HCMSQ SoB domain score = Hypertrophic Cardiomyopathy Symptom Questionnaire shortness of breath domain score; LS = least squares; LVOT = left ventricular outflow tract

[a] The mean difference estimate, its 95% CI, and p-values are from the ANCOVA which controls for treatment group (mavacamten vs placebo), baseline value of the corresponding endpoint of interest, and the 3 stratification factors (beta-blocker use, NYHA class, ergometer type based on IXRS).

[b] Based on Mixed Model for Repeated Measurements with data up to Week 30 which includes baseline value, treatment group, visit, interaction between treatment group and visit, and the 3 stratification factors (beta-blocker use, NYHA class, exercise type based on IXRS) as fixed effect, and subject as random effect.

Table 21. Changes from Baseline at Week 30 in Measures of Cardiac Structure (ITT Population)

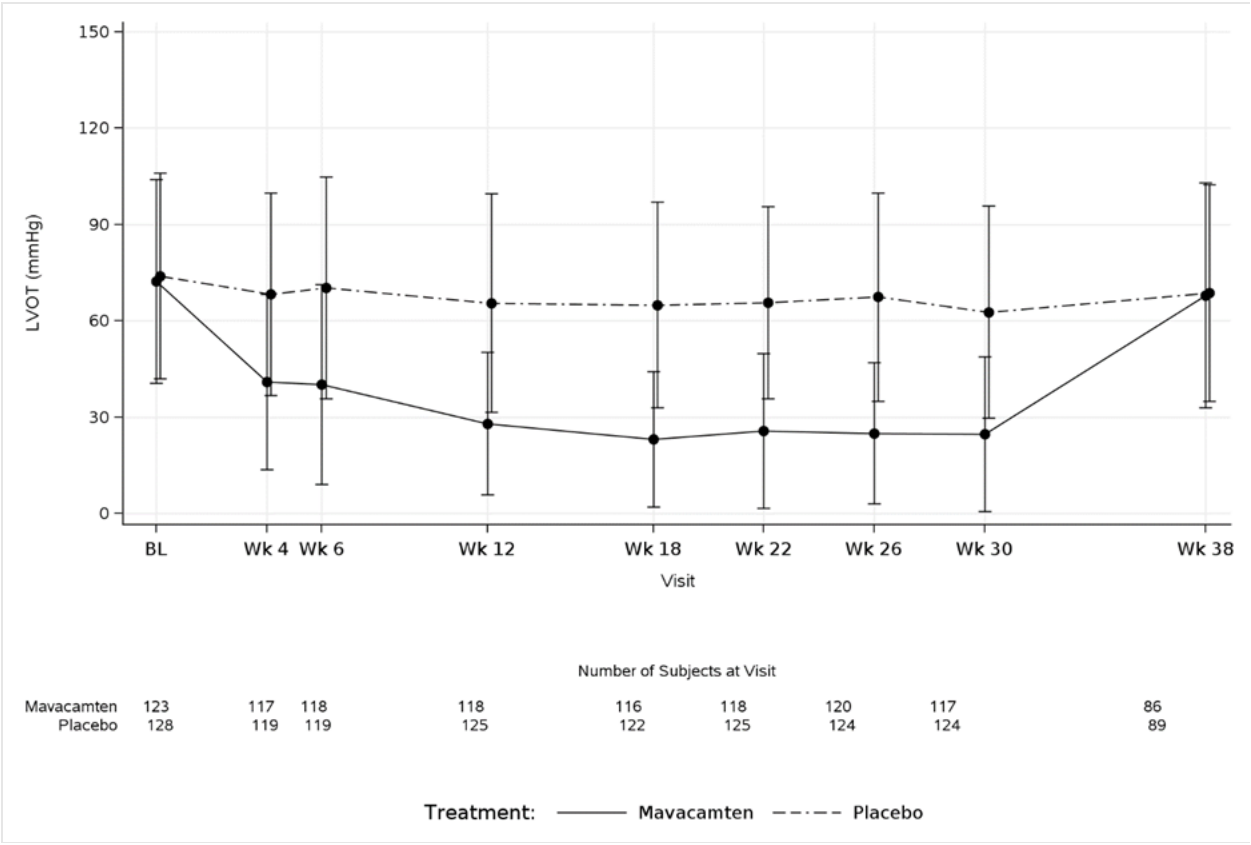
	Mavacamten (N = 123)			Placebo (N = 128)		
NYHA Class	**Class II n (%)**	**Class III n (%)**	**Total n (%)**	**Class II n (%)**	**Class III n (%)**	**Total n (%)**
Baseline	88 (71.5)	35 (28.5)	123 (100.0)	95 (74.2)	33 (25.8)	128 (100.0)
Week 30, n (%)						
Class I	52 (42.3)	9 (7.3)	61 (49.6)	24 (18.8)	3 (2.3)	27 (21.1)
Class II	33 (26.8)	19 (15.4)	52 (42.3)	61 (47.7)	13 (10.2)	74 (57.8)
Class III	1 (0.8)	7 (5.7)	8 (6.5)	9 (7.0)	16 (12.5)	25 (19.5)
Missing	2 (1.6)	0	2 (1.6)	1 (0.8)	1 (0.8)	2 (1.6)

NYHA = New York Heart Association
Baseline is defined as the last nonmissing measurement prior to the first dose of study drug.
All assessments are summarized by analysis visits per SAP.
Missing NYHA class at Week 30 was imputed using available NYHA at Week 26.

Additional analyses of these secondary endpoints are presented below (exploratory analysis).

An LVOT peak gradient ⩾50 mmHg at rest or post-exercise is the threshold for SRT eligibility. In the mavacamten group, 74.3% of subjects with postexercise LVOT peak gradient ⩾50 mmHg at baseline achieved a gradient <50 mmHg at Week 30 compared with 20.8% in the placebo group (Difference 53.5 [95% CI: 42.0, 65.0](exploratory endpoint). A peak LVOT gradient ⩾30 mmHg is the criterion that defines obstruction in the HCM patient population. In the mavacamten group, 56.6% of subjects with postexercise LVOT peak gradient ⩾30 mmHg at baseline achieved LVOT peak gradient <30 mmHg at Week 30 compared with 7.0% in the placebo group (Difference 49.6 [95% CI: 39.3, 59.9])(exploratory endpoint). With respect to Valsava LVOT peak gradient, these decreased rapidly upon initiation of mavacamten treatment to Week 4, decreased more gradually from Week 4 to Week 18, and stabilized from Week 18 to Week 30 (Figure 30). The overall mean (SD) change from baseline to Week 30 was -49 (34.4) mmHg in the mavacamten group and -12 mmHg in the placebo group. The Valsalva LVOT gradient returned to baseline following 8 weeks of study drug washout. Similar findings were observed for changes from baseline to Week 30 in resting LVOT gradient (-39 mmHg and -6 mmHg for the mavacamten and the placebo group, respectively). A complete response, defined as a reduction in resting and provoked LVOT gradients to <30 mmHg and achieving NYHA Class I, was demonstrated by 27% of mavacamten-treated subjects compared with 0.8 % of placebo subjects (Difference 26.6 [95% CI: 18.3, 34.8])(exploratory endpoint).

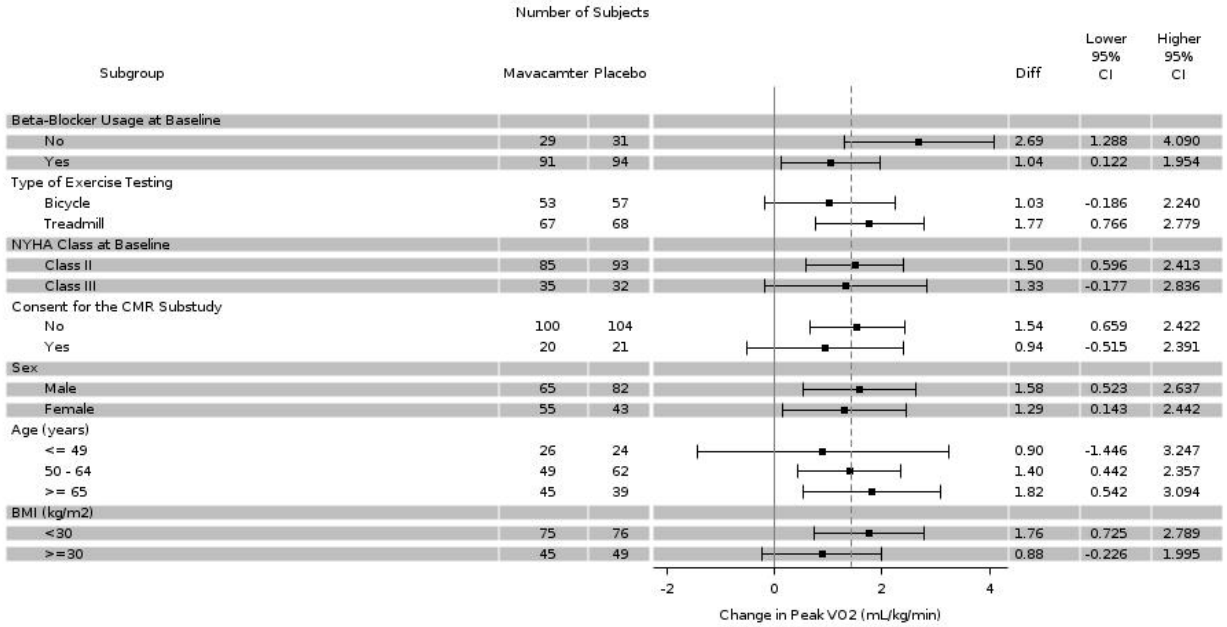
Figure 30. EXPLORER-HCM: Mean (SD) Valsalva LVOT Peak Gradient by Treatment and Visit (ITT Population)

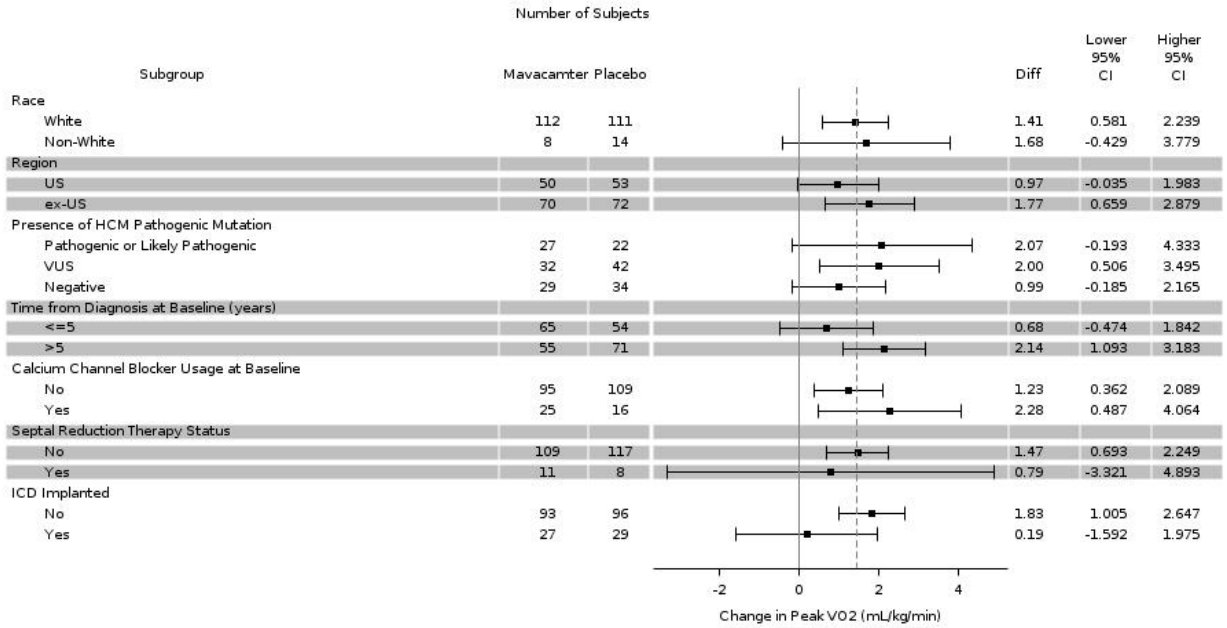


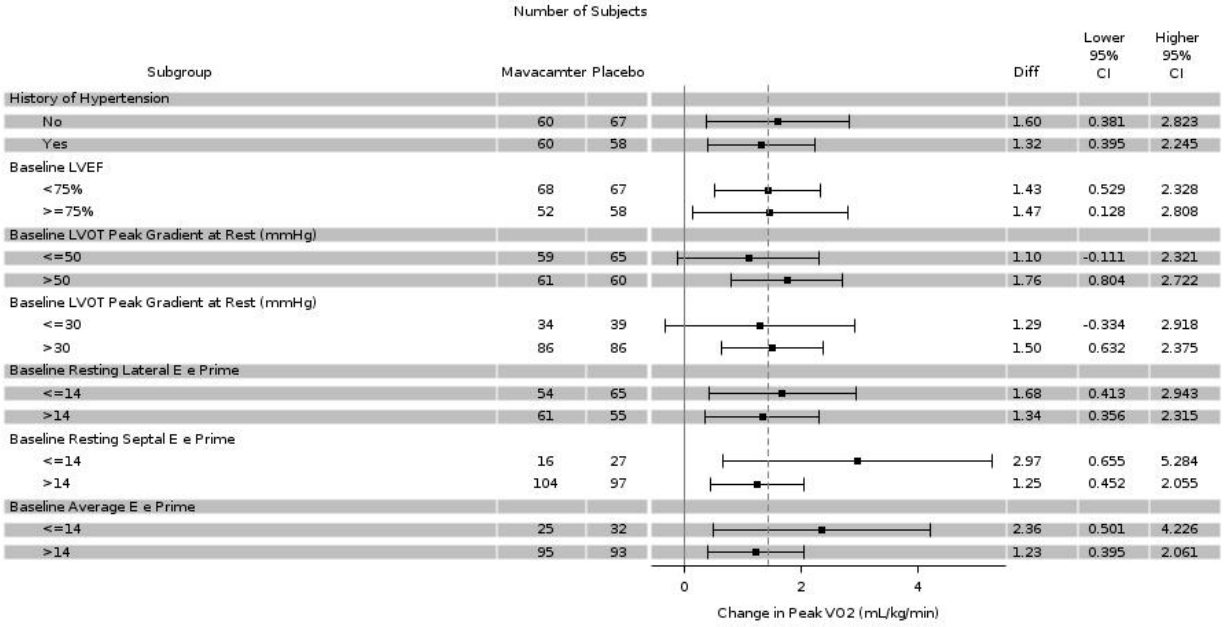
With respect to pVO_2max, the proportion of subjects with improvements from baseline in pVO_2max was greater for the mavacamten group compared with the placebo group across all thresholds of improvement. At Week 30, the proportion of subjects with an increase in pVO_2max ≥1.5 mL/kg/min in the mavacamten group vs. the placebo group was 42% vs. 25%; the proportion of subjects with an increase ≥3.0 mL/kg/min was 24% vs 13%, respectively. Consistent pVO2 treatment effect in favour

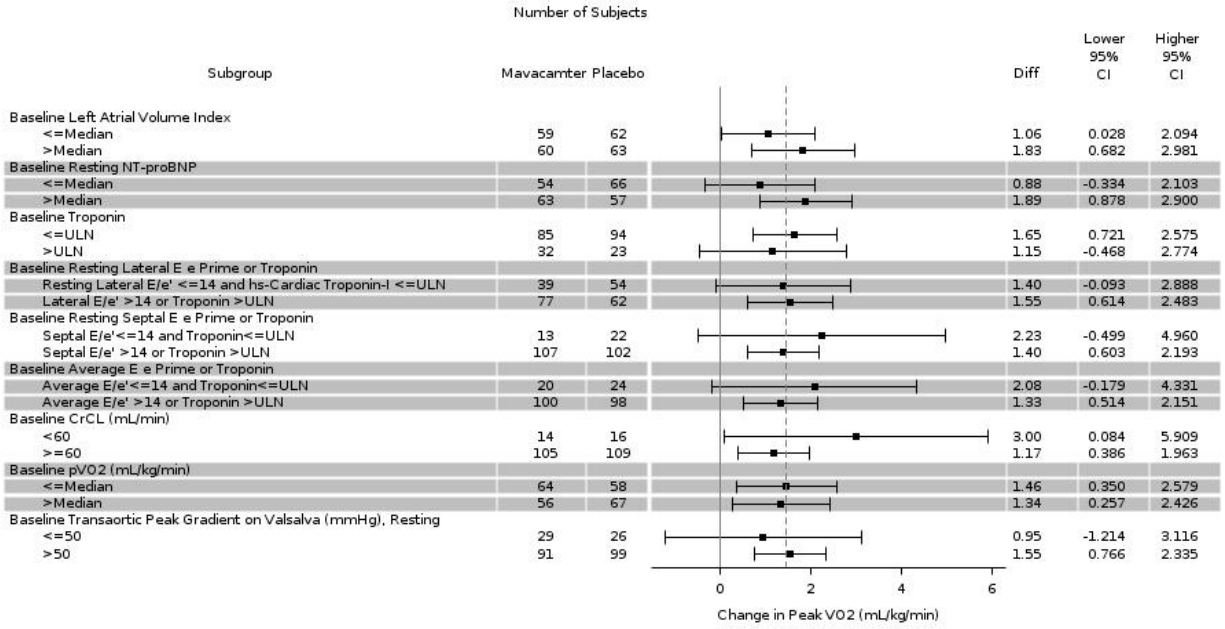
of mavacamten was observed across all baseline demographic and disease characteristics including by Valsalva LVOT gradient at baseline (Valsalva LVOT [(≤ 50 vs > 50 mmHg)])(Figure 31).

Figure 31. Forest Plot of Treatment Effect on the Change of pVO_2 (mL/kg/min) from Baseline to Week 30 across Subgroups (ITT Population)









Note: BMI=Body Mass Index; CrCL=Creatinine clearance; HCM = Hypertrophic Cardiomyopathy; ICD=Implanted Cardioverter Defibrillator; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; VUS = Variant of Uncertain Significance; ULN=Upper Limit Normal.
Dotted line represents the overall estimate. The 95% CIs of the response differences between mavacamten and placebo groups are based on normal approximation.
The subgroups by stratification factors were determined using the data in eCRF. The subgroup by HCM gene mutation was determined using the current test results

For a majority of subjects in the mavacamten group (and more than twice as many as in the placebo group), mavacamten treatment was associated with ⩾1 class improvement from baseline in NYHA class (65.0% mavacamten vs. 31.3% placebo, difference 33.8; 95% CI: 22.15, 45.43; p <0.0001). At baseline, all subjects were NYHA Class II or III; no subjects were Class I. In the mavacamten group, 52 (42.3%) subjects improved from Class II to Class I, 19 (15.4%) subjects who improved from Class III to Class II, and 9 (7.3%) subjects who improved from Class III to Class I. One subject (0.8%)

worsened from NYHA Class II at baseline to Class III at Week 30 (Table 21). In the placebo group, 31.3% (40 of 128 subjects) had an improvement of ⩾1 NYHA class at Week 30, including 24 (18.8%) subjects who improved from Class II to Class I, 13 (10.2%) subjects who improved from Class III to Class II, and 3 (2.3%) subjects who improved from Class III to Class I. Nine subjects (7.0%) worsened from NYHA Class II at baseline to Class III at Week 30

With respect to KCCQ-23 CCS, a greater proportion of subjects in the mavacamten group compared with placebo achieved a clinically meaningful improvement of ≥10 points from baseline to Week 30 in the KCCQ-23 CSS (53.9% vs 33.8%, respectively). Similarly, a greater proportion of patients taking mavacamten compared to placebo achieved a clinically meaningful improvement (decrease) of ≥ 2.5 points between baseline and Week 30 in the HCMSQ SoB domain score (50.0% vs 21.3%). At Week 38, following 8 weeks of study drug washout, both mean KCCQ-23 CSS and HCMSQ SoB had returned to baseline values for the mavacamten group; the small increases from baseline seen in the placebo group were maintained.

Exploratory endpoints

Exercise performance by cardiopulmonary testing

Changes from baseline in CPET parameters, including increases in peak circulatory power, peak MET, percent predicted pVO_2max, and ventilatory power and decrease in VE/VCO2 slope, were all greater for subjects in the mavacamten group compared with the placebo group, demonstrating overall improvements in exercise performance and cardiac output with mavacamten treatment (Table 22). Changes from baseline in RER were small and similar for both treatment groups, indicating that subjects attained their peak exercise in both groups.

Table 22. Changes from Baseline to Week 30 and Between-Group Comparisons for Exploratory CPET Endpoint (ITT Population)

	Mavacamten				Placebo					
	Baseline		Change at Week 30		Baseline		Change at Week 30		LS Mean Difference (95% CI)	p-value
CPET Parameter	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)		
Peak VE/VCO_2	123	35.4 (5.18)	120	-1.9 (3.67)	128	34.2 (5.54)	125	0.5 (3.83)	-2.2 (-3.05, -1.26)	< 0.0001
VE/VCO_2 Slope	123	33.6 (6.24)	120	-2.4 (4.59)	128	32.4 (6.18)	125	0.4 (4.14)	-2.6 (-3.58, -1.52)	< 0.0001
Peak Circulatory Power	122	3087 (1165.2)	119	414.1 (971.98)	125	3284 (1173.33)	121	-17.94 (869.06)	372.9 (153.12, 592.61)	0.0010
Ventilatory Power	122	4.9 (1.40)	119	0.7 (1.40)	125	5.2 (1.54)	121	-0.03 (1.23)	0.6 (0.29, 0.90)	0.0002
Peak MET	123	5.4 (1.39)	120	0.40 (0.89)	128	5.7 (1.40)	125	-0.0 (0.86)	0.4 (0.17, 0.60)	0.0006
Peak RER	123	1.1 (0.09)	120	0.03 (0.09)	128	1.1 (0.09)	125	-0.0 (0.09)	0.02 (-0.00, 0.04)	0.0885
Percent predicted VO_2	123	77.2 (20.81)	120	7.7 (13.10)	127	77.0 (22.09)	125	-0.6 (12.09)	8.4 (5.31, 11.51)	< 0.0001
Ventilatory Threshold	114	11.5 (2.35)	106	0.7 (2.49)	125	11.5 (2.62)	116	0.1 (2.60)	0.6 (-0.03,1.17)	0.0603

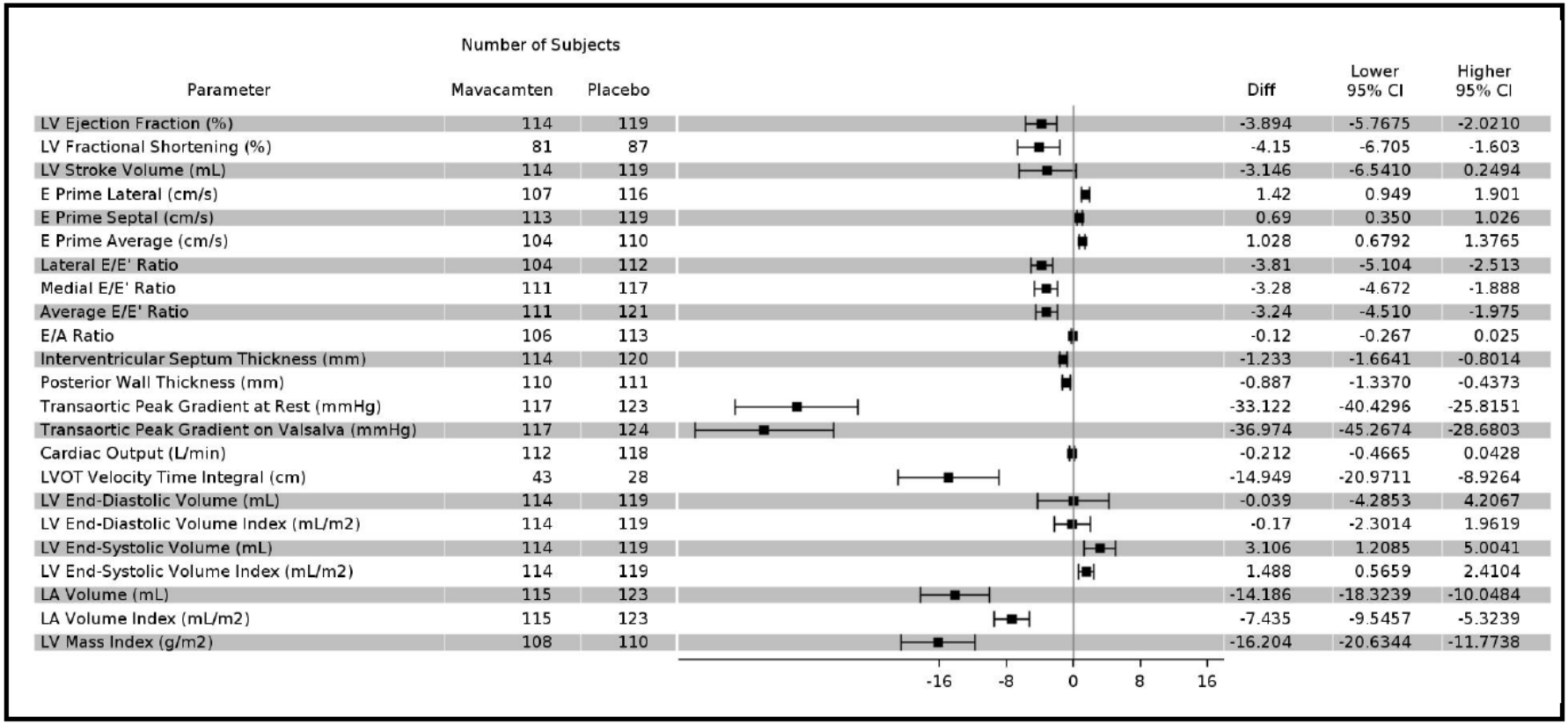
LS = least squares; MET = metabolic equivalents of task; RER = respiratory exchange ratio; VE/VCO_2 = volume expired/ carbon dioxide production; VO_2 = oxygen consumption
The least squares means (95% CI) and the p-values are from a mixed model for repeated measurements with data up to Week 30, which includes baseline value, treatment group, visit, interaction between treatment group and visit, and the 3 stratification factors (beta-blocker use, NYHA class, and exercise type based on IXRS) as fixed effect and subject as random effect.

Cardiac function and structure measured by TTE

Figure 32 below presents the mean differences and 95% CIs of the between-group differences in changes from baseline at Week 30 in TTE parameters. For all evaluated parameters, the difference in change from baseline was directionally favourable for the mavacamten group compared with the

placebo group. LVSV increased in both treatment groups, but less so in the mavacamten group, leading to the difference shown in the figure.

Figure 32. Between-group differences in change from baseline at Week 30 in resting TTE parameters (Mavacamten vs Placebo) (ITT Population)



LA = left atrium; LV = left ventricular; LVOT = left ventricular outflow tract
95% CIs of the mean differences between mavacamten and placebo groups are based on normal approximation.

Systolic anterior motion of the mitral valve and mitral regurgitation

Systolic anterior motion (SAM) is a paradoxical motion of the anterior leaflet of the mitral valve during systole which can lead to septal contact, worsening LVOT obstruction and causing mitral regurgitation (MR). It occurs commonly in oHCM. At baseline, the proportion of subjects with SAM was similar for the mavacamten and placebo groups (82% and 81%, respectively). Of the subjects with SAM at baseline with nonmissing values at Week 30, no SAM was detected in 80.9% of subjects in the mavacamten group at Week 30 (76 of 94 subjects with nonmissing values) versus 34.0% of subjects in the placebo group (33 of 97 subjects) (Difference 46.8 [95% CI: 34.5, 59.2]). In addition, of the subjects with MR at baseline, 9.0% in the mavacamten group and no subjects in the placebo group had this resolved at Week 30 (Difference 9.0 [95% CI: 3.7, 14.3]).

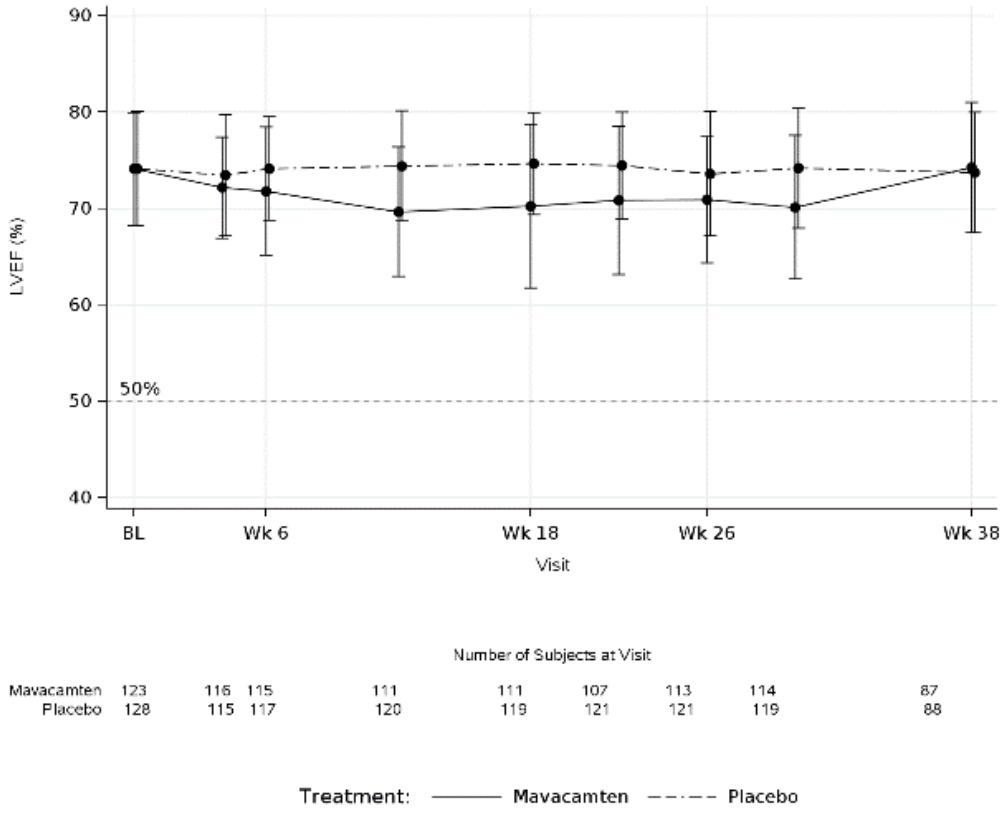
Cardiac biomarkers

In mavacamten-treated subjects, NT-proBNP levels decreased rapidly during the initial 4 weeks of treatment and remained stable to the end of the 30 week treatment period. At Week 30, the reduction from baseline in NT-proBNP after mavacamten treatment was 80% greater than for placebo (proportion of geometric mean ratio between the 2 groups 0.20 [95% CI, 0.17 to 0.24]). With respect to cardiac troponin, at Week 30, the reduction from baseline in high-sensitivity (hs) cardiac troponin I (cTnI) after mavacamten treatment was 41% greater than for placebo (0.59 [95% CI, 0.50 to 0.69]). At Week 38, following 8 weeks of study drug washout (for subjects with Week 38 evaluations), NT-proBNP levels returned to baseline for the mavacamten group and remained unchanged for the placebo group.

LVEF

At baseline, LVEF was similar and hypercontractile for the mavacamten (74% [5.8%]) and placebo (74% [5.9%]) groups. There was a small mean (SD) decrease in LVEF (absolute change -4% [7.7%]) during 30 weeks of treatment with mavacamten compared with placebo (-0.0 [6.8]), which is within the variability of the measure (Figure 33). LVEF returned to baseline values following discontinuation of mavacamten.

Figure 33. EXPLORER-HCM: Mean (SD) LVEF by Treatment and Visit (ITT Population)



Cardiac Magnetic Resonance (CMR) substudy

In patients with HCM, CMR is the gold standard for measurement of ventricular mass, volumetric assessments, and noninvasive tissue characterization for the presence and extent of replacement myocardial fibrosis by late gadolinium enhancement (LGE).

Results from the CMR substudy of EXPLORER-HCM showed structural changes represented by a reduction in left ventricular mass index (LVMI) (mean between-group difference -16 g/m^2; 95% CI:-22.6, -9.0), global LV maximal wall thickness (mean between-group difference -2 mm; 95% CI: -3.9, -0.9), and left atrial volume index (LAVI) (mean between-group difference -10 mL/m^2; 95% CI: -16.0, -4.6) over the 30 week treatment period (Table 23). LV hypertrophy and LA volumes are both indices of adverse prognosis in oHCM. The contractile function remains in the normal range with mavacamten treatment. Myocardial contraction fraction and contractile fraction (stroke volume/LV mass ratio) were maintained as load independent measures of LV pump reserve. No increase in cardiac fibrosis was observed among the mavacamten-treated subjects. Most of the subjects in the CMR substudy exhibited little or no replacement fibrosis at baseline as assessed by global mass of LGE and global percent of LGE, and there were no within- or between-group changes from baseline at Week 30.

Table 23. Between-Group Comparisons in Changes from Baseline at Week 30 in CMR Parameters (CMR substudy population)

CMR Parameter	Mavacamten (N = 17)	Placebo (N = 18)	Mavacamten vs Placebo Mean Diff. (95% CI)
LV Mass Index (g/m^2), mean (SD)			
Baseline	95 (29.6)	101 (21.9)	
Change from Baseline at Week 30	-17 (12.0)	-2 (7.4)	-16 (-22.6, -9.0)
P-value	< 0.0001	0.64	< 0.0001
Absolute Myocardial Mass Index (g/m^2), mean (SD)	n = 16	n = 18	
Baseline	66 (20.7)	69 (14.6)	
Change from Baseline at Week 30	-14 (9.5)	-1 (6.5)	-13 (-18.7, -7.5)
P-value	< 0.0001	0.67	0.0002
Global LV Maximum Wall Thickness (mm), mean (SD)			
Baseline	18 (4.3)	19 (3.9)	
Change from Baseline at Week 30	-2 (2.5)	-0 (1.9)	-2 (-3.9, -0.9)
P-value	0.0017	0.92	0.0079
LVEF (%), mean (SD)			
Baseline	78 (6.6)	79 (4.4)	

CMR Parameter	Mavacamten (N = 17)	Placebo (N = 18)	Mavacamten vs Placebo Mean Diff. (95% CI)
Change from Baseline at Week 30	-7 (6.3)	-0 (5.1)	-6 (-10.3, -2.4)
P-value	0.0003	0.97	0.0025
MCF (%), mean (SD)[a]			
Baseline	61 (17.9)	60 (17.3)	
Change from Baseline at Week 30	2 (12.8)	0 (6.6)	2 (-4.5, 9.3)
P-value	0.93	0.97	0.70
LVEDVI (mL/m^2), mean (SD)			
Baseline	66 (14.6)	71 (17.5)	
Change from Baseline at Week 30	-4 (10.1)	-1 (6.8)	-3 (-9.4, 2.4)
P-value	0.15	0.94	0.31
LVESVI (mL/m^2), mean (SD)			
Baseline	14 (4.9)	15 (5.0)	
Change from Baseline at Week 30	4 (5.2)	0.1 (2.9)	4 (0.6, 6.4)
P-value	0.0032	0.73	0.02
LVSV (mL), mean SD			
Baseline	106 (29.6)	115 (35.2)	
Change from Baseline at Week 30	-16 (17.1)	-2 (13.2)	-13.5 (-23.9, -3.0)
P-value	0.0021	0.83	0.02
LVSVI (mL/m^2), mean SD			
Baseline	52 (12.6)	56 (14.1)	
Change from Baseline at Week 30	-8 (9.0)	-1 (6.9)	-7 (-12.5, -1.5)
P-value	0.0038	0.84	0.02
Contractile Fraction, mean (SD)[b]			
Baseline	1 (0.2)	1 (0.2)	
Change from Baseline at Week 30	0 (0.1)	0 (0.1)	0 (-0.0, 0.1)
P-value	0.93	0.96	0.70
Cardiac Output (L/min), mean (SD)			
Baseline	6 (1.6)	7 (3.0)	
Change from Baseline at Week 30	-0.5 (0.91)	0 (1.1)	-1 (-1.5, -0.1)
P-value	0.06	0.17	0.01
LAVI Maximum (mL/m^2), mean (SD)			
Baseline	52 (13.1)	73 (28.5)	

CMR Parameter	Mavacamten (N = 17)	Placebo (N = 18)	Mavacamten vs Placebo Mean Diff. (95% CI)
Change from Baseline at Week 30	-11 (10.6)	-0 (5.3)	-10 (-16.0, -4.6)
P-value	< 0.0001	0.47	0.0004
LAVI Minimum (mL/m^2), mean (SD)			
Baseline	29 (12.1)	44.7 (22.9)	
Change from Baseline at Week 30	-7 (11.1)	1 (6.8)	-9 (-15.1, -2.5)
P-value	0.01	0.58	0.02
Global Mass of LGE 6SD (g), mean (SD)			
Baseline	1 (3.3)	2 (3.1)	
Change from Baseline at Week 30	0.2 (1.2)	-1 (1.9)	1 (-0.3, 2.0)
P-value	0.34	0.92	0.89
Global Mass of LGE 6SD (%)			
Baseline	0.9 (2.1)	1.5 (1.9)	
Change from Baseline at Week 30	0.4 (1.4)	-0.3 (1.1)	0.8 (-0.1, 1.6)
P-value	0.02	0.56	0.06
Global Average ECVF, mean (SD)	n = 16	n = 18	
Baseline	0.3 (0.1)	0.3 (0.1)	
Change from Baseline at Week 30	0.02 (0.1)	0 (0.0)	0 (-0.0, 0.1)
P-value	0.25	0.65	0.13

6SD = 6 standard deviations; ECVF = extracellular volume fraction; LAVI = left atrial volume index; LGE = late gadolinium enhancement; LV = left ventricular; LVEDVI = left ventricular end diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end systolic volume index; LVSVI = left ventricular stroke volume index; MCF = myocardial contraction fraction

Baseline was defined as the last nonmissing measurement prior to the first dose of study drug.

Change from baseline was calculated as postbaseline value minus baseline value.

p-values for the within-group tests are based on Wilcoxon's signed-rank test; p-values for the between-group comparisons are based on Wilcoxon's rank sum test.

[a] MCF was calculated as SV/LV myocardial volume.

[b] Contractile fraction was calculated as SV/LV mass ratio.

Ancillary analyses

N.A.

Study MYK-461-017

Study MYK-461-017 - A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Mavacamten in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy who are Eligible for Septal Reduction Therapy (VALOR-HCM; ongoing)

The clinical cut-off data of the primary CSR was 07-Feb-2022.

Methods

MYK-461-017 is an ongoing Phase 3, randomized, double-blind, placebo-controlled, multicenter study of mavacamten vs placebo in adults with symptomatic oHCM who met 2011 ACCF/AHA guideline criteria for SRT and have been referred for an SRT procedure within the past 12 months in the USA.

Study Participants

The main inclusion/exclusion criteria are provided in Table 24 below

Table 24. Key inclusion/exclusion criteria of VALOR-HCM

Study MYK-461-017
Inclusion Criteria
- At least 18 years old at screening
- Body weight > 45 kg at screening
- Adequate acoustic windows to enable accurate transthoracic echocardiography (TTEs)
- Diagnosed with oHCM (unexplained LV hypertrophy with nondilated ventricular chambers in the absence of other cardiac [eg. Aortic stenosis, hypertension]) or systemic disease. Patient has maximal septal wall thickness ≥15 mm or ≥13 mm with family history of HCM consistent with current ACCF/AHA 2011 guidelines. Patient must meet ACCF/AHA 2011 guideline recommendations for invasive SRT therapies as: a. Clinical criteria: Despite maximally tolerated drug therapy severe dyspnea or chest pain (NYHA Class III or IV) or for the purposes of the Valor Study, subjects who are NYHA Class II with exertion-induced syncope or near syncope b. Hemodynamic criteria: dynamic LVOT gradient at rest or with provocation (ie, Valsalva or exercise) ≥50 mmHg associated with septal hypertrophy of ≥15mm (or ≥13mm with family history of HCM) (read by the core echocardiography laboratory) c. Anatomic criteria: targeted anterior septal thickness sufficient to perform the procedure safely and effectively in the judgment of the individual operator
- Referred or under active consideration within the past 12 months for SRT procedure and willing to have SRT procedure
- Subjects referred or considered for ASA must have an adequate first septal perforating branch of left anterior descending (LAD) coronary artery, amenable for the interventionalist to perform the procedure
- Documented oxygen saturation at rest ≥90% at screening
- Documented LVEF ≥60% at screening according to core echocardiography laboratory reading
- Female subjects not pregnant or lactating and, if sexually active, must either practice true abstinence or use 1 of the following highly effective birth control methods from screening through 4 months after the last dose of study drug: • Estrogen- and progestogen-containing hormonal contraception associated with inhibition of ovulation or progestogen-only hormonal contraception associated with inhibition of ovulation by oral, implantable, or injectable route of administration • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion • Female surgically sterile or postmenopausal for 1 year. Permanent sterilization includes hysterectomy, bilateral oophorectomy, bilateral salpingectomy, and/or documented bilateral tubal occlusion. Females are considered postmenopausal if they have had amenorrhea for ≥1 year after cessation of all exogenous hormonal treatments, and follicle stimulating hormone (FSH) levels are in the postmenopausal range. Male partners of female subjects must also use a contraceptive (eg, barrier, condom, or vasectomy) from screening through 4 months after the last dose of study drug.
Exclusion Criteria
- Previously participated in a clinical study with mavacamten

- Hypersensitivity to any of the components of the mavacamten formulation
- Participated in a clinical trial in which the subject received any investigational drug (or was currently using an investigational device) within 30 days prior to screening or at least 5 times the respective elimination half-life (whichever was longer)
- Known infiltrative or storage disorder causing cardiac hypertrophy that mimicked oHCM, such as Fabry disease, amyloidosis, or Noonan syndrome with LV hypertrophy
- Planned invasive procedure during the first 32 weeks of the study
- Papillary muscle or mitral valve in need of repair or any other intracardiac procedure planned (however, if need for mitral valve repair is discovered during SRT procedure, the subject will continue to be followed on study)
- For individuals on beta blockers, calcium channel blockers, or disopyramide, any dose adjustment of these medications <14 days prior to screening or an anticipated change in regimen during the first 16 weeks of the study
- Any medical condition that precluded upright exercise stress testing
- Paroxysmal, intermittent atrial fibrillation with atrial fibrillation present at screening per the investigator's evaluation of the subject's ECG at screening
- Persistent or permanent atrial fibrillation and subject not on anticoagulation for ≥4 weeks prior to screening and/or not adequately rate controlled ≤ 6 months of screening.
- Previously treated with invasive septal reduction (surgical myectomy or percutaneous ASA). However, if the subject has a history of a suboptimal or a failed alcohol septal ablation and there is no evidence on site read prescreening echocardiogram of an ASA, the subject may be included after consultation with the MyoKardia or CRO medical monitor.
- Planned ICD placement or pulse generator change during the first 32 weeks of the study
- ECG abnormality considered by the investigator to pose a risk to subject safety (eg, second degree atrioventricular block type II)
- Acute or serious comorbid condition (eg, major infection or hematologic, renal, metabolic, gastrointestinal, or endocrine dysfunction) that in the judgment of the investigator could lead to premature termination of study participation or interfere with the measurement or interpretation of the efficacy and safety assessments in the study a. Pulmonary disease that limits exercise capacity or systemic arterial oxygen saturation b. History of malignant disease within 10 years prior to screening: • Subjects who have been successfully treated for nonmetastatic cutaneous squamous cell or basal cell carcinoma or have been adequately treated for cervical carcinoma in situ or breast ductal carcinoma in situ may be included in the study • Subjects with other malignancies who are cancer-free for more than 10 years prior to screening may be included in the study
- History or evidence of any other clinically significant disorder, condition, or disease that, in the opinion of the investigator, would pose a risk to subject safety or interfere with study evaluations, procedures, or completion
- Safety laboratory parameters (chemistry, hematology, coagulation, and urinalysis) outside normal limits (according to the central laboratory reference range) at screening as assessed by the central laboratory; however, a subject with safety laboratory parameters outside the normal limits may be included if all the following criteria are met: a. Safety laboratory parameters outside normal limits are considered by the investigator to be clinically not significant b. If an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) result, the value must be <3 × the upper limit of the laboratory reference range c. Body size–adjusted estimated glomerular filtration rate is ≥30 mL/min/1.73 m2
- Has known moderate or severe aortic valve stenosis or moderate to severe aortic stenosis determined at screening (as read by the echocardiography core laboratory)
- Positive serologic test at screening for infection with human immunodeficiency virus (HIV); hepatitis C virus (HCV); or hepatitis B virus (HBV), with the exception of HBV s-antibody positive which is a marker of immunity
- Known active infection with Covid-19 (PCR+) within 90 days of screening. If subject had a PCR+ test within 6 months of screening, they must have a negative Covid-19 test at screening.
- Prior treatment with cardiotoxic agents, such as doxorubicin or similar
- Unable to comply with the study requirements, including the number of required visits to the study site
- First-degree relative of personnel directly affiliated with the study at the study site, any study vendor, or the study sponsor

Treatments

The design of the study included a screening period and three dosing periods (placebo-controlled dosing or double-blind period, active-controlled dosing period and a long-term extension (LTE) dosing period)(Figure 34).

After screening, subjects were randomized in a 1:1 ratio to the mavacamten or placebo treatment groups and stratified by the type of SRT procedure recommended (myectomy or alcohol septal ablation [ASA]) and NYHA functional class.

Placebo-controlled dosing or double-blind period (Day 1 to Week 16): On Day 1, subjects began dosing (blinded dose) with mavacamten 5 mg or placebo once daily for 16 weeks and were evaluated for possible down-titration at Week 4 based on VLVOT <30mmHg and up-titration at Weeks 8 and 12 to a maximum dose of mavacamten 15 mg based on LVEF ≥50% and VLVOT ≥30 mmHg (Table 25).

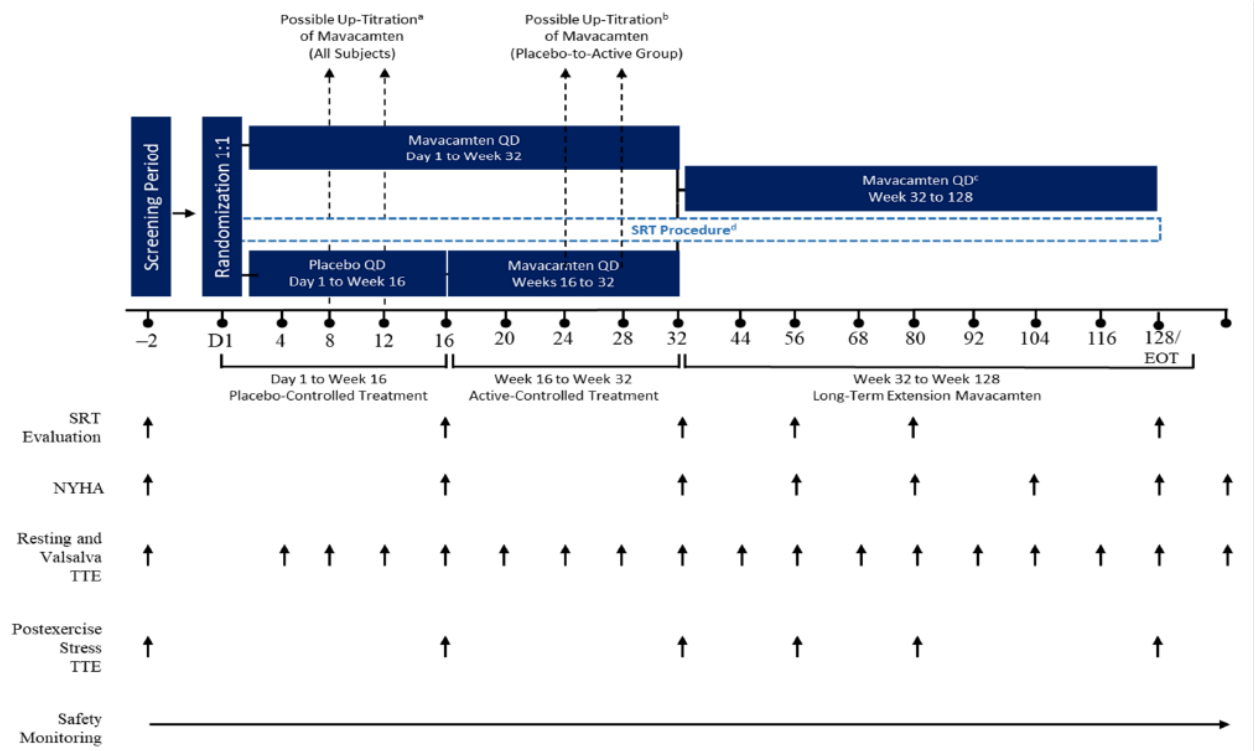
Active-controlled dosing period (Week 16 to Week 32): After the Week 16 assessments, subjects in the mavacamten group continued blinded mavacamten administration on the dose they were receiving at W16, and subjects in the placebo group began dosing with mavacamten 5 mg (blinded dose), once daily from Weeks 16 to 32. Placebo to mavacamten subjects were evaluated for possible down-titration at Week 20 based on VLVOT <30 mmHg and up-titration at Weeks 24 and 28 based on TTE dose titration guidelines of LVEF ≥50% and VLVOT ≥30 mmHg.

LTE dosing period (Week 32 to Week 128): After the Week 32 assessments, all subjects continued once-daily mavacamten (blinded dose) until Week 128. During this period, mavacamten dose may be up-titrated at any scheduled visit after Week 32 (visits scheduled every 12 weeks) if the site-read LVOT gradient with Valsalva manoeuvre is ≥30 mmHg and LVEF is ≥50%. Subjects whose mavacamten dose was increased during the LTE period attend an unscheduled study visit 4 weeks after the dose increase and then resume the regular study visit schedule.

At any time if LVEF <50%, then a protocol-defined temporary interruption occurred with follow-up 2-4 weeks later. If LVEF was ≥50% at that visit, then dosing resumed at one lower dose strength. Dose may be down-titrated for safety at any time during the 3 dosing periods.

The study continues until Week 136 (EOS visit), following an 8-week posttreatment period. Throughout the study, all dose adjustments occur in a blinded manner via the IXRS.

Figure 34. Study Design Schematic



Source: Synopsis of the protocol (Appendix 1.1)

Abbreviations: EOS = end of study; EOT = end of treatment; NYHA = New York Heart Association (functional classification); QD = once daily; SRT = septal reduction therapy; TTE = transthoracic echocardiogram.

a During the placebo-controlled dosing period (Day 1 to Week 16) subjects will be evaluated for possible down-titration at Week 4 and up-titration at Weeks 8 and 12 by independent assessment of TTE by the echocardiography core laboratory and according to dose-titration guidelines. Dose may be down-titrated for safety at any time.

b Subjects in the placebo-to-active group, who begin dosing with mavacamten at Week 16, will be evaluated for possible down-titration at Week 20 and up-titration at Weeks 24 and 28. Dose may be down-titrated for safety at any time.

c During the long-term extension (LTE) dosing period (Weeks 32 to 128), mavacamten dose may be up-titrated at any scheduled visit after Week 32 if the site-read LVOT gradient with Valsalva maneuver is ≥ 30 mmHg and LVEF is ≥ 50%. All dose increases during LTE dosing must be approved by the MyoKardia or CRO medical monitor before they are implemented. Subjects who have their mavacamten dose increased during the LTE period will attend an unscheduled study visit 4 weeks after the dose increase and then resume the regular study visit schedule. Dose may be down-titrated for safety at any time.

d At any time during the study, subjects may withdraw from study drug and proceed with SRT at a recognized HCM center after a recommended study drug washout period ≥ 6 weeks. Subjects who discontinue study drug to undergo SRT will undergo EOT assessments within 14 days and will have a telephone follow-up with the study site to assess adverse events 8 weeks after treatment discontinuation (or prior to SRT, whichever is earlier). Discontinuation due to opting for SRT that occurs before Week 32 will require TTEs to be read by the core lab in a blinded fashion. Subjects will be followed every 24 weeks from the date of SRT to Week 128.

Table 25. MYK-461-017: Dose Titration Guidelines

	LVEF ≥ 50%					
	Mavacamten Group Placebo-Controlled Dosing Period (Day 1 to Week 16)			**Placebo-to-Active Group Active-Controlled Dosing Period (Week 16 to Week 32)**		
	Study Week			**Study Week**		
	4	**8**	**12**	**20**	**24**	**28**
Valsalva LVOT ≥ 30 mmHg	Remain on 5 mg	Increase dose 2.5mg to 5mg 5 mg to 10 mg	Increase dose 2.5 mg to 5 mg 5 mg to 10 mg 10 mg to 15 mg[a]	Remain on 5 mg	Increase dose 2.5mg to 5mg 5 mg to 10 mg	Increase dose 2.5 mg to 5 mg 5 mg to 10 mg 10 mg to 15 mg[a]
Valsalva LVOT < 30 mmHg	Decrease dose 5 mg to 2.5 mg	Dose remains unchanged	Dose remains unchanged	Decrease dose 5 mg to 2.5 mg	Dose remains unchanged	Dose remains unchanged
LVOT not applicable	**LVEF < 50%**					
	If at any time LVEF < 50%, discontinue mavacamten 2-4 weeks until follow-up visit If at follow-up[b] LVEF ≥ 50%, resume at 1 step decreased dose: 15 mg to 10 mg 10 mg to 5 mg 5 mg to 2.5 mg 2.5 mg to a retrial of 2.5mg. If LVEF again falls to < 50%, mavacamten will be permanently discontinued. Placebo to placebo					
	LVEF ≤ 30%					
	If at any time LVEF ≤ 30%, permanently discontinue mavacamten					

LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract.
[a] 15 mg once daily is the maximum allowable dose of mavacamten.
[b] Follow-up visit will be an unscheduled visit.

The study treatments administered in this study are mavacamten and placebo-to-match mavacamten. Mavacamten is supplied as 2.5, 5, 10, and 15 mg capsules. Mavacamten capsules of all strengths are identical in appearance. Placebo-to-match mavacamten is supplied as a single capsule to match all mavacamten strengths and is identical in appearance to mavacamten capsules.

Objectives/ Endpoints

The objectives and endpoints can be found in the table below.

Table 26. Objectives and Endpoints

Objectives	Endpoints	Included in this CSR[a] (Yes/No)?
Primary:		
To evaluate the effect of mavacamten on the need for SRT in guideline-eligible subjects with oHCM who are referred for SRT	The primary endpoint will be a composite of: • Decision to proceed with SRT prior to or at Week 16 • SRT guideline eligible at Week 16 based on the 2011 ACCF/AHA HCM Guidelines	Yes
Secondary:		
To evaluate the effect of mavacamten on a hemodynamic parameter	Change from baseline to Week 16 in the mavacamten group compared with the placebo group in post-exercise LVOT gradient	Yes
To evaluate the effect of mavacamten on subject symptoms	Change from baseline to Week 16 in the mavacamten group compared with the placebo group in: • NYHA functional class • Kansas City Cardiomyopathy Questionnaire-23 (KCCQ-23) Clinical Summary Score (CSS)	Yes
To evaluate the effect of mavacamten on cardiac biomarkers	Change from baseline to Week 16 in the mavacamten group compared with the placebo group in NT-proBNP and cardiac troponin I	Yes
Exploratory:		
To evaluate the effect of mavacamten on the need for SRT in a long-term follow-up period (assessments at Weeks 32, 56, 80, and 128)	The endpoint will be a composite of the outcomes: • Decision to proceed with SRT, • SRT guideline eligible based on the 2011 ACCF/AHA HCM Guidelines	Yes[b]
To evaluate the effect of mavacamten on the need for SRT as determined by the investigator (assessments at Weeks 16, 32, 56, 80, and 128)	The endpoint will be a composite of the outcomes: • Decision to proceed with SRT • SRT eligible based on the Investigator determination as recorded on the SRT evaluation CRF	Yes[c]
To evaluate the effect of mavacamten on hemodynamic parameters and cardiac biomarkers and to improve subject activity level and quality of life (QoL)	Analysis of left ventricular outflow tract (LVOT) gradient at rest and induced by Valsalva, LVEF, LV filling pressures, left atrium size, cardiac biomarkers, accelerometry, and EuroQol 5-dimensions 5-level (EQ-5D-5L) questionnaire will be performed for: Change from baseline to Week 16 in the mavacamten group compared with the placebo group	Yes
To evaluate the long-term effect of mavacamten on symptoms, hemodynamic parameters, cardiac biomarkers, subject activity level, and quality of life through Week 128.	Analysis of NYHA functional class, KCCQ-23 (Overall Summary Score [OSS], Total Summary Score [TSS], and individual domains), LVOT gradients, LVEF, LV filling pressures, left atrium size, cardiac biomarkers, accelerometry, and EQ-5D-5L, throughout to Week 128	Yes

Objectives	Endpoints	Included in this CSR[a] (Yes/No)?
Evaluate the effects of mavacamten on type and dose of cardiac medications	Change from baseline to Week 16, Week 16 to 32, and Week 32 to Week 128 in HCM standard of care cardiac medications	Yes
Safety:		
To evaluate the safety of mavacamten for the duration of the study	• Incidence of LVEF < 50% determined by transthoracic echocardiogram (TTE) • Incidence and severity of TEAEs, treatment-emergent SAEs, and laboratory abnormalities • Incidence of SAEs before and after SRT among subjects who undergo SRT • Incidence of major adverse cardiac events (MACE: death, stroke, acute myocardial infarction, heart failure hospitalization) • Incidence of hospitalizations (due to CV and non-CV causes) • Incidence of HF events, (including hospitalizations and urgent emergency room/outpatient visits for HF and escalation in HF treatment) • Incidence of atrial fibrillation/flutter (new from screening and recurrent) • Incidence of implantable cardioverter-defibrillator (ICD) therapy and resuscitated cardiac arrest • Incidence of ventricular tachyarrhythmias (includes ventricular tachycardia, ventricular fibrillation, and Torsades de Pointe) • Incidence of adverse events of special interest (AESIs; symptomatic overdose, outcomes of pregnancy, LVEF ≤ 30%)	Yes
Pharmacokinetics:		
Evaluate plasma concentrations of mavacamten	Summarize mavacamten plasma concentrations from on-treatment sample collection	Yes

Source: Section 2, MYK-461-017 Protocol Amendment 3.0 (Appendix 1.1)

a: For endpoints assessed after week 16, the CSR reports results only for subjects who have reached those time points by 07-Feb-2022.

b: SRT assessment completed for Week 32 only and in partial completed state.

c: Results for Week 16 and Week 32 included in this CSR.

Sample size

Randomisation and blinding (masking)

Eligible subjects will be randomized via an IXRS in a 1:1 ratio to receive double-blind treatment with mavacamten or matching placebo. Randomization will be stratified by the type of SRT recommended (myectomy or ASA) and NYHA functional class.

During the placebo-controlled treatment period (Day 1 to Week 16), study drug and dose will be blinded; and during the active-controlled treatment period (Week 16 to Week 32) and the LTE treatment period (Week 32 to 128) mavacamten dose will be blinded.

Sites and investigators will not be actively adjusting doses. All dose adjustments will occur in a double-blind manner via IXRS, and all subjects, whether receiving mavacamten or matching placebo, will undergo assessments that could lead to a dose adjustment. Throughout the study, all study drug (mavacamten 2.5, 5, 10, or 15 mg and placebo-to-match mavacamten) will be dosed as a single capsule once daily. The sponsor, central and core laboratories, and clinical site monitors will also be blinded to assigned treatment. In addition, 1 or more sham temporary dose discontinuations for subjects in the placebo group may be performed by the IXRS to maintain the study blind during placebo-controlled dosing (Day 1 to Week 16).

Statistical methods

Approximately 100 subjects were to be randomized in a 1:1 ratio to mavacamten group and placebo group. This sample size provides adequate power to determine the superiority of mavacamten in reducing election of SRT or eligibility for SRT at the end of a 16-week treatment period. The proposed sample size of 50 subjects in each treatment group was to provide 95% power at a 2-sided 5% statistical significance level if the true SRT eligibility rates were 70% and 35% for the placebo and mavacamten groups respectively.

Efficacy (Primary Endpoint)

The comparison of the proportions of subjects meeting the primary endpoint between the mavacamten and placebo treatment groups stratified by the type of SRT procedure recommended and NYHA class was performed using the Cochran-Mantel-Haenszel (CMH) test. The point estimate and the 95% CIs for the treatment difference was provided.

Early termination from the study or lost to follow up prior to week 16 or other events (e.g. missed visit, inadequate ECHO imaging quality or other clerical reason) that led to missing data were imputed as SRT eligible (i.e. meeting the primary endpoint). For the intercurrent events that do not lead to missing data such as discontinuation of treatment or change in cardiac medication, all data collected was included for analysis under the ITT principle, which is the treatment policy strategy.

An additional stratification factor, baseline maximum LVOT gradient was included in the CMH test as a sensitivity analysis to estimate the treatment effect. A tipping point analysis was performed to assess the impact of the missing data and the robustness of the primary endpoint result.

Efficacy (Secondary Endpoints)

Secondary endpoints were tested in a pre-specified sequential order to control for multiplicity. Secondary endpoints were summarized for each treatment group at each visit using descriptive statistics. Change from baseline to Week 16 in post-exercise LVOT gradient was analyzed using an analysis of covariance (ANCOVA) model including treatment group, stratification factors, and baseline value. Proportion of subjects who had at least 1 class of improvement from baseline in NYHA class at Week 16 was analyzed using the same method as for the primary endpoint. Change from baseline to Week 16 in KCCQ-CSS, NT-proBNP and cardiac troponin I was analyzed using a mixed model with repeated measures (MMRM) including treatment group, stratification factors, baseline value, visit and visit by treatment interaction.

Missing data for LVOT gradient was imputed using a placebo-based MI approach via a regression model consists of placebo subjects only and including stratification factors and baseline LVOT values as

covariates. Missing data in NYHA class was imputed as 'non-responder', ie, for any subject whose NYHA class is missing at Week 16, they were considered as no improvement from the baseline. Missing data in KCCQ CSS, NT-proBNP, and cardiac troponin I was handled using a placebo-based MI via FCS regression model. For the intercurrent events that do not lead to missing data such as discontinuation of treatment or change in cardiac medication, all data collected was included for analysis under the ITT principle, which is the treatment policy strategy.

Results

Participant flow

In this study, a total of 112 subjects were randomized (56 subjects to each arm), of which 111 received at least 1 dose of study drug (Table 27).

The 07-Feb-2022 data cut-off date was chosen to allow all randomized subjects the opportunity to reach 16 week visit prior to the cut-off date. All randomized subjects have completed follow-up for 16-week double-blind treatment period at the time of data cut-off, except 2 subjects in placebo arm that discontinued study (1 subject who was withdrawn from study after receiving 1 dose as they met exclusion criterion of moderate to severe aortic stenosis, and 1 subject who withdrew consent after randomization but prior to taking their first dose).

In addition to subjects who discontinued study follow-up during the double-blind period, 2 subjects in mavacamten and 2 subjects in Placebo discontinued treatment as they proceeded with SRT. Therefore, 54/56 mavacamten randomized subjects and 52/56 placebo randomized subjects completed treatment during the double-blind period.

Table 27. Subject Disposition and Analysis Populations - Double-Blind Period

	Mavacamten (N=56) n (%)	Placebo (N=56) n (%)	Overall (N-112) n (%)
Total Number of Subject			
Randomized	56 (100.0)	56 (100.0)	112 (100.0)
Treated	56 (100.0)	55 (98.2)	111 (99.1)
Discontinued Treatment during the DB Period [1]	2 (3.6)	3 (5.4)	5 (4.5)
Proceeding With SRT	2 (3.6)	2 (3.6)	4 (3.6)
Protocol Violation	0	1 (1.8)	1 (0.9)
Discontinued Study during the DB Period [2]	0	2 (3.6)	2 (1.8)
Other	0	1 (1.8)	1 (0.9)
Withdrawal By Subject	0	1 (1.8)	1 (0.9)

Note: Percentages are based on N, number of subjects in the ITT Population.
[1]: Subjects who terminated study drug before the start of the active-control period

Dose titration and modification

The most frequent dose received was 10 mg. Other doses were evenly distributed during the double-blind period at Week 16 (Table 28).

Table 28. Summary of Dose Levels at Week 16 - Safety Analysis Population

Last Dose Level (mg)	Mavacamten N = 56 n (%)
2.5	12 (21.4)
5	13 (23.2)
10	19 (33.9)
15	12 (21.4)

Source: Table 14.1.5.3.

Note: The dose level is based on the last dose level prior to week 16, including the unscheduled visits. For subjects who terminated the study drug early during the double-blind period, the last on-study dose level is used.

Discontinuation of Study Therapy

In the double-blind period, 2 subjects in the mavacamten treatment group and no subjects in the placebo treatment group met the temporary discontinuation criterion of LVEF <50%. Both events occurred at Week 16. Both subjects were asymptomatic. After temporary discontinuation of mavacamten both subjects were able to resume mavacamten at 1 dose lower than they had been receiving at the time of the temporary discontinuation and remain in the study. Furthermore, 1 subject in the mavacamten group had 2 temporary interruptions of study drug for worsening atrial fibrillation (interruption of 1 day and 5 days; each time mavacamten was resumed at the same dose). 1 subject in the mavacamten group had temporary interruption of study drug for worsening palpitations, fatigue, and shortness of breath (subject proceeded to SRT without resuming mavacamten). 1 subject in the placebo group had temporary dose interruption for worsening dizziness and dyspnea (subject proceeded to SRT without resuming IP).

No subjects met the permanent discontinuation criteria of LVEF ≤ 30% in the double-blind period. However, during the long-term follow-up period, four subjects (1 in previous mavacamten group and 3 in the previous placebo group) discontinued mavacamten to proceed to SRT.

Protocol deviations

The proportion of subjects with important protocol deviations (IPD) was approximately similar for the mavacamten and placebo groups (25.0% vs 26.8%, respectively) (Table 29). None of the IPDs were related to COVID-19.

Table 29. Important Protocol Deviations- ITT Population Double-blind Period

	Mavacamten (N = 56) n (%)	Placebo (N = 56) n (%)	Overall (N = 112) n (%)
Total Number of Important Protocol Deviations	20	34	54
Not Related to COVID-19	20	34	54
Related to COVID-19	0	0	0
Total Number of Subjects with Important Protocol Deviations	14 (25.0)	15 (26.8)	29 (25.9)
Not Related to COVID-19	14 (25.0)	15 (26.8)	29 (25.9)
ICH/GCP Deviation	2 (3.6)	2 (3.6)	4 (3.6)
Data Privacy	2 (3.6)	2 (3.6)	4 (3.6)
Not coded	0	1 (1.8)	1 (0.9)
Not coded	0	1 (1.8)	1 (0.9)
Protocol Deviation	13 (23.2)	14 (25.0)	27 (24.1)
Trial Procedures	9 (16.1)	10 (17.9)	19 (17.0)
Study Intervention	5 (8.9)	4 (7.1)	9 (8.0)
Inclusion/Exclusion	1 (1.8)	6 (10.7)	7 (6.3)
Prohibited Concomitant Medication	1 (1.8)	3 (5.4)	4 (3.6)
Related to COVID-19	0	0	0

Recruitment

This study was conducted at 19 study centers in USA.

The first patient was screened on June 2020 and the first patient was randomized on 29 July 2020.

Conduct of study

The original protocol for study MYK-461-017 was dated 16 December 2019. As of 15 April 2022, there were 3 protocol amendments and 4 administrative letters. Key study level changes to Study MYK-461-017 after the original protocol are provided in the table below.

Table 30. Summary of Key Changes to Protocol MYK-461-017

Document (Amendment)/ Date	Summary of Key Changes	Planned Sample Size	Subjects Randomized under Protocol Version
Original Protocol	Original protocol	100	19
Protocol Amendment 1.0 29-Jun-2020	Clarified blinding requirements for ECHO results and dose blinding requirements and HCM medication management after Week 32. Added additional safety monitoring measure for subjects with LVEF ≤30% and blinding requirements for TTE results. Changed optional HCM and PG collections at screening to week 4 or any visits thereafter. Allowed the CRO medical monitor to approve reintroduction into study post-overdose, approve dose up-titrations during the LTE period, notify study monitor of changes to protocol due to protocol deviations, and added as a contact for questions on medications.	100	25

	Clarified NYHA functional assessment required for SRT evaluation. Outcome of a pregnancy was clarified as AESI and safety endpoint. Added an appendix with guidance on remote health assessments, drug dispensation, temporary discontinuation of mavacamten in pandemic/natural disaster. Distinguished between required site visits vs home health or community-based physician visits. Added KCCQ-23 and EQ-5D-5L assessments at weeks 4 and 20. Clarified KCCQ-23 scoring to be used for secondary and exploratory endpoints. Added exception to exclusion criterion based on history of invasive septal reduction. Added that medical monitor is to be consulted before dose down titration. Revised ECG exclusion parameters to exclude only those with an ECG abnormality considered by the investigator to pose a risk to participant safety to mitigate risk. Added exclusion criteria for subjects with COVID-19 infection by PCR within 30-days of screening. Added biotin supplements as prohibited medication ≤ 14-days of screening and multivitamins containing biotin within 24 hours of clinical visit. Added option to use direct to subject drug shipment for the duration of study rather than up through week 32 visits. Added body weight measurements at Weeks 4, 8,12, 20, 24, 28, and 44.		
Protocol Amendment 2.0 09-Nov-2020	Clarified the restart time point and re-entry assessments for subjects who discontinued due to a Pandemic or a natural disaster and clarified inclusion requirement for NYHA Class II patients with exertion induced syncope or near syncope. Added requirement for a negative Covid-19 test at Screening by PCR if COVID-19 positive within 6 months of screening. Updated eligibility criteria to exclude patients with aortic stenosis. Added SRT evaluation and post-exercise TTE at week 56. Deleted secondary endpoint to evaluate the persistence of the effects of mavacamten in reducing the number of SRT procedures at Week 32. Added the exploratory objective to evaluate the effect of mavacamten on the need for SRT in the long-term follow-up period. Deleted the exploratory objective to evaluate the ability of mavacamten to reduce symptoms and hemodynamic gradient. Adjusted the duration for the exploratory endpoint to evaluate the ability of mavacamten to reduce	100	61

	hemodynamic parameter and cardiac biomarkers and to improve activity level and quality of life to 16-weeks; added LVOT gradient at rest and induced by Valsalva to endpoint. Deleted safety endpoint for incidence of SAEs in subjects taking mavacamten compared with subjects taking placebo and with those who undergo SRT. Updated safety endpoint for the incidence of SAEs before and after SRT among subjects who undergo SRT. Added ICD download at Weeks 24, 48, 72 and 96. Updated status/results of MyoKardia trials and updated risk/benefit profile. Updated unblinding requirements to allow Sponsor to unblind after 100 subjects complete week 16 and if DMC recommends early termination after interim analysis. IA will occur after 50 subjects have completed week 16 or early termination.		
Protocol Amendment 3.0 03-Aug-2021	Revised the criteria (SRT guideline eligibility at Week 16) for primary endpoint. Defined that the interim analysis will be performed for guideline-based SRT primary endpoint. Added an exploratory objective/endpoint to evaluate the investigator-determined eligibility for SRT. Added time point (Week 16) for the SRT eligibility recommendation by the investigator. Added composite (clinical and hemodynamic) outcome measure criteria for primary efficacy endpoint analyses. Updated contraception and pregnancy reporting period to 4 months post last dose. Removed required waiting period between permanent sterilization procedure in females and enrollment for eligibility. Other changes include removing the option for home health assessments, time from last dose until blood or plasma can be donated, and clarification that maximum LVOT can be at rest or with provocation.	100	7

Source: Protocol, protocol amendments and administrative letters in Appendix 1.1

COVID-19

The first subject was randomized on 29 July 2020, which occurred during the global COVID-19 pandemic. A COVID-19 Risk Assessment Plan was implemented to identify potential risks and mitigation strategies. AE's and protocol deviations pertaining to COVID-19 were assessed and reported per FDA issued guidance. There were two subjects who were unable to complete a study visit within window due to COVID-19 infection (Week 12 and Week 32). Additionally, one subject was hospitalized with COVID-19 and had a delay in week 16 study visit, but the visit was completed within the allowed window.

Virtual/remote Site Initiation Visits (SIV) and interim monitoring visits were performed in lieu of in-person visits as needed due to country and site restrictions, as indicated in the SMP.

Activity monitors (accelerometers) were originally distributed to sites by ActiGraph, but due to restrictions imposed by COVID-19, the CRO distributed in lieu of ActiGraph. Overall, there was minimal impact to the study conduct due to COVID-19 pandemic over the past two years.

Baseline data

Subject demographics and baseline characteristics were generally similar for the mavacamten and placebo groups (Table 31). The study included an US population, average age 60 years, and with a balanced gender ratio and average disease duration of 7 years. At baseline, the majority of subjects had NYHA Class III (92.0% overall) and most subjects were using beta-blocker monotherapy (45.5% overall). A total of 15.2% of subjects were using calcium channel blocker monotherapy. Overall, 33% of subjects were on combination therapy and 20% of subjects were on disopyramide monotherapy or in combination. The 6 subjects on no HCM medications did not tolerate standard of care (SoC) medications.

The proportion of subjects with each CYP2C19 metabolizer phenotype was similar across treatment groups. Overall, majority of the subjects were rapid metabolizers, normal metabolizers, or intermediate metabolizers. There were 2 poor metabolizers.

The type of septal reduction therapy recommended at baseline was well balanced between the mavacamten and placebo groups (alcohol septal ablation 14.3% each and myectomy 85.7% each).

Table 31. Demographics and Baseline Characteristics Summary – ITT Population

	Mavacamten (N = 56)	**Placebo (N = 56)**	**Overall (N = 112)**
Age (Years) [1]	n = 56	n = 56	n = 112
Mean (SD)	59.8 (14.18)	60.9 (10.55)	60.3 (12.45)
Min, Max	22, 84	36, 82	22, 84
Age, n (%)			
<= 49	12 (21.4)	7 (12.5)	19 (17.0)
50 - 64	20 (35.7)	28 (50.0)	48 (42.9)
>= 65	24 (42.9)	21 (37.5)	45 (40.2)
Sex, n (%)			
Male	29 (51.8)	28 (50.0)	57 (50.9)
Female	27 (48.2)	28 (50.0)	55 (49.1)

Region, n (%)			
US	56 (100.0)	56 (100.0)	112 (100.0)
Race, n (%)			
Asian	2 (3.6)	0	2 (1.8)
American Indian or Alaska Native	0	1 (1.8)	1 (0.9)
Black or African American	3 (5.4)	0	3 (2.7)
Native Hawaiian or Other Pacific Islander	0	0	0
White	48 (85.7)	52 (92.9)	100 (89.3)
Unknown	3 (5.4)	3 (5.4)	6 (5.4)
Ethnicity, n (%)			
Hispanic or Latino	0	1 (1.8)	1 (0.9)
Not Hispanic or Latino	56 (100.0)	54 (96.4)	110 (98.2)
Not Reported	0	1 (1.8)	1 (0.9)
Baseline Height (cm) [1]	n = 56	n = 56	n = 112
Mean (SD)	169.2 (9.59)	168.6 (11.73)	168.9 (10.67)
Baseline Weight (kg) [1]	n = 56	n = 56	n = 112
Mean (SD)	83.78 (14.936)	90.96 (20.752)	87.37 (18.355)
Baseline Body Mass Index (BMI) (kg/m^2) [1]	n = 56	n = 56	n = 112
Mean (SD)	29.25 (4.792)	31.89 (6.181)	30.57 (5.662)
Baseline Body Surface Area BSA (m^2) [1]	n = 56	n = 56	n = 112
Mean (SD)	1.942 (0.1943)	2.002 (0.2651)	1.972 (0.2333)
Baseline Heart Rate (beats/min) [1]	n = 56	n = 56	n = 112
Mean (SD)	64.1 (10.33)	63.0 (9.77)	63.6 (10.02)
Baseline Systolic Blood pressure (mmHg) [1]	n = 56	n = 56	n = 112
Mean (SD)	130.4 (16.52)	131.2 (16.63)	130.8 (16.50)
Baseline Diastolic Blood pressure (mmHg) [1]	n = 56	n = 56	n = 112
Mean (SD)	74.0 (10.52)	74.2 (8.85)	74.1 (9.68)
Duration of oHCM disease (Years) [1]	n = 56	n = 56	n = 112
Mean	7.51 (9.396)	6.65 (7.377)	7.08 (8.420)
Median	5.53	5.40	5.44
Presence of HCM Pathogenic Mutation [2], n (%)			

	Mavacamten (N = 56)	Placebo (N = 56)	Overall (N = 112)
Pathogenic	12 (21.4)	8 (14.3)	20 (17.9)
VUS	8 (14.3)	10 (17.9)	18 (16.1)
Negative	25 (44.6)	26 (46.4)	51 (45.5)
Missing [3]	11 (19.6)	12 (21.4)	23 (20.5)
History of Hyptertension, n (%)			
Yes	36 (64.3)	34 (60.7)	70 (62.5)
No	20 (35.7)	22 (39.3)	42 (37.5)
Background SOC HCM Therapy, n (%)			
Beta-Blocker Monotherapy	26 (46.4)	25 (44.6)	51 (45.5)
Calcium Channel Blocker Monotherapy	7 (12.5)	10 (17.9)	17 (15.2)
Disopyramide Monotherapy	0	1 (1.8)	1 (0.9)
Beta-Blocker + Calcium Channel Blocker	6 (10.7)	10 (17.9)	16 (14.3)
Beta-Blocker + Disopyramide	11 (19.6)	4 (7.1)	15 (13.4)
Calcium Channel Blocker + Disopyramide	1 (1.8)	2 (3.6)	3 (2.7)
Beta-Blocker + Calcium Channel Blocker + Disopyramide	2 (3.6)	1 (1.8)	3 (2.7)
No SOC HCM Medication	3 (5.4)	3 (5.4)	6 (5.4)
Baseline NT-proBNP (ng/L) [1]	n = 56	n = 56	n = 112
Median (Q1, Q3)	724 (291, 1913)	744 (275, 1196)	743 (288, 1440)
Baseline Cardiac Troponin I (ng/L) [1]	n = 56	n = 56	n = 112
Median (Q1, Q3)	17.3 (7.0, 31.6)	12.9 (6.1, 26.0)	14.7 (6.4, 27.3)
Baseline Cardiac Troponin T (ug/L) [1]	n = 56	n = 56	n = 112
Median (Q1, Q3)	0.014 (0.01, 0.02)	0.011(0.008, 0.02)	0.013 (0.009, 0.02)
NYHA Class (CRF), n (%)			
II	4 (7.1)	4 (7.1)	8 (7.1)
III	51 (91.1)	52 (92.9)	103 (92.0)
IV	1 (1.8)	0	1 (0.9)
Baseline KCCQ CSS Score [1]	n = 56	n = 56	n = 112
Mean (SD)	69.54 (16.330)	65.56 (19.917)	67.55 (18.240)
Baseline LV Max Wall thickness (cm) [1]	n = 56	n = 56	n = 112
Mean (SD)	2.02 (0.330)	1.95 (0.283)	1.99 (0.308)
CYP2C19 Metabolizer Phenotypes, n (%)			

Ultrarapid Metabolizer	1 (1.8)	0	1 (0.9)
Rapid Metabolizer	15 (26.8)	17 (30.4)	32 (28.6)
Normal Metabolizer	19 (33.9)	12 (21.4)	31 (27.7)
Intermediate Metabolizer	11 (19.6)	14 (25.0)	25 (22.3)
Not Poor Metabolizer	0	1 (1.8)	1 (0.9)
Poor Metabolizer	2 (3.6)	0	2 (1.8)
Unknown	0	1 (1.8)	1 (0.9)
Missing [3]	8 (14.3)	11 (19.6)	19 (17.0)

Note: BMI = (body weight in kilograms)/(height in meters). BSA = 0.007184 * Height(cm).725 * Weight(kg).425.
CV=coefficient of variation, VUS = variants of uncertain significance

Baseline is defined as last non-missing measurement prior to the first dose. For subject randomized but not treated, the date of randomization was used to define the baseline value.
[1] n is the number of subjects with non-missing data.
[2] Pathogenic represents subjects with pathogenic result for at least one variant; VUS represents subjects with uncertain significance results and without pathogenic results; Negative represents subjects with benign or negative results; Missing include subjects who were not tested; Categories are mutually exclusive.
[3] HCM genome and CYP phenotype testing was optional and a separate informed consent form was signed if subject consented to these tests.

Echocardiography parameters

Baseline values for all echocardiography parameters evaluated were similar for the mavacamten and placebo groups (Table 32).

Table 32. MYK-461-017 Baseline Echocardiography parameters- ITT population

	Mavacamten N = 56	**Placebo N = 56**	**Total N = 112**
LVEF (%), mean (SD)[a]	67.91 (3.748)	68.34 (3.181)	68.13 (3.467)
LVOT Gradient (mm Hg), mean (SD)[a]			
Resting	51.19 (31.366)	46.28 (30.481)	48.74 (30.886)
Valsalva	75.25 (30.804)	76.23 (29.851)	75.74 (30.198)
Post-exercise	82.51 (34.735)	85.21 (37.026)	83.86 (35.763)
Left Atrial Volume Index (mL/m^2), mean (SD) [n]	41.346 (16.448) [55]	40.914 (15.193) [56]	41.128 (15.756) [111]

HCM genotype

Overall, 79.5% of subjects had HCM genotype assayed in this study, including 80.4% (45 of 56 subjects) in the mavacamten group and 78.6% (44 of 56 subjects) in the placebo group. The proportion of subjects with >=1 pathogenic or likely pathogenic mutation was 26.7% in the mavacamten and 18.2% in the placebo group. For both treatment groups, the most common mutations identified were in the MYBPC3 (17.8% of mavacamten subjects and 9.1% of placebo subjects) and MYH7 (2.2% of mavacamten subjects and 4.5% of placebo subjects) genes.

A total of 17.8% of mavacamten subjects and 25.0% of placebo subjects had at least 1 variant of uncertain significance (VUS). The most common VUSs identified were contained within the MYH7 genes and was similar across treatment groups.

HCM-related medical history

HCM-related medical history was generally similar for the mavacamten and placebo groups. Atrial fibrillation is a known complication of HCM. Of note, higher proportion of subjects in the mavacamten group compared with the placebo group had a history of atrial fibrillation (19.6% vs 14.5%, respectively)(Table 33). Accordingly, more subjects in the mavacamten group compared with the placebo group had cardioversion procedure for AF. Ventricular arrythmias are a known complication of HCM. The proportion of subjects with a history of non-sustained ventricular tachycardia (NSVT) and implanted cardioverter defibrillator and/or pacemaker was similar for the mavacamten and the placebo groups (9 [16.1%] mavacamten, 10 [18.2%] placebo). History of prior septal myectomy (SRT) was not allowed in VALOR. One subject in the mavacamten group and 2 subjects in the placebo group had prior failed ASA procedures, which was allowed on approval by the MyoKardia or MedPace medical monitor.

Table 33. Prior Hypertrophic Cardiomyopathy History - Safety Analysis Population

	Mavacamten (N = 56) n (%)	Placebo (N = 55) n (%)	Overall (N = 111) n (%)
Subjects with family history of HCM	17 (30.4)	15 (27.3)	32 (28.8)
Subjects with family history of sudden cardiac death at less than age 50	4 (7.1)	8 (14.5)	12 (10.8)
Subjects with the following symptoms in the past 12 months	56 (100.0)	55 (100.0)	111 (100.0)
Shortness Of Breath At Rest	13 (23.2)	19 (34.5)	32 (28.8)
Ongoing	13 (23.2)	17 (30.9)	30 (27.0)
Shortness Of Breath After Exertion	55 (98.2)	55 (100.0)	110 (99.1)
Ongoing	54 (96.4)	52 (94.5)	106 (95.5)
Chest Pain	29 (51.8)	26 (47.3)	55 (49.5)
Ongoing	25 (44.6)	21 (38.2)	46 (41.4)
Fatigue	44 (78.6)	44 (80.0)	88 (79.3)
Ongoing	43 (76.8)	42 (76.4)	85 (76.6)
Palpitations	36 (64.3)	33 (60.0)	69 (62.2)
Ongoing	28 (50.0)	25 (45.5)	53 (47.7)
Near Syncope Without Exertion	14 (25.0)	9 (16.4)	23 (20.7)
Ongoing	12 (21.4)	6 (10.9)	18 (16.2)
Dizziness Without Exertion	15 (26.8)	9 (16.4)	24 (21.6)
Ongoing	13 (23.2)	8 (14.5)	21 (18.9)
Near Syncope With Exertion	21 (37.5)	25 (45.5)	46 (41.4)
Ongoing	15 (26.8)	18 (32.7)	33 (29.7)
Syncope Without Exertion	4 (7.1)	1 (1.8)	5 (4.5)
Syncope With Exertion	3 (5.4)	1 (1.8)	4 (3.6)
Ongoing	1 (1.8)	0	1 (0.9)
Subjects with any history of the following cardiac events	22 (39.3)	21 (38.2)	43 (38.7)
Non-Sustained Ventricular Tachycardia (NSVT)	15 (26.8)	14 (25.5)	29 (26.1)
Sustained Ventricular Tachycardia (VT)	0	0	0
Atrial Fibrillation (Afib)	11 (19.6)	8 (14.5)	19 (17.1)
Paroxysmal Atrial Fibrillation (Afib)	11 (19.6)	7 (12.7)	18 (16.2)
Persistent Atrial Fibrillation (Afib)	1 (1.8)	1 (1.8)	2 (1.8)
Long Standing Persistent Atrial Fibrillation (Afib)	0	1 (1.8)	1 (0.9)
Permanent Atrial Fibrillation (Afib)	0	2 (3.6)	2 (1.8)
Moderate to Severe Aortic Stenosis	0	0	0
Myocardial Infarction	2 (3.6)	1 (1.8)	3 (2.7)
Electrophysiological (Ep) Study/Radiofrequency (Rf) Ablation	0	1 (1.8)	1 (0.9)
Subjects with any history of the following surgeries or procedures	15 (26.8)	14 (25.5)	29 (26.1)
Implanted Cardioverter Defibrillator (ICD) And/Or Pacemaker	9 (16.1)	10 (18.2)	19 (17.1)
CRT Implanted	0	1 (1.8)	1 (0.9)
Cardioversion Procedure For Atrial Fibrillation	7 (12.5)	4 (7.3)	11 (9.9)
Maze Procedure	0	0	0
Electrophysiological (EP) Study/Radiofrequency (RF) Ablation	0	0	0
Septal Myectomy (SRT)	0	0	0
Atrial Lead	3 (5.4)	3 (5.5)	6 (5.4)
Alcohol Septal Ablation (ASA)	1 (1.8)	2 (3.6)	3 (2.7)

Source: Table 14.1.3.2

Note: The prior HCM history summary is based on the events entered on the HCM history form

HCM-Related Concomitant Medication

During the double-blind period, 92.9% of subjects in the mavacamten and 94.5% of subjects in the placebo group were taking at least 1 concomitant medication related to HCM. Across treatment groups, the 3 most common ATC classes of concomitant medications were as follows:

- Beta blocking agents (78.6% in the mavacamten group and 69.1% in the placebo group)
- Calcium channel blockers (25.0% in the mavacamten group and 38.2% in the placebo group)
- Cardiac therapy use (23.2% in the mavacamten group and 14.5% in the placebo group)

Numbers analysed

Populations analyzed as part of these interim results are summarized in the table below.

Table 34. Analysis Populations Presented in this Primary CSR

Population	Mavacamten	Placebo	Total
Randomized: All subjects who are randomized to any treatment group.	56	56	112
Intention-to-treat: All randomized subjects, regardless of whether they receive study drug.	56	56	112
Safety: All randomized subjects who received at least 1 dose of study drug.	56	55	111
PK: All randomized subjects who received at least 1 dose of mavacamten and have at least 1 detectable mavacamten plasma drug concentration.	56	46	102
LTE: All subjects who received at least one dose of mavacamten. This population will be used for all long-term follow up analysis. Exposure is counted from the start of the mavacamten treatment regardless of the DB period or LTFU.	56	52	108

Outcomes and estimation

Primary endpoint

Proportion of subjects that decided to proceed with SRT or remained guideline eligible at the end of the double-blind period [Week 16]) for mavacamten vs. placebo was (10 of 56) 17.9% vs. (43 of 56) 76.8% (difference (95% CI), 58.93 (43.989,73.868), p <0.0001), respectively (Table 35).

Table 35. Proportion of Subjects Meeting the Primary Endpoint at Week 16 – ITT Population

Parameters	Mavacamten N = 56	Placebo N = 56
Number of subjects meeting the primary endpoint[a], n (%)	10 (17.9)	43 (76.8)
Number of subjects decided to proceed with SRT prior to or at Week 16, n (%)	2 (3.6)	2 (3.6)
Number of subjects SRT Eligible based on the Guideline Criteria[b] at week 16 and did not decide to proceed with SRT, n (%)	8 (14.3)	39 (69.6)
Number of subjects whose SRT status not evaluable and did not decide to proceed with SRT, n (%)	0	2 (3.6)
	Diff (Placebo vs. Mavacamten) (95% CI) Stratified analysis[c]	
Proportion Difference (95% CI)	58.93 (43.989,73.868)	
p-value	<0.0001	

a Meeting the primary endpoint is defined as either decided to proceed with SRT or was eligible for SRT per protocol specified guideline at week 16. Subjects with missing primary endpoint assessments were classified as meeting the primary endpoint (did not improve).

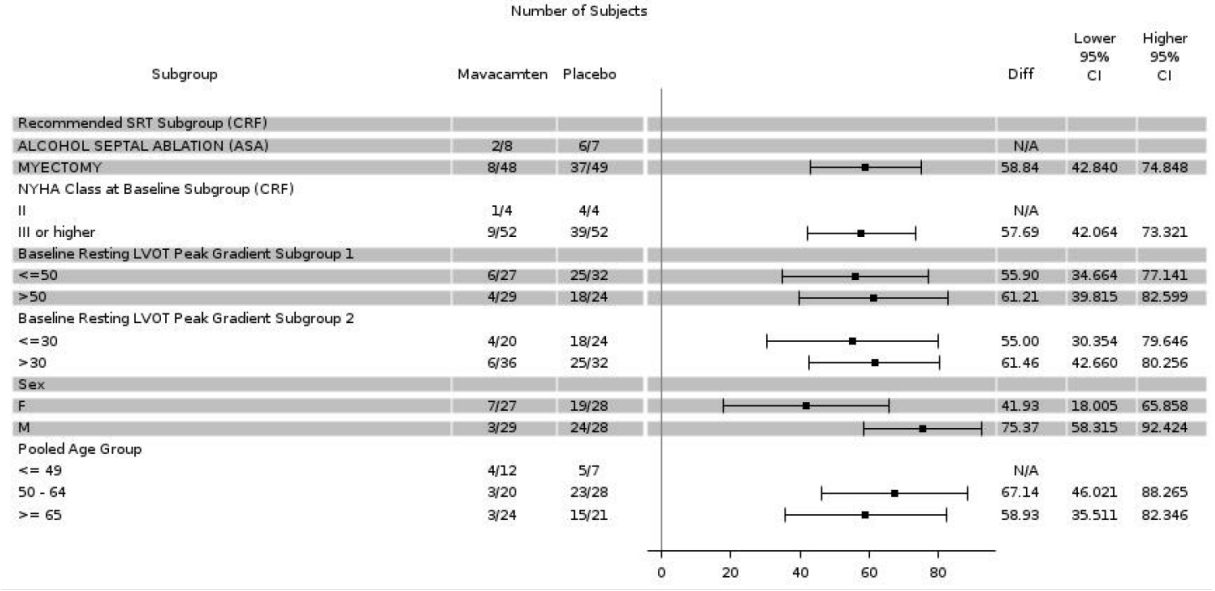
b The guideline criteria are based on 2011 ACCF/AHA HCM clinical and hemodynamic criteria.

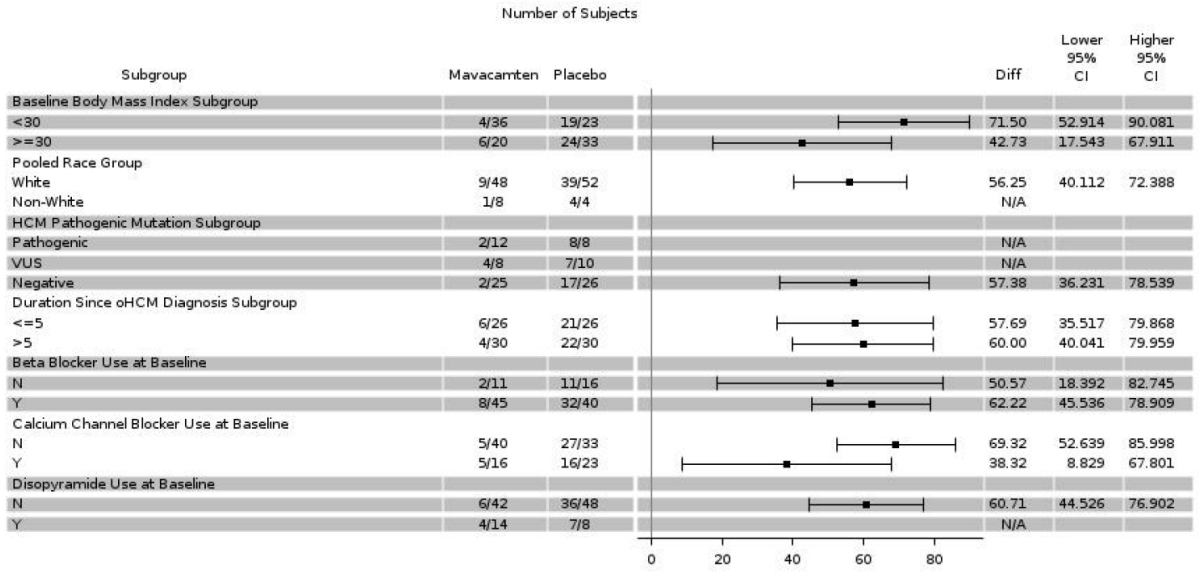
c Cochran-Mantel-Haenszel (CMH) method stratified by Type of SRT recommended (myectomy vs. alcohol septal). NYHA class is removed from the stratification due to only one subject in the Class II and ASA stratum, which follows the SAP pre-specified rule in section 8. Proportion difference (placebo-mava) is estimated using the MH method

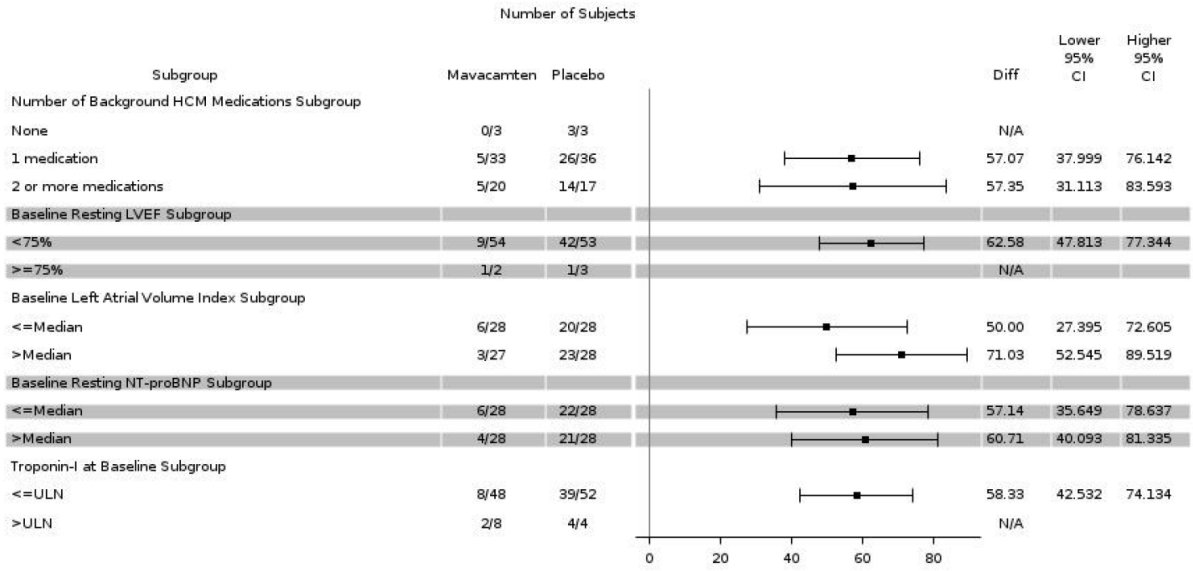
Subgroup analysis of the primary endpoint

Subgroup analyses showed larger treatment effects for males compared to females (treatment difference: 75% vs. 42%), baseline BMI ≤ 30 kg/m^2 compared with > 30 kg/m^2 (treatment difference: 71% vs. 43%), LAVI > median vs. LAVI <= median (treatment difference: 71% vs. 50%), subjects without baseline calcium channel blocker usage vs subjects with calcium channel blocker usage (69% vs. 38%) (Table 36). The treatment effect was similar in subjects without beta blocker usage (treatment difference 51%) and among subjects with beta blocker usage (treatment difference 62%).

Table 36. Differences in primary endpoint response between treatment groups at Week 16 across Subgroups- ITT Population







Secondary endpoint

Hierarchical testing of secondary endpoint results showed significant differences between groups (mavacamten - placebo) ($p<0.001$) favouring mavacamten, mean differences in post-exercise peak LVOT gradient, -37.2 mmHg (-48.08, -26.24); ≥1 NYHA class improvement 41.07% (24.481, 57.662); improvement in KCCQ- 23 CSS 9.45 (4.868, 14.041) points; and NT-proBNP and cardiac troponin I between groups geometric mean ratio, 0.33 (0.266, 0.421) and 0.53 (0.406, 0.700)(Table 37).

Table 37. Secondary Efficacy Endpoints - ITT Population

Secondary Endpoints	Mavacamten N = 55	Placebo N = 53	Mavacamten vs Placebo Difference (95% CI) p-value
Post-exercise LVOT peak gradient, mmHg, mean (SD) change from BL at W16	-39.1 (36.51)	-1.8 (28.82)	LS mean of treatment difference: -37.2 (-48.08, -26.24) <0.0001
NYHA improved ≥ 1 Class, n/N (%)	35 (62.5)	12 (21.4)	Stratified analysis proportion difference: 41.07 (24.481, 57.662) <0.0001
KCCQ-23 CSS, mean (SD) change from BL at W16	10.4 (16.06)	1.8 (12.01)	LS mean of treatment difference: 9.45 (4.868, 14.041) <0.0001
NT-proBNP (ng/L), geometric mean ratio to BL at W16 (95% CI)	0.35 (83.677)	1.13 (57.809)	Model Based Proportion of Geometric Mean Ratio: 0.33 (0.266, 0.421) <0.0001
hs-Cardiac Troponin-I (ng/L), geometric mean ratio to BL at W16 (95% CI)	0.50 (100.992)	1.03 (85.716)	Model Based Proportion of Geometric Mean Ratio: 0.53 (0.406, 0.700) <0.0001

Exploratory endpoints

The table below summarizes the change from baseline to Week 16 for the exploratory endpoints (Table 38).

Table 38. Summary of Exploratory Endpoints (Continuous Variables) at Week 16- ITT population – Double-Blind Period

	Baseline				Week 16				Change from Baseline to Week 16				
	Mavacamten		Placebo		Mavacamten		Placebo		Mavacamten		Placebo		Mavacamten vs. Placebo
Parameter	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	LS Mean of Difference (95% CI)[1] p-value
LVOT Gradient, Resting (mmHg)	56	51.2 (31.37)	56	46.3 (30.48)	55	14.2 (9.32)	53	45.9 (29.28)	55	-36.0 (28.81)	53	-1.5 (26.52)	-33.4 (-42.27, -24.48) <0.0001
LVOT Gradient, Valsalva (mmHg)	56	75.3 (30.80)	56	76.2 (29.85)	55	28.4 (21.18)	53	78.0 (31.03)	55	-45.2 (28.51)	53	0.4 (29.74)	-47.6 (-58.16, -37.03) <0.0001
LVEF, CRF (%)	56	67.9 (3.75)	56	68.3 (3.18)	55	64.7 (6.90)	52	68.7 (3.09)	55	-3.4 (6.23)	52	0.3 (4.19)	-4.0 (-5.50, -2.45) <0.0001
Lateral E/E' Ratio	56	15.5 (7.44)	54	13.5 (5.73)	54	12.2 (5.50)	52	14.0 (5.60)	54	-3.5 (5.60)	50	0.7 (3.75)	-3.3 (-4.92, -1.76) <0.0001
Septal E/E' Ratio	56	19.6 (9.11)	52	18.1 (7.61)	54	16.2 (6.86)	49	18.0 (7.93)	54	-3.3 (6.02)	46	0.7 (4.57)	-3.6 (-5.56, -1.65) 0.0004
E/E' Average	56	17.5 (7.99)	52	15.9 (6.44)	54	14.2 (5.95)	49	15.8 (6.18)	54	-3.4 (5.33)	46	0.7 (3.70)	-3.5 (-5.06, -1.85) <0.0001
LV Stroke Volume Index (mL/m2)	52	32.9 (7.71)	47	33.8 (7.38)	47	31.1 (6.65)	42	33.6 (6.89)	45	-1.4 (6.58)	38	0.1 (5.65)	-1.9 (-4.29, 0.52) 0.1226
LA Volume Index (mL/m2)	55	41.3 (16.45)	56	40.9 (15.19)	54	36.1 (14.59)	52	40.2 (15.23)	54	-5.2 (7.78)	52	-0.5 (8.07)	-4.4 (-7.12, -1.66) 0.0019
LV End Systolic Volume Index (mL/m2)	52	15.9 (5.14)	47	15.8 (4.41)	47	17.2 (6.27)	42	15.5 (3.48)	45	1.4 (3.65)	38	0.1 (3.34)	1.1 (-0.34, 2.63) 0.1282
LV End-Diastolic Volume Index (mL/m2)	52	49.1 (13.21)	47	49.7 (11.48)	47	48.3 (10.37)	42	49.2 (10.01)	45	0.0 (8.30)	38	0.2 (8.34)	-0.7 (-4.00, 2.59) 0.6693
LV Mass Index (g/m2)	55	119.2 (29.49)	55	122.3 (30.66)	52	111.0 (25.25)	47	119.1 (33.46)	51	-7.9 (17.71)	47	-1.9 (16.58)	-6.5 (-13.18, 0.11) 0.0537
Cardiac Troponin T (ug/L)	56	0.018 (0.0156)	56	0.015 (0.0132)	55	0.011 (0.0094)	53	0.014 (0.0091)	55	-0.007 (0.0079)	53	-0.001 (0.0116)	-0.004 (-.0069, -.0013) 0.0040
EQ-5D-5L Index Score	56	0.77 (0.179)	56	0.74 (0.206)	55	0.81 (0.188)	53	0.76 (0.185)	55	0.04 (0.190)	53	0.02 (0.143)	0.03 (-0.022, 0.087) 0.2380
EQ VAS Score	56	69.2 (17.38)	56	66.6 (19.21)	55	73.9 (17.66)	53	68.8 (16.37)	55	4.0 (16.00)	53	2.8 (15.53)	2.6 (-2.45, 7.71) 0.3083
KCCQ Overall Summary Score	56	64.1 (17.43)	56	59.5 (19.51)	55	76.2 (19.67)	53	61.9 (20.01)	55	11.6 (16.57)	53	2.5 (13.19)	10.2 (5.18, 15.19) <0.0001
KCCQ Total Symptom Score	56	70.2 (17.04)	56	64.7 (21.47)	55	81.1 (18.48)	53	66.9 (19.94)	55	10.3 (15.64)	53	2.2 (13.65)	9.6 (4.72, 14.56) 0.0002
KCCQ Symptom Frequency Score	56	69.8 (18.61)	56	63.8 (25.71)	55	81.3 (19.22)	53	64.4 (24.83)	55	10.8 (17.93)	53	0.8 (16.70)	11.7 (5.88, 17.48) 0.0001
KCCQ Symptom Burden Score	56	70.5 (17.19)	56	65.6 (19.27)	55	80.9 (18.75)	53	69.3 (16.97)	55	9.8 (15.64)	53	3.6 (13.13)	7.9 (3.05, 12.69) 0.0015
KCCQ Social Limitation Score	55	67.5 (22.75)	56	61.4 (24.40)	55	79.2 (22.11)	53	60.3 (27.28)	54	11.1 (19.56)	53	-0.6 (23.06)	13.7 (6.62, 20.78) 0.0002

KCCQ Physical Limitation Score	56	68.9 (19.03)	56	66.4 (20.89)	55	79.8 (18.41)	53	67.6 (20.61)	55	10.4 (19.34)	53	1.5 (16.84)	10.1 (4.47, 15.81) 0.0005
KCCQ Quality of Life Score	56	49.4 (22.52)	56	45.7 (22.92)	55	64.7 (25.10)	53	52.7 (21.17)	55	14.8 (21.32)	53	6.9 (16.24)	9.1 (2.52, 15.63) 0.0070
Average Daily Accelerometry Unit	54	1799519.9 (460090.50)	52	1736038.4 (626874.33)	49	1870472.6 (545236.37)	46	1844734.5 (682382.68)	48	65843.6 (303346.76)	46	109370.4 (316016.69)	-43503.9 (-173322, 86314.14) 0.5072
Average Daily Step Counts	54	3232.5 (2228.72)	52	3227.2 (2243.39)	49	3697.4 (2293.72)	46	3214.2 (2478.40)	48	355.9 (1355.02)	46	-37.9 (1446.74)	428.2 (-142.0, 998.36) 0.1392
Average Daily Active Minutes	54	628.0 (105.56)	52	583.2 (118.34)	49	631.8 (120.15)	46	606.0 (118.40)	48	4.5 (75.74)	46	25.7 (65.56)	-16.4 (-46.10, 13.25) 0.2744
Average Daily Minutes in Moderate of Higher Activity Level	54	107.8 (55.95)	52	114.7 (78.99)	49	120.9 (61.52)	46	126.2 (90.34)	48	8.8 (34.56)	46	9.9 (43.99)	-1.2 (-17.73, 15.34) 0.8862

Long-term follow-up

As of the 07-Feb-2022 data cut, 71 subjects were randomized at least 32 weeks prior to the data cut-off, permitting them the opportunity to have evaluable Week 32 data for this report. There were 38 subjects in the previous mavacamten group (corresponding to 32 weeks of mavacamten treatment) and 33 subjects with evaluable data in the previous placebo group, (corresponding to 16 weeks of mavacamten exposure). Overall, 89 subjects had been exposed to at least 16 weeks of mavacamten treatment.

In the previous placebo group, 2 (6.1%) subjects proceeded to SRT and 3 (9.1%) subjects remain SRT eligible. While these subjects received mavacamten treatment in the active-controlled period of the study, these results are similar to those in the mavacamten arm of the double-blind period. In the previous mavacamten group, 2 (5.3%) subjects have proceeded to SRT and 2 (5.3%) are SRT guideline eligible.

Of the original mavacamten treated subjects who were SRT eligible at Week 16, 7/8 (87.5%) subjects were randomized at least 32 Weeks prior to the data cut-off (Table 39). These 7 subjects have available Week 32 SRT guideline eligible data for this report. At Week 32, 6/7 (85.7%) subjects were not SRT eligible and 1 subject was SRT eligible. Of the original mavacamten treated subjects who were not SRT eligible at Week 16, 30/46 subjects were randomized at least 32 Weeks prior to the data cut-off. These 30 subjects have available Week 32 SRT guideline eligible data for this report. At Week 32, 27/30 (90%) subjects were not SRT eligible, 1 subject was SRT eligible, 1 subject was not evaluable, and 1 subject proceeded with SRT.

Table 39. Summary of Week 32 SRT Status by Week 16 SRT Status in Previous Mavacamten Subjects who reached Week 32

		Week 32 Status n(%)			
Week 16 Status	**N**	**Proceed with SRT**	**SRT Eligible**	**SRT Not Eligible**	**Not Evaluable**
Proceed With SRT	1	1 (100.0)	0	0	0
SRT Eligible	7	0	1 (14.3)	6 (85.7)	0
Not SRT Eligible	30	1 (3.3)	1 (3.3)	27 (90.0)	1 (3.3)
Not Evaluable	0	0	0	0	0
Total	38	2 (5.3)	2 (5.3)	33 (86.8)	1 (2.6)

Table 40 summarizes the key (Week 32 endpoints corresponding to secondary endpoints at week 16) exploratory efficacy endpoints in the ITT Population at Week 32 for previous placebo subjects.

Table 40. Summary of Key Exploratory Endpoints at Week 32 for Previous Placebo Subjects (16 weeks of Mavacamten Treatment) – ITT Population

Exploratory Endpoints	**n**	
		Mean (SD), Change from BL
Post Exercise LVOT (mmHg)	30	-39.225 (45.2328)
		n (%)[a]
Number of subjects with at least 1 NYHA class improvement	33	23 (69.7)
		Mean (SD), Change from BL
KCCQ-23 CSS	33	8.242 (18.4872)
NT-proBNP (ng/L)	33	-669.1 (995.26)
Cardiac Troponin I (ng/L)	33	-13.024 (17.1879)

[a] Percentages are based on number of subjects with NYHA assessment at each exposure time point

Source: Table 14.2.1.8.2 (post-exercise LVOT), Table 14.2.13 (NYHA Class), Table 14.4.4.1 (Cardiac biomarkers), Table 14.2.1.9.2 (KCCQ-23)

Note: For long-term follow up analysis, baseline represents the last assessment prior to the first dose of mavacamten for both groups. The time points represent exposure time to mavacamten. Due to unevenly spaced visit schedule, the time points may not be exact and may include data from the nearest visit.

Table 41 summarizes the key exploratory efficacy endpoints in the ITT Population at Week 32 for previous mavacamten subjects.

Table 41. Summary of Key Exploratory Endpoints at Week 32 for Previous Mavacamten Subjects (32 weeks of Mavacamten Treatment) – ITT Population

Exploratory Endpoints	**n**	
		Mean (SD), Change from BL
Post Exercise LVOT (mmHg)	36	-34.322 (41.3854)
		n (%)[a]
Number of subjects with at least 1 NYHA class improvement	36	32 (88.9)
		Mean (SD), Change from BL
KCCQ-23 CSS	43	11.288 (14.4539)
NT-proBNP (ng/L)	36	-951.7 (1645.68)
Cardiac Troponin I (ng/L)	36	-18.429 (37.4570)

[a] Percentages are based on number of subjects with NYHA assessment at each exposure time point

Source: Table 14.2.1.8.2 (post-exercise LVOT), Table 14.2.13 (NYHA Class), Table 14.4.4.1 (Cardiac biomarkers), Table 14.2.1.9.2 (KCCQ-23)

Note: For long-term follow up analysis, baseline represents the last assessment prior to the first dose of mavacamten for both groups. The time points represent exposure time to mavacamten. Due to unevenly spaced visit schedule, the time points may not be exact and may include data from the nearest visit.

Ancillary analyses

N.A.

Summary of main efficacy results

Table 42 Summary of efficacy for trial EXPLORER-HCM (MYK-461-005)

Title: A Randomized, Double-blind, Placebo-controlled Clinical Study to Evaluate Mavacamten (MYK 461) in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy			
Study identifier	MYK-461-005 (EXPLORER-HCM)		
Design	This was a Phase 3, double-blind, randomized (1:1), placebo-controlled study of adult subjects with symptomatic oHCM who received mavacamten or placebo once daily for 30 weeks with an 8-week posttreatment follow-up period. Randomization was stratified by New York Heart Association (NYHA) functional classification II or III, current treatment with beta-blocker (yes or no), planned type of ergometer used during the study (treadmill or exercise bicycle), and consent for the CMR substudy (yes or no).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		30 weeks There was no run-in phase 8 weeks washout period followed by a 5-year long-term extension study (MYK-461-007; ongoing)
Hypothesis	Superiority of mavacamten over placebo in addition to guideline-directed HCM therapy		
Treatments groups	Mavacamten		2.5, 5, 10, or 15 mg once daily for 30 weeks, n= 123
	Placebo		Matching placebo once daily for 30 weeks, n= 128
Endpoints and definitions	Primary endpoint	Composite endpoint of $_{pVO2max}$ and NYHA class	A composite functional response at Week 30, defined as achieving: 1. an improvement of ⩾ 1.5 mL/kg/min in pVO_2max as determined by CPET and a reduction of ⩾1 NYHA class or 2. an improvement of ⩾3.0 mL/kg/min in pVO_2max with no worsening in NYHA class
	Secondary endpoint	Post-exercise LVOT peak gradient	Change from baseline to Week 30 in post-exercise LVOT peak gradient
		pVO_2max	Change from baseline to Week 30 in pVO_2max as determined by CPET
		NYHA Class	Proportion of subjects who had a least 1 class of improvement from baseline in NYHA class at Week 30
		KCCQ-23 CSS	Change from baseline to Week 30 in subject-reported health status as assessed by the Kansas City Cardiomyopathy Questionnaire (23 item version) (KCCQ-23 CSS)
		HCMSQ SoB domain score	Change from baseline to Week 30 in subject-reported severity of HCM symptoms as assessed by the Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ) shortness of breath (SoB) domain score
Database lock	FPFV: 30-May-2018; LPLV: 06-May-2020; Database lock (DBL): 30-Jun-2020		
Results and Analysis			

Title: A Randomized, Double-blind, Placebo-controlled Clinical Study to Evaluate Mavacamten (MYK 461) in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy			
Study identifier	MYK-461-005 (EXPLORER-HCM)		
Analysis description	Primary Analysis		
Analysis population and time point description	ITT Population included all randomized subjects, regardless of whether or not they received study drug, with analyses conducted according to randomized treatment assignment. Primary and secondary efficacy endpoints were analyzed at the end of the treatment period at Week 30		
Descriptive statistics and estimate variability	Treatment group	Mavacamten	Placebo
	Number of subject	n= 123	n=128
	Composite primary endpoint		
	Achieved composite functional endpoint at Week 30, 1) an improvement of at least 1.5 mL/kg/min in pVO_2max and improvement of 1 or more NYHA class or Type 2) an improvement of at least 3.0 mL/kg/min in pVO_2max with no worsening in NYHA class (n (%))	45 (36.6)	22 (17.2)
	Treatment difference (95% CI)	19.4 (8.67, 30.13)	
	p-value	0.0005	
	Proportion of subjects with ⩾1.5 mL/kg/min in pVO_2max and improvement ⩾1 NYHA class (n(%))	41 (33.3)	18 (14.1)
	Treatment difference (95% CI)	19.3 (8.99, 29.55)	
	Proportion of subjects with ⩾3 mL/kg/min in pVO_2max and no worsening in NYHA class (n(%))	29 (23.6)	14 (10.9)
	Treatment difference (95% CI)	12.6 (3.39, 21.89)	
Analysis description	Secondary endpoints		
	Post-exercise LVOT gradient (mmHg) (mean (SD))	-47 (40.3)	-10 (29.6)
	LS mean treatment difference (95% CI)	-35 (-43.2, -28.1)	
	p-value	<0.0001	
	pVO_2max ml/kg/min (mean (SD))	1.4 (3.12)	-0.05 (3.02)
	LS mean treatment difference (95% CI)	1.4 (0.5, 2.12)	
	p-value	0.0006	

Title: A Randomized, Double-blind, Placebo-controlled Clinical Study to Evaluate Mavacamten (MYK 461) in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy			
Study identifier	MYK-461-005 (EXPLORER-HCM)		
	Improved by ≥1 NYHA Class from Baseline to Week 30 (n (%))	80 (65.0)	40 (31.3)
	LS mean treatment difference (95% CI)	33.8 (22.15, 45.43)	
	p-value	<0.0001	
	KCCQ-23 CSS (mean(SD))	13.6 (14.42)	4.2 (13.68)
	LS mean treatment difference (95% CI)	9.1 (5.46, 12.66)	
	p-value	<0.0001	
	HCMSQ SoB Domain Score (mean (SD))	-2.8 (2.68)	-0.9 (2.41)
	LS mean treatment difference (95% CI)	-1.8 (-2.4, -1.2)	
	p-value	<0.0001	

Table 43. Summary of efficacy for trial VALOR-HCM (MYK-461-017)

Title: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Mavacamten in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy who are Eligible for Septal Reduction Therapy (VALOR-HCM; ongoing)			
Study identifier	MYK-461-017 (VALOR-HCM)		
Design	This is an ongoing Phase 3, double-blind, randomized (1:1), placebo-controlled, multicenter study of of mavacamten vs placebo in adults with symptomatic oHCM who met 2011 ACCF/AHA guideline criteria for SRT and have been referred for an SRT procedure within the past 12 months in the USA. Randomization was stratified by New York Heart Association (NYHA) functional classification and type of SRT recommended (myectomy or ASA).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		16 weeks There was no run-in phase 16 weeks active-controlled dosing period (Week 16 to Week 32) followed by a long-term extension period (Week 32 to Week 128)
Hypothesis	Superiority of mavacamten over placebo in addition to guideline-directed HCM therapy		
Treatments groups	Mavacamten		2.5, 5, 10, or 15 mg once daily for 16 weeks, n= 56
	Placebo		Matching placebo once daily for 16 weeks, n= 56
Endpoints and definitions	Primary endpoint	Composite endpoint of the need for SRT	A composite of: - Decision to proceed with SRT prior to or at Week 16 - SRT guideline eligible at Week 16 based on the 2011 ACCF/AHA HCM Guidelines
	Secondary endpoint	Post-exercise LVOT peak gradient	Change from baseline to Week 16 in post-exercise LVOT peak gradient

Title: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Mavacamten in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy who are Eligible for Septal Reduction Therapy (VALOR-HCM; ongoing)			
Study identifier	MYK-461-017 (VALOR-HCM)		
		NYHA Class	Proportion of subjects who had a least 1 class of improvement from baseline in NYHA class at Week 16
		KCCQ-23 CSS	Change from baseline to Week 16 in subject-reported health status as assessed by the Kansas City Cardiomyopathy Questionnaire (23 item version) (KCCQ-23 CSS)
		NT-proBNP	Change from baseline to Week 16 in NT-proBNP
		Cardiac troponin I	Change from baseline to Week 16 in cardiac troponin I
Database lock	First patient randomized: June-2020; Study is still ongoing Clinical cut-off date: 07-Feb-2022		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	ITT Population included all randomized subjects, regardless of whether they receive study drug, with analyses conducted according to randomized treatment assignment.		
Descriptive statistics and estimate variability	Treatment group	Mavacamten	Placebo
	Number of subject	n= 56	n=56
	Composite primary endpoint		
	Achieved composite of: - Decision to proceed with SRT prior to or at Week 16 - SRT guideline eligible at Week 16 based on the 2011 ACCF/AHA HCM Guidelines (n (%))	10 (17.9)	43 (76.8)
	Treatment difference (%(95% CI))	58.93 (43.989, 73.868)	
	p-value	<0.0001	
	Number of subjects decided to proceed with SRT prior to or at Week 16 (n (%))	2 (3.6)	2 (3.6)
	Treatment difference (%)	0	
	Number of subjects SRT eligible based on the Guideline criteria at week 16 and did not decide to proceed with SRT (n (%))	8 (14.3)	39 (69.6)
	Treatment difference (%)	55.3	
Analysis description	Secondary endpoints		
	Post-exercise LVOT gradient (mmHg), mean (SD) change from BL at W16	-39.1 (36.51)	-1.8 (28.82)

Title: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Mavacamten in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy who are Eligible for Septal Reduction Therapy (VALOR-HCM; ongoing)			
Study identifier	MYK-461-017 (VALOR-HCM)		
	LS mean treatment difference (95% CI)	-37.2 (-48.08, -26.24)	
	p-value	<0.0001	
	Improved by ⩾1 NYHA Class from BL to Week 16 (n (%))	35 (62.5)	12 (21.4)
	Stratified analysis proportion difference (95% CI)	41.07 (24.48, 57.66)	
	p-value	<0.0001	
	KCCQ-23 CSS, mean (SD) change from BL to Week 16	10.4 (16.06)	1.8 (12.01)
	LS mean treatment difference (95% CI)	9.45 (4.87, 14.04)	
	p-value	<0.0001	
	NT-proBNP, geometric mean ratio from BL to Week 16 (95% CI)	0.35 (83.68)	1.13 (57.81)
	Model Based Proportion of Geometric Mean Ratio (95% CI)	0.33 (0.266, 0.421)	
	p-value	<0.0001	
	hs-Cardiac Troponin-I (ng/L), geometric mean ratio from BL to Week 16 (95% CI)	0.50 (100.99)	1.03 (85.72)
	Model Based Proportion of Geometric Mean Ratio (95% CI)	0.53 (0.41, 0.70)	
	p-value	<0.0001	

2.5.5.3. Clinical studies in special populations

No separate studies were performed in special patient populations.

2.5.5.4. In vitro biomarker test for patient selection for efficacy

N/A

2.5.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

N/A

2.5.5.6. Supportive study(ies)

Interim analysis (cut-off date 31 August 2021) of the ongoing long-term extension (LTE) studies MYK-461-007 (MAVA-LTE) and MYK-461-008 (PIONEER-OLE) provide supportive efficacy (Table 4).

Study MYK-461-007 has cohorts with both nHCM and oHCM subjects, enrolled from the parent Phase 2 MYK-461-006 (MAVERICK-HCM) study and the Phase 3 MYK-461-005 (EXPLORER-HCM), respectively. Study MYK-461-006 was a Phase 2 study conducted in patients with nHCM that does not contribute to the efficacy analysis presented in this application; therefore, data from study MYK-461-007 is presented only for oHCM subjects enrolled from the parent Phase 3 MYK-461-005 (referred to as the EXPLORER-LTE cohort).

MYK-461-007: 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 (MYK-461-007; MAVA-LTE)

Methods

The MAVA-LTE study (Study MYK-461-007) is an ongoing Phase II/III, dose-blinded, 5-years long-term extension (LTE) study to evaluate the safety, tolerability of mavacamten in subjects with symptomatic oHCM who completed the pivotal Phase 3 MYK-461-005 (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): Considering the proposed indication, i.e. treatment of symptomatic oHCM subjects, only results of the EXPLORER-LTE Cohort are discussed in the efficacy section. After the washout period (minimal 8 weeks) of the parent study, subjects enrolled in this LTE started with 5 mg mavacamten once daily unless at the end of treatment (EOT) in the parent study the subject had a dose of 5 mg and mavacamten plasma concentration ≥700 ng/mL, in which case the starting dose in this LTE study was 2.5 mg mavacamten. At Week 4, the mavacamten dose could be down-titrated based on site-read echocardiograms of Valsalva LVOT gradient and LVEF, i.e. assessment for an early response. At Week 8 and 12, the dose could be up-titrated, down-titrated, or remained unchanged based on Valsalva LVOT gradient and LVEF. At week 24, the dose could also be up-titrated, down-titrated, or remained unchanged; however, this dose adjustment was based on post-exercise LVOT gradient and LVEF. Stress echocardiography with assessment by the site of the post-exercise gradient was conducted at Week 24 to determine if further dose adjustment could be considered by the investigator. At any visit after Week 24, if the site-read LVOT gradient with Valsalva manoeuvre was > 30 mmHg and LVEF ≥50%, then a dose increase may have been considered after discussion with the Medical Monitor. Temporary discontinuation criteria were defined per protocol as LVEF <50%, mavacamten concentration ≥1000 ng/mL, and/or increase in the Fridericia-corrected QT interval (QTcF) interval 15% above baseline or QTcF ≥520 ms.

Results

As of the interim data cut-off date of 31 August 2021, 231 subjects (97.9%) with symptomatic oHCM who completed the pivotal Phase 3 study EXPLORER-HCM had enrolled in the EXPLORER-LTE cohort of MAVE-LTE. Among the 231 subjects enrolled, 11 (4.8%) had discontinued the study as of the data cut-off date due to an adverse event (n=2), death (n=3), stopping criteria (n=3), withdrawal by subject (n=2) or other (n=1). The high retention rates on the study have contributed to 317 patient-years of exposure. Due to the COVID-19 pandemic, there were subjects who either had a dose interruption or missed clinic visits. As such, 28 subjects re-enrolled in the study and started treatment again. As of

the data cut-off date, the majority (88.7%) of subjects in the EXPLORER-LTE cohort had completed mavacamten treatment through at least Week 48 and 14.7% of subjects reached Week 96.

The majority of subjects had hypercontractile left ventricular function as evidenced by elevated LVEF (mean LVEF 74%) and demonstrated worsening obstruction with provocation (mean resting LVOT gradient 48 mmHg, increasing to 69 mmHg with Valsalva). The majority of subjects (65.8%) were NYHA Class II at baseline. The baseline median (Q1, Q3) NT-proBNP concentration was 783 (326, 1593) ng/L.

Dose titration and modification

Table 44 provides the mavacamten dose by study visit from Day 1 through to Week 120 (number of subjects per study dose over time) of all available data in the MAVA-LTE study per data-cut 31-Aug-2021. At Week 4, 109 subjects were dose reduced from 5 mg to 2.5 mg. In the SmPC posology, the applicant proposes to use a lower LVOT of <20 mmHg as criteria for dose reduction. This proposal is based on an analysis that indicated that many of these subjects would have avoided a down-titration at Week 4 if the LVOT criteria had been <20 mmHg (35% of 80 patients) (see also dose-response studies).

Table 44. MYK-461-007 (EXPLORER-LTE Cohort) - Mavacamten Dose by Study Visit (Safety Population)

	Study Visit, n (%)													
Daily Dose	**Day 1[a] N = 231**	**Week 4 N = 229**	**Week 8 N = 225**	**Week 12 N = 224**	**Week 16 N = 223**	**Week 24 N = 221**	**Week 36 N = 215**	**Week 48 N = 205**	**Week 60 N = 149**	**Week 72 N = 106**	**Week 84 N = 67**	**Week 96 N =34**	**Week 108 N = 13**	**Week 120 N =2**
2.5 mg	0	109 (47.6)	109 (48.4)	108 (48.2)	104 (46.6)	73 (33.0)	63 (29.3)	58 (28.3)	44 (29.5)	30 (28.3)	17 (25.4)	7 (20.6)	3 (23.1)	0
5 mg	231 (100.0)	115 (50.2)	23 (10.2)	14 (6.3)	19 (8.5)	48 (21.7)	51 (23.7)	53 (25.9)	45 (30.2)	33 (31.1)	22 (32.8)	12 (35.3)	4 (30.8)	1 (50.0)
10 mg	0	3 (1.3)	90 (40.0)	58 (25.9)	51 (22.9)	59 (26.7)	62 (28.8)	60 (29.3)	39 (26.2)	29 (27.4)	18 (26.9)	9 (26.5)	3 (23.1)	1 (50.0)
15 mg	0	0	1 (0.4)	42 (18.8)	41 (18.4)	38 (17.2)	35 (16.3)	33 (16.1)	17 (11.4)	13 (12.3)	9 (13.4)	5 (14.7)	2 (15.4)	0
Missing[b]	0	2 (0.9)	2 (0.9)	2 (0.9)	8 (3.6)	3 (1.4)	4 (1.9)	1 (0.5)	4 (2.7)	1 (0.9)	1 (1.5)	1 (2.9)	1 (7.7)	0

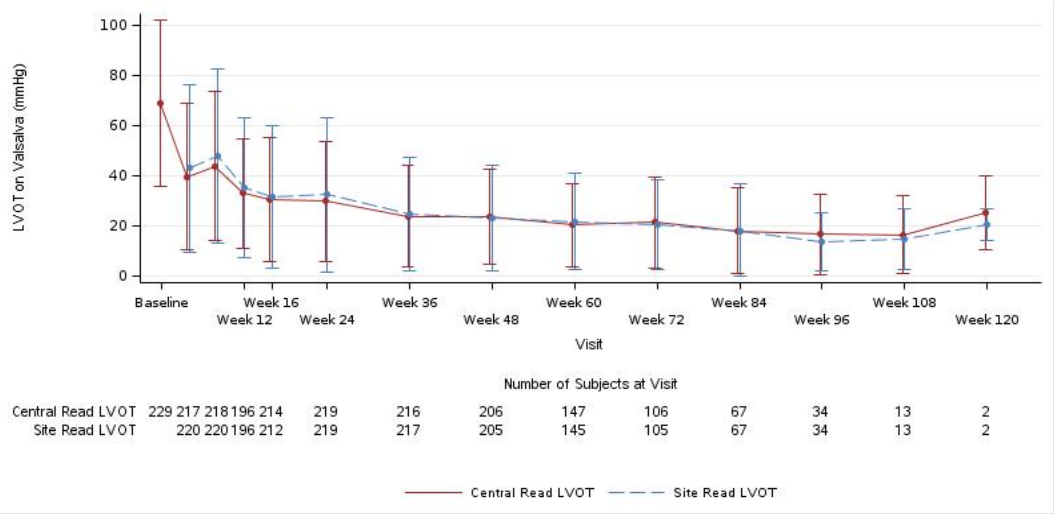
While on treatment, 26 (11.3%) subjects underwent a temporary discontinuation due to LVEF <50% (n=10), LVEF <50% and mavacamten plasma trough concentration ≥1000 ng/ml (n=2), only mavacamten plasma trough concentration ≥1000 ng/ml (n=6), both mavacamten plasma trough concentration ≥1000 ng/ml and QTcF (n=1), and only prolonged QTcF (n=7). Out of the 26 subjects, a total of 9 subjects permanently discontinued the study. Of these 9 subjects, 3 subjects were later re enrolled as allowed per protocol. Additionally, 5 patients underwent a dose decrease based on the decision by the principal investigator.

LVOT peak gradient

Improvements from baseline in LVOT obstruction assessed by echocardiography in this LTE was consistent with those observed in study EXPLORER-HCM. There were rapid and sustained improvements in Valsalva LVOT gradients as early as Week 4 sustained through Week 96 of mavacamten treatment and beyond (Figure 35). Early gradient improvement was seen between Day 1 (study treatment is commenced on Day 1) and Week 4, reduction in gradient are seen through dose titrations stages at Week 4,8,12 and then some further adjustment in the gradient is seen at Week 24 and beyond with dose titrations that are allowed per protocol. Overall, site-read echocardiographic

values were consistent and in agreement with central laboratory readings resulting in the same dosing decisions up to Week 96 of mavacamten treatment.

Figure 35. EXPLORER-LTE Cohort: Mean (SD) Plot of LVOT Gradient on Valsalva Over Time by Lab Type, EXPLORER-LTE Cohort (ITT Population)

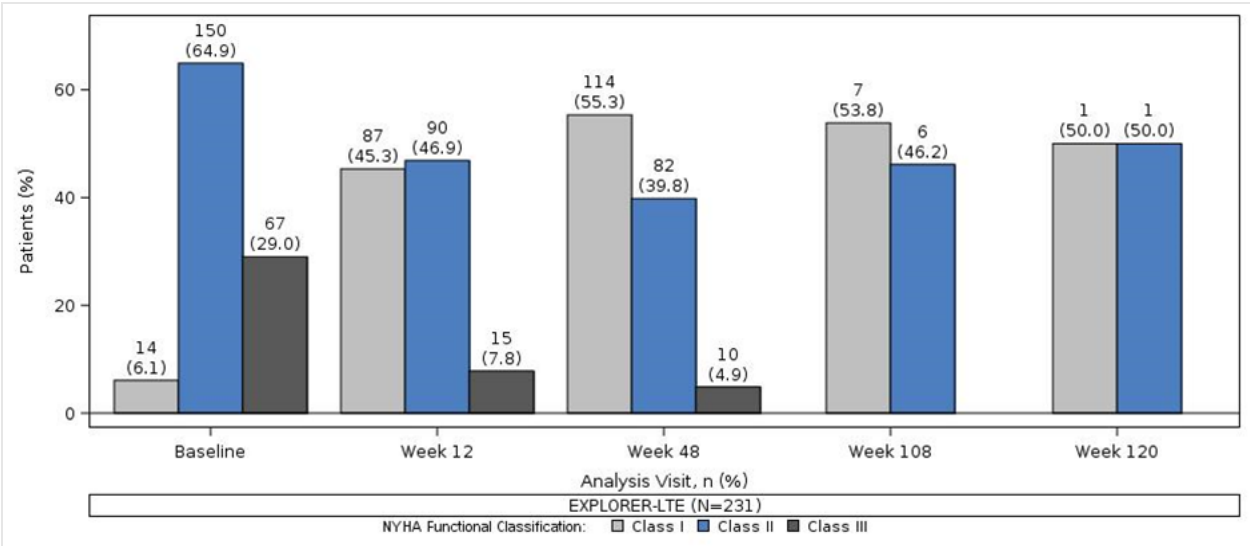


Note: ITT = Intent-To-Treat, LVEF = Left Ventricular Ejection Fraction, SD = Standard Deviation.ITT population is defined as all randomized participants regardless of whether they received study drug, with analyses conducted according to the randomized treatment assignment.
Bars indicate SD.
Baseline is defined as last non-missing measurement prior to the first dose. For subject randomized but not treated, the date of randomization was used to define the baseline value.
All assessments are summarized by analysis visits per SAP. Only resting LVEF quantative results are presented.

NYHA class

Clinical status based on NYHA functional class improved from baseline (Figure 36) and was generally sustained throughout the duration of the observation period. At Week 48, 67.4% of subjects had an improvement in ≥1 NYHA class relative to the baseline assessment that was sustained through Week 108 and Week 120, although numbers are small at these later timepoints.

Figure 36. EXPLORER-LTE Cohort: Bar Plot of NYHA Class over Time (ITT Population)

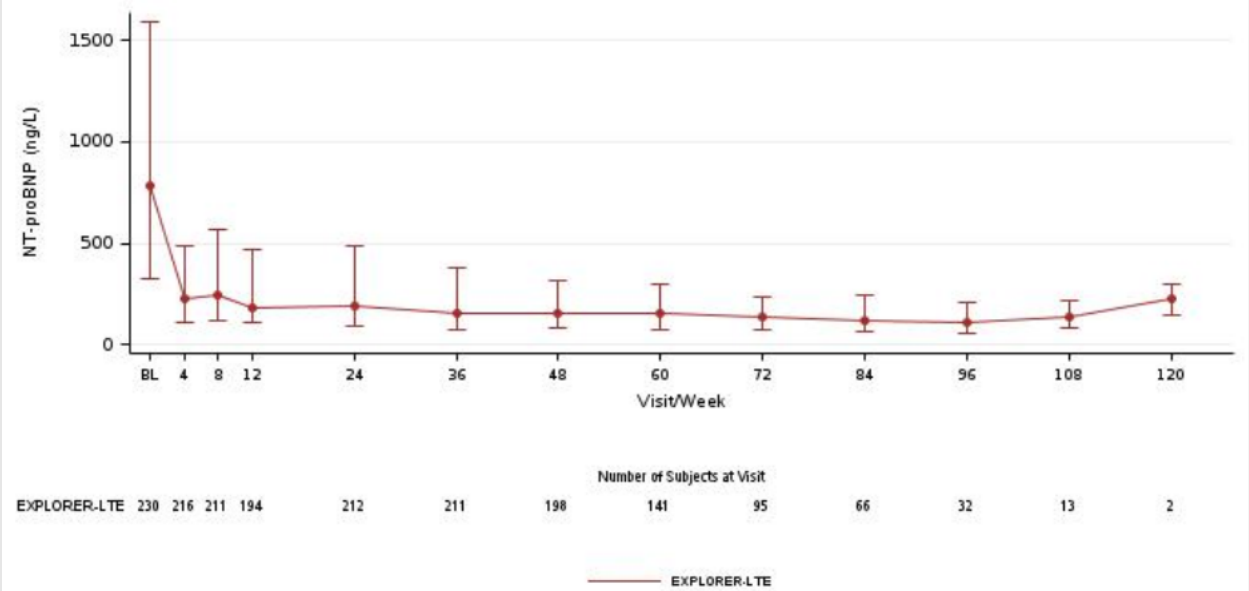


ITT Population is defined as all randomized participants regardless of whether they received study drug, with analyses conducted according to the randomized treatment assignment.
Last enrollment period is presented for subjects who enrolled more than once in the study.

NT-proBNP

Rapid and sustained improvements in NT-proBNP (core lab) were seen as early as Week 4 with start of treatment; some adjustment is seen during the dose titration stages, and further reductions are noted at Week 24 and beyond with dose adjustments that are allowed per protocol (Figure 37).

Figure 37. EXPLORER-LTE Cohort: Median (Q1, Q3) Serum NT-proBNP Over Time (ITT Population)

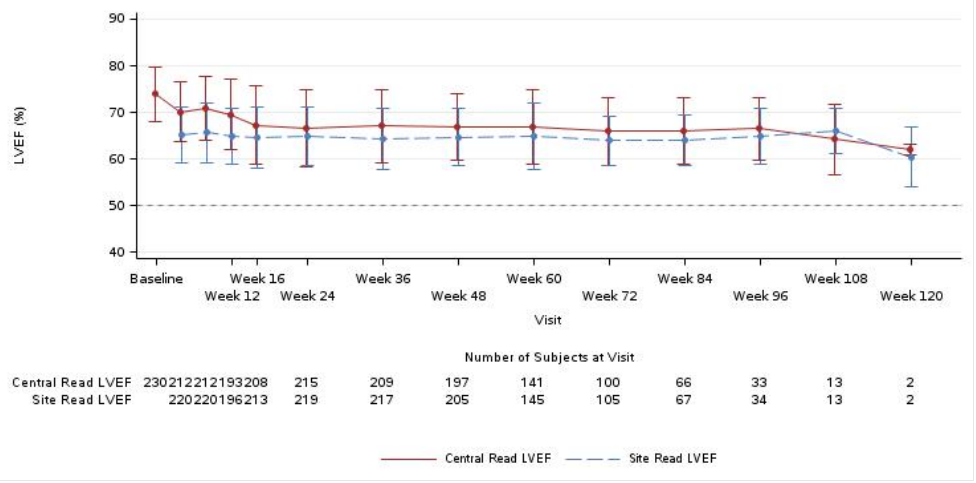


ITT population is defined as all randomized participants regardless of whether they received study drug, with analyses conducted according to the randomized treatment assignment.
Baseline is defined as last non-missing measurement prior to the first dose. For subject randomized but not treated, the date of randomization was used to define the baseline value.
All assessments are summarized by analysis visits per the SAP. Only resting NT-proBNP result is presented.

LVEF

Mean baseline LVEF was hypercontractile, at 74%. Consistent with the mechanism of action of mavacamten, a small reduction in mean LVEF is seen upon initiation of treatment at study Day 1 (Figure 38). A further reduction in LVEF is seen between baseline and Week 24 (titration stages), which then levels to steady and consistent measurements. The number of subjects reaching Week 84 and beyond in this data cut decreases to <100. At Week 120, only 2 patient's data are represented and thus, the mean LVEF is maintained and similar to prior timepoints.

Figure 38. EXPLORER-LTE Cohort: Mean (SD) Plot of LVEF Over Time by Lab Type, EXPLORER-LTE Cohort



Other echocardiogram parameters

At the conclusion of the 24-week dose-titration period and consistent with the known mavacamten mechanism of action and as seen in the parent study, mean (SD) LVESVI had increased by 2.7 (4.6) mL/m^2 and LVEDVI had remained stable throughout the assessment period (0.1 ml/m^2) (Table 45). At Week 96, the mean (SD) changes from baseline in LVES and LVEDVI were 2.5 (3.9) mL/m^2 and 0.19 (8.2) mL/m^2, respectively. Consequently, mean (SD) LVSV as measured by resting echocardiographic parameters had decreased from baseline by 5.4 (11.6) mL at Week 24 and by 5.2 (12.3) mL at Week 96. Little to no change from baseline in echocardiographic measures of interventricular septal or posterior wall thicknesses or the LVMI, which is derived in part from these parameters, were reported for the ITT Population up to Week 96 of mavacamten treatment (Table 45).

Table 45. Actual and Change from Baseline in Wall Thickness Measurements by Study Visit (ITT Population, Central-Read Echocardiogram)

Resting Echocardiographic Parameter	n	N = 231
IVST (mm), mean (SD)		
Baseline	230	18.457 (3.0537)
Absolute value at Week 24	215	18.500 (3.2546)
Change from Baseline at Week 24	214	0.088 (1.8746)
95% CI		-0.1643, 0.3409
Absolute value at Week 48	201	18.255 (2.8357)
Change from Baseline at Week 48	200	-0.032 (2.3721)
95% CI		-0.3629, 0.2986
Absolute value at Week 72	105	18.139 (2.8014)
Change from Baseline at Week 72	105	0.659 (2.3289)
95% CI		0.2085, 1.1099
Absolute value at Week 96	34	18.505 (2.9759)
Change from Baseline at Week 96	34	1.775 (2.7144)
95% CI		0.8276, 2.7218
PWT (mm), mean (SD)		
Baseline	226	11.922 (2.3632)
Absolute value at Week 24	210	11.542 (2.2582)
Change from Baseline at Week 24	208	-0.371 (1.2446)
95% CI		-0.5412, -0.2009
Absolute value at Week 48	197	11.365 (1.8659)
Change from Baseline at Week 48	193	-0.516 (1.6194)
95% CI		-0.7462, -0.2864
Absolute value at Week 72	103	10.782 (1.8923)
Change from Baseline at Week 72	100	-0.544 (1.8548)
95% CI		-0.9121, -0.1761
Absolute value at Week 96	34	11.156 (1.5541)
Change from Baseline at Week 96	34	0.154 (1.6901)
95% CI		-0.4361, 0.7433

Resting Echocardiographic Parameter	n	N = 231
LVMI (g/m^2), mean (SD)		
Baseline	224	119.813 (31.1231)
Absolute value at Week 24	206	118.717 (32.0689)
Change from Baseline at Week 24	203	-1.257 (16.3520)
95% CI		-3.5204, 1.0055
Absolute value at Week 48	195	114.332 (27.0349)
Change from Baseline at Week 48	190	-4.156 (19.7059)
95% CI		-6.9763, -1.3362
Absolute value at Week72	102	109.027 (23.3746)
Change from Baseline at Week 72	99	-2.844 (17.7018)
95% CI		-6.3742, 0.6869
Absolute value at Week 96	33	109.844 (25.2036)
Change from Baseline at Week 96	33	0.944 (15.3474)
95% CI		-4.4983, 6.3856

ITT population is defined as all randomized participants regardless of whether they received study drug, with analyses conducted according to the randomized treatment assignment.
Baseline is defined as last non-missing measurement prior to the first dose. For subject randomized but not treated, the date of randomization was used to define the baseline value.
All assessments are summarized by analysis visits per SAP.
95% CI is calculated for the mean and based on normal approximation. The treatment group is determined based on current study treatment. Last enrollment period is presented for subjects who enrolled more than once into the study

Resting Echocardiographic Parameter	n	N = 224
Actual at Week 48	46	110 (23.6)
Change from Baseline at Week 48	45	0.2 (18.2)
95% CI		-5.3, 5.6

Abbreviations: CI = confidence interval; ITT = intention-to-treat; IVST = interventricular septum thickness; LTE = long-term extension; LVMI = left ventricular mass index; PWT = posterior wall thickness; SAP = statistical analysis plan; SD = standard deviation
ITT population is defined as all randomized participants regardless of whether they received study drug, with analyses conducted according to the randomized treatment assignment.
Baseline is defined as last non-missing measurement prior to the first dose. For subject randomized but not treated, the date of randomization was used to define the baseline value.
All assessments are summarized by analysis visits per SAP.
95% CI is calculated for the mean and based on normal approximation.

Diastolic function and left atrial size

Doppler parameters of diastolic function and LA size were assessed at baseline and every 24 weeks thereafter. For each of these parameters, changes over time were directionally favourable (Table 46). There were decreases in E/e' (both lateral and septal), consistent with a reduction in LV filling pressure, during long-term treatment with mavacamten. Consistent with the beneficial trends seen for diastolic function parameters, reductions from baseline in LAVI were constantly seen from Week 24 through Week 96.

Table 46. Baseline and Change from Baseline in Measures of Left Atrial Size and Diastolic Function by Study Visit (ITT Population, Central-Read Echocardiogram)

Resting Echocardiographic Parameter	N = 231			
	n	Absolute value	n	Change from Baseline
E/e′(septal), mean (SD)				
Baseline	225	20.23 (7.945)		NA
Week 24	213	16.86 (6.840)	208	-2.98 (5.712)
95% CI		15.939, 17.786		-3.757, -2.195
Week 48	198	15.74 (6.267)	194	-4.25 (6.582)
95% CI		14.862, 16.618		-5.180, -3.316
Week 60	140	16.62 (6.655)	139	-3.79 (5.965)
95% CI		15.510, 17.734		-4.788, -2.787
Week 72	102	15.96 (5.788)	101	-4.28 (5.201)
95% CI		14.827, 17.101		-5.305, -3.252
Week 84	61	15.97 (6.207)	61	-3.70 (4.576)
95% CI		14.382, 17.562		-4.877, -2.533
Week 96	31	15.05 (5.688)	31	-4.14 (3.729)
95% CI		12.959, 17.132		-5.503, -2.768

Resting Echocardiographic Parameter	N = 231			
	n	Absolute value	n	Change from Baseline
E/e´(lateral), mean (SD)				
Baseline	224	14.79 (7.333)		NA
Week 24	210	11.67 (5.450)	204	-2.94 (5.191)
95% CI		10.931, 12.414		-3.661, -2.227
Week 48	194	10.94 (4.486)	190	-3.45 (4.918)
95% CI		10.308, 11.579		-4.154, -2.746
Week 72	98	11.48 (4.765)	97	-3.83 (7.364)
95% CI		10.525, 12.436		-5.316, -2.348
Week 96	31	11.50 (4.171)	31	-2.90 (3.915)
95% CI		9.970, 13.030		-4.333, -1.461
LAVI (mL/m^2), mean (SD)				
Baseline	227	38.300 (13.0167)		NA
Week 24	213	32.963 (12.0320)	210	-5.047 (8.7139)
95% CI		31.3376, 34.5879		-6.2327, -3.8619
Week 48	200	30.949 (9.7353)	197	-6.809 (8.4430)
95% CI		29.5920, 32.3069		-7.9956, -5.6230
Week 72	104	31.948 (9.9236)	102	-7.791 (9.1909)
95% CI		30.0180, 33.8778		-9.5962, -5.9857
Week 96	33	30.775 (9.9197)	33	-11.616 (9.9797)
95% CI		27.2575, 34.2923		-15.1549, -8.0776

ITT population is defined as all randomized participants regardless of whether they received study drug, with analyses conducted according to the randomized treatment assignment.
Baseline is defined as last non-missing measurement prior to the first dose. For subject randomized but not treated, the date of randomization was used to define the baseline value.
All assessments are summarized by analysis visits per SAP.
95% CI is calculated for the mean and based on normal approximation.

Systolic anterior motion and mitral regurgitation

Among the subjects who had non-missing data of SAM and MR at both baseline and Week 24, the percentage of subjects with presence of SAM decreased from 78.7% to 34.3% and the percentage of subjects with presence of MR decreased from 94% to 83.4%. Among the subjects who had non-missing data of SAM and MR at both baseline and Week 48, the percentage of subjects with presence of SAM decreased from 77.7% to 19.8%, and the percentage of subjects with presence of MR decreased from 94.5% to 74.1% (Table 47).

Table 47. Systolic Anterior Motion and Mitral Regurgitation for Subjects with Non-Missing Assessments (Central-Read Echocardiogram, ITT Population)

Echocardiographic Parameter[a]	Study Visit N = 231			
	Week 24 n (%)		Week 48 n (%)	
	Baseline	Week 24	Baseline	Week 48
SAM, n	216	216	202	202
Yes, n (%)	170 (78.7)	74 (34.3)	157 (77.7)	40 (19.8)
No, n (%)	46 (21.3)	142 (65.7)	45 (22.3)	162 (80.2)
MR, n	217	217	201	201
Yes, n (%)	204 (94.0)	181 (83.4)	190 (94.5)	149 (74.1)
No, n (%)	13 (6.0)	36 (16.6)	11 (5.5)	52 (25.9)

a Only subjects with both a baseline and visit assessment are included in the analysis
ITT population is defined as all randomized participants regardless of whether they received study drug, with analyses conducted according to the randomized treatment assignment.
Last enrollment period is presented for subjects who enrolled more than once into the study.
Baseline is defined as last non-missing measurement prior to the first dose. For subjects randomized but not treated, the date of randomization was used to define the baseline value.
All assessments are summarized by analysis visits per SAP
Percentages for 'Yes' and 'No' are based on all non-missing data for each visit.

MYK-461-008: An Open-label Extension Study of Mavacamten (MYK-461) in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy Previously Enrolled in Study MYK-461-004 (PIONEER-HCM)

Methods

MYK-461-008 is an ongoing Phase II, multicenter, open-label 5-year long-term extension study evaluating the long-term safety and tolerability of mavacamten in subjects with symptomatic oHCM who completed the 16-week PIONEER-HCM (MYK-461-004) study. Eligible subjects underwent baseline assessments and started a once-daily (QD) dosing regimen with 5 mg mavacamten. Individualized target doses, which were based on maintaining a study drug plasma concentration between approximately 250 ng/mL and 500 ng/mL, were determined for each subject prior to the start of the study. The target dose (5, 10 or 15 mg) was based on the subject's mavacamten plasma concentrations and study drug dose in the parent study. If the target dose was greater than the 5 mg QD starting dose, the dose was increased at Week 6, unless any of the following conditions were met: a) left ventricular ejection fraction (LVEF) was <55%, and/or b) LVOT gradient was <30 mmHg after exercise, and/or c) trough mavacamten plasma concentration was > 350 ng/mL, and/or d) a dose increase was not warranted in the clinical judgment of the Investigator. System-guided notification for temporary discontinuation was triggered if a subject had any of the following values: mavacamten plasma concentration ≥1000 ng/mL, LVEF <45%, or prolonged Fridericia-corrected QT (QTcF) interval [defined as a 15% increase over baseline or an absolute QTcF ≥520 ms (if QRS <120 ms) or ≥550 ms (if QRS ≥120 ms)]. Study drug dosing could be resumed at a lower dose per protocol upon appropriate clinical assessment within the pre-specified time period.

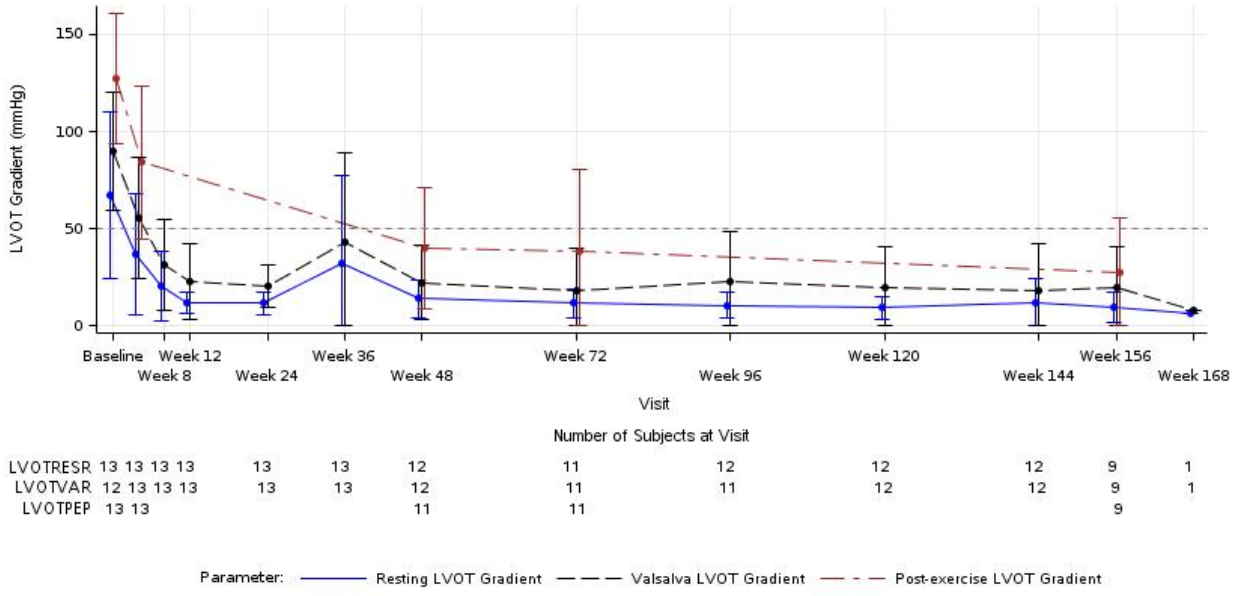
Results

The mean (SD) duration of treatment interval between parent and extension study was 53.30 (15.704) weeks (median (min, max): 52.57 (30.9, 76.3). Thirteen 13 subjects with symptomatic oHCM who completed the Phase 2 PIONEER-HCM study had enrolled Study MYK-461-008 (PIONEER-OLE). Twelve subjects were on-treatment during the previous data cut-off date of 30-Oct-2020 and have remained on-treatment as of the latest data cut-off date of 31 Aug 2021. Of the 13 subjects who entered the study, 12 (92%) completed assessments at least through Week 144 and 9 (69%) completed through Week 156. No subject met the study stopping criteria, or the protocol defined temporary discontinuation criteria. One subject discontinued treatment on Day 175 (Week 25) due to a TEAE and subsequently discontinued the study (Day 182). Nine (69.2%) subjects had a planned dose increase per protocol from the 5-mg starting dose based on a pre-determined target dose. One subject had an interruption in treatment of 18 days at the Week 72 visit due to conditions created by the COVID-19 pandemic. The subject resumed treatment at the same dose level following this interruption.

LVOT peak gradient

Similar to the MAVA-LTE study (EXPLORER LTE cohort), in the PIONEER-OLE study there were rapid and sustained improvements in resting and Valsalva LVOT gradients from baseline to Week 12 and in post-exercise LVOT gradient from baseline to Week 48, all sustained through Week 156 (Figure 39).

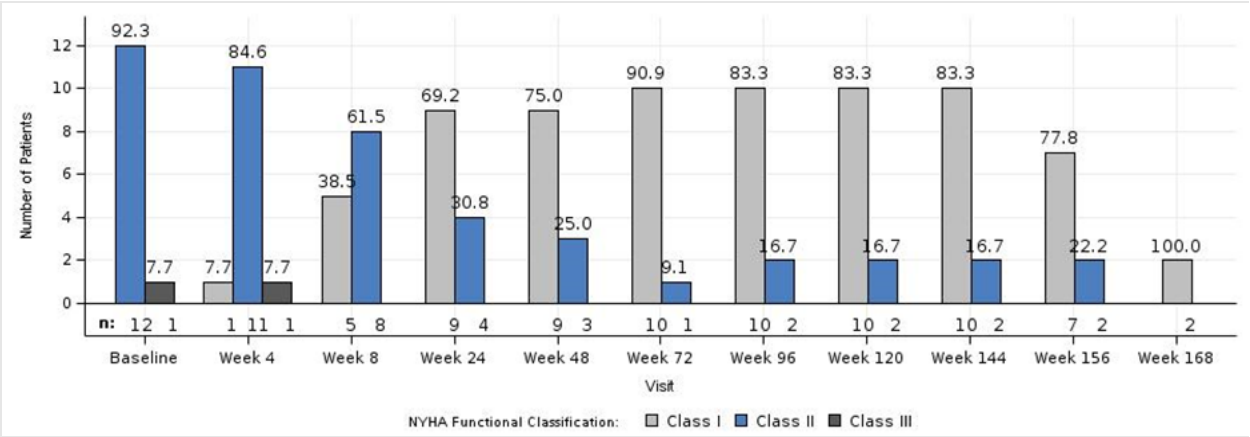
Figure 39. MYK-461-008 Study - Mean (SD) of Resting, Valsalva, and Post-exercise LVOT Gradient by Visit (Safety Population)



NYHA class

Improvements from baseline in oHCM symptoms assessed by NYHA class in Study MYK-461-008 was consistent with those observed in study MYK 461-005 (Figure 40).

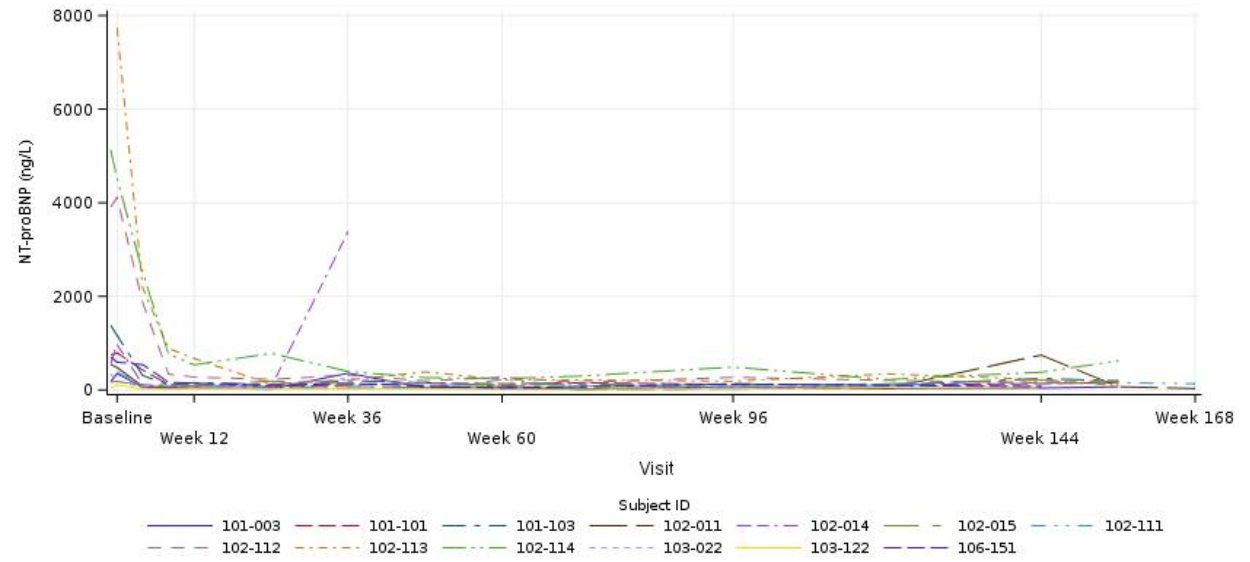
Figure 40. MYK-461-008 - NYHA Functional Classification by Visit



NT-proBNP

NT-proBNP levels were sustained through Week 156 (Figure 41).

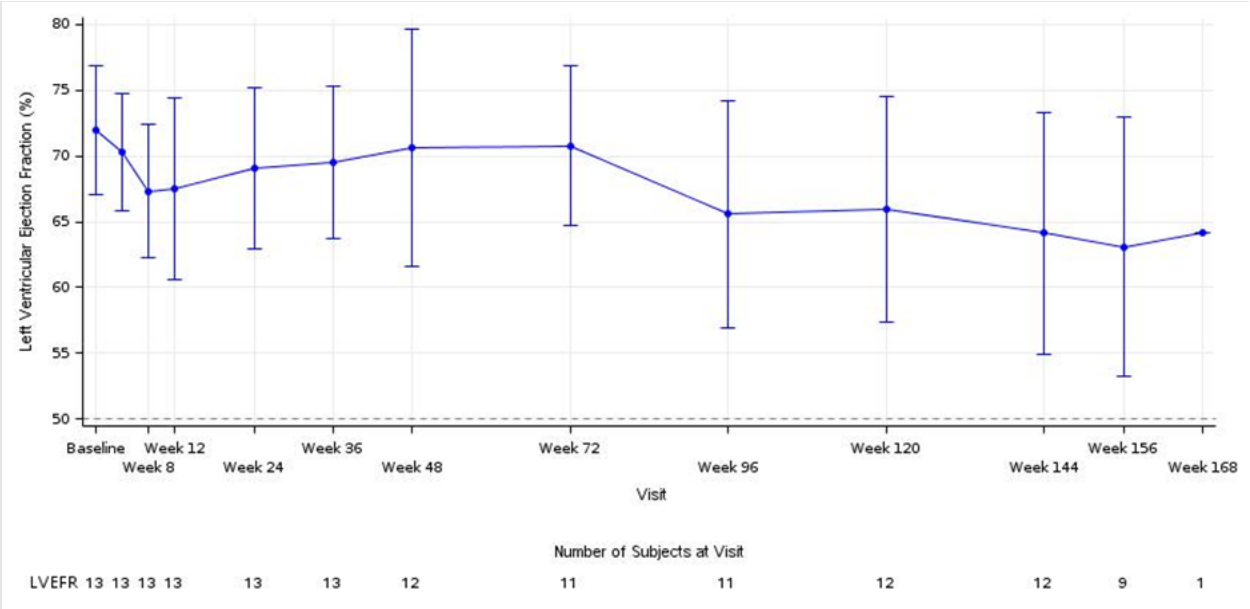
Figure 41. MYK-461-008 Subject-Level Spaghetti Plot of NT-proBNP by Visit (Safety Population)



LVEF

Group mean (SD) LVEF was 72% (4.9%) at baseline. Subsequently, at each scheduled clinic visit after initiating mavacamten dosing, as expected, modest mean changes from baseline were noted (at Week 96 mean [SD] change, -6% [8.3%]); LVEF was maintained above 50% in all subjects throughout the observation period (Figure 42).

Figure 42. Resting Mean LVEF over Time (Safety Analysis Population)



Patient Reported Outcomes (KCCQ)

As the study progressed, group mean scores increased across all categories indicating improvement in all domains, which translates to a subjective impression of decreased disease burden and increased satisfaction with outcome. Of note, there was improvement in mean scores as early as Week 4, with clinically meaningful improvements noted from Week 8 that were sustained throughout the observation period. At Week 96, the mean (SD) change in the clinical summary score (CSS) was 17.6 (17.4).

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

This application is based on efficacy data from the phase II dose-finding study PIONEER-HCM (Study MYK-461-004) and the pivotal phase III studies EXPLORER-HCM (Study MYK-461-005) and VALOR-HCM (Study MYK-461-017; ongoing). Supportive data are obtained from the EXPLORER-LTE cohort of the ongoing long-term extension study MAVA-LTE (Study MYK-461-007) and the ongoing PIONEER-OLE study(Study MYK-461-008).

Dose selection. Available clinical data of the phase I studies and the phase II dose-finding study PIONEER-HCM and modelling/simulation (see section regarding clinical pharmacology) have been used to select the most appropriate dosing regimen for the pivotal study EXPLORER-HCM. PIONEER-HCM was an open-label, dose-finding phase II study to evaluate PK/PD at different drug concentrations and to define the minimum inhibitory dose over 12 weeks in patients with oHCM. The study consisted of two parts with a dose range of 5 to 25 mg in Part A (n=13) and a dose range of 2 to 5 mg in Part B (n=12). The primary efficacy endpoint, change in post-exercise peak LVOT gradient from baseline to week 12, showed a significant 82% mean reduction from 103 ± 50 mmHg at baseline to 19 ± 13 mmHg at Week 12 (p = 0.008) in Part A and a significant 27% mean reduction from 86 ± 43 to 63 ± 26 mmHg (p = 0.020) in Part B. The primary efficacy endpoints were further supported by improvements in the secondary efficacy endpoints, dyspnoea scores, exercise capacity (pVO_2max) and NYHA FC for both Part A and Part B and systolic anterior motion (SAM) for Part A only. The observed effect is reversible considering that the LVOT gradient values returned toward baseline at week 16, i.e. 4 weeks after discontinuing mavacamten. Exposure-response analyses showed a clear relationship

between mavacamten plasma concentration and Valsalva LVOT gradient and LVEF. Reductions in Valsalva LVOT gradient to below 30 mmHg as a peak LVOT gradient ≥30 mmHg is the criterion that defines obstruction in the HCM patient population. LVEF was measured to ensure subject safety/tolerability (normal range: LVEF > 50%). Mavacamten plasma concentrations <1000 ng/mL were generally well tolerated, while concentrations > 1000 ng/mL were associated with changes to below-normal values in LVEF. To conclude, exposure-response analyses showed on average reductions in LVOT gradient to levels <30 mmHg while maintaining normal LVEF (50%-70%) at mavacamten plasma concentrations between 350 ng/ml and 1000 ng/ml. Furthermore, PK analysis showed that there is no clear dose-exposure relationship on the individual level due to high PK intra- and interindividual variability (See section "Pharmacokinetics"). Overall, results from the dose-ranging PIONEER-HCM provided the rationale for the individualized dosing algorithm based on PD and concentration targets used in the pivotal phase III study EXPLORER (MYK-461-005), i.e., a starting dose of mavacamten 5 mg and a provisional target therapeutic range of mavacamten plasma trough concentration between 350 and 1000 ng/mL.

Changes to the dosing regimen from those used in the pivotal studies EXPLORER-HCM (and its extension study) and VALOR-HCM have been proposed for the product information. The changes included the use of a more stringent down titration cut-off value (Valsalva LVOT gradient <20 mmHg vs <30 mmHg), a minimum of 12 weeks and LVEF ≥55% prior to dose up-titration, and a follow-up visit at 4 weeks after any up-titration. The rationale and justification for the different components for the proposed dosing regimen in the SmPC are discussed below.

The starting dose of 5 mg has been selected based on the results of the dose-finding phase II study PIONEER-HCM, the pivotal phase 3 study EXPLORER-HCM, and the EXPLORER-LTE cohort, which demonstrated that this dose was well tolerated, with a minority of subjects requiring down-titration to the 2.5 mg dose at the early-down titration point or later during the study. The starting dose was further justified by modelling and simulation. Furthermore, the applicant claims that this starting dose of 5 mg can be used for all patients regardless of age, sex, body weight, CYP2C19 metabolizer status, mild or moderate hepatic or renal impairment, and concomitant medication. Considering that CYP2C19 poor metabolizers have a ~3-fold increase in mavacamten plasma exposure, an adjusted posology for CYP2C19 poor metabolizers is recommended in the SmPC (see also "Pharmacokinetics").

Due to high intra- and interindividual PK variability, echocardiogram-guided dosing based on LVEF and LVOT gradient instead of dosing based on mavacamten plasma concentration to ensure patient safety and monitoring of response, has been proposed. In the pivotal study EXPLORER-HCM, dose adjustments were based on echocardiogram parameters Valsalva LVOT and LVEF combined with mavacamten plasma concentrations. Nevertheless, the safety of echocardiogram-guided dosing proposed for use in clinical practice is supported by data from the ongoing EXPLORER-LTE and the ongoing VALOR-HCM study.

The starting dose is followed by echocardiogram-guided dose-titration based on LVOT gradient to attain the target efficacy criteria (Valsalva LVOT gradient <30 mmHg) and LVEF to ensure subject safety (LVEF > 50%, which is the lower limit of the normal range). After initiation of treatment, an initial follow-up visit at Week 4 and Week 8 is proposed to assess for an early efficacy response and tolerability. More specifically, in the pivotal EXPLORER-HCM, subjects were down-titrated to 2.5 mg if the mavacamten concentration was 700 to 1000 ng/ml (based on Week 4 PK). Moreover, in the EXPLORE-LTE cohort, subjects were down-titrated to 2.5 mg if the Valsalva LVOT gradient was <30 mmHg, whereas in the SmPC, subjects will down-titrate to 2.5 mg if Valsalva LVOT gradient is <20 mmHg. The lower LVOT gradient threshold of <20 mmHg was based on simulations which showed that with this level, fewer patients would experience a "yo-yo" effect in their dosing as was observed in the EXPLORER-LTE. Moreover, the target efficacy criterion of Valsalva LVOT gradient <30 mmHg is endorsed since, according to the ESC guideline, obstructive HCM is defined as peak LVOT gradient ≥30

mmHg at rest or during the Valsalva manoeuvre. Also, in this respect, the lower Valsalva LVOT gradient threshold of <20 mmHg for down-titration is considered more appropriate than the 30 mmHg threshold. Otherwise, in both the clinical studies and the proposed SmPC, if LVEF remains > 50%, the dose of 5 mg once daily should be maintained, whereas if the LVEF <50% (at any visit), treatment should be temporarily discontinued.

According to the proposed SmPC, a dose increase may be considered 12 weeks after treatment initiation or after at least 12 weeks on a stable dose if symptoms of oHCM persist, i.e. Valsalva LVOT gradient is > 30 mmHg and LVEF > 55% (e.g., 2.5 to 5 mg; 5 to 10 mg; 10 to 15mg; 15 mg is the maximum daily dose), followed by a 4-week follow-up visit. The higher criterion of LVEF> 55% than the LVEF > 50% used in the clinical studies is considered a conservative approach, which is endorsed. Once an individualised maintenance dose is achieved, patients should be assessed every 12 weeks. Regarding re-dosing, if at any visit the patients LVEF is <50%, the treatment with mavacamten should be interrupted for 4 weeks until LVEF returns to ≥50%. Thereafter, the treatment may resume on the next lower dose level.

Design of the main clinical studies

EXPLORER-HCM; Study MYK-461-005

EXPLORER-HCM was a phase III, double-blind, randomized, placebo-controlled, multicenter, international, parallel-group study to evaluate the efficacy, safety, and tolerability of mavacamten compared with placebo in subjects with symptomatic oHCM.

The inclusion criteria are reflected in the indication as proposed. Key inclusion criteria included diagnosis with oHCM defined by 1) unexplained LV hypertrophy with nondilated ventricular chambers in the absence of other cardiac (e.g., hypertension, aortic stenosis) or systemic disease and 2) with maximal LV wall thickness ≥15 mm (or ≥13 mm with a positive family history of HCM) and LVOT peak gradient ≥50 mmHg during screening as assessed by echocardiography at rest, after Valsalva manoeuvre, or post-exercise; LVOT gradient with Valsalva manoeuvre at screening ≥30 mmHg; and NYHA Class II or III symptoms at screening. The diagnosis of oHCM is in line with the ESC guidelines. According to the ESC guideline, LVOT obstruction is defined as LVOT gradient ≥30 mmHg at rest or during physiological provocation, such as Valsalva. Additionally, a LVOT gradient of ≥50 mmHg at rest or LVOT gradient of ≥50 mmHg during Valsalva or post-exercise in symptomatic patients is usually considered to be the threshold at which LVOT obstruction becomes haemodynamically important, and treatment of LVOT obstruction is recommended. As such, the inclusion criteria identify patients with oHCM for whom (additional) treatment is recommended according to the guideline. Since mavacamten causes a reduction in LVEF, the higher criterion of LVEF> 55% than the lower limit of the normal range (LVEF > 50%) was used as an inclusion criterion to ensure subject safety, which is considered appropriate. According to the ESC guideline, the current medicinal standard of care for patients with oHCM includes non-vasodilating beta-blockers (first-line therapy), calcium channel blockers (recommended for patients intolerant or have contraindications to beta-blockers), and disopyramide (in addition to a beta-blocker (or, if this is not possible, with verapamil). The combination of a beta-blocker and a calcium channel blocker is not recommended according to the ESC guideline which is also reflected in the exclusion criteria. However, since the optimal standard of care for oHCM was not included as an inclusion criterion, the applicant was requested to confirm that the proportion of patients on beta-blockers (75.3%) or calcium channel blockers (16.7%) as background therapy is in line with the current standard of care. The same issue applied to septal reduction therapy (7.6%). The applicant argued that the percentage of patients using beta-blockers and calcium channel blockers or underwent septal reduction therapy enrolled in the EXPLORER-HCM study is generally in line with what is observed in the Cardiomyopathy Registry of the EURObservational Research Program (ERP). Patients treated with disopyramide were excluded from the EXPLORER-HCM study due to the possibility of

excessively reducing cardiac contractility with the concomitant use of 2 negative inotropes. Two patients were excluded from the study as they were taking disopyramide and 21 subjects had previously taken disopyramide (11 vs 10 in the mavacamten and placebo group, respectively), but discontinued at least 14 days prior to mavacamten therapy. Considering that the number of subjects who previously took disopyramide is well balanced between the groups, any potential rebound effect would be similarly balanced between the two groups resulting in no effect on the results of EXPLORER-HCM. In the ongoing VALOR-HCM study disopyramide was allowed as a concomitant mediation. Approximately 20% of the patients were receiving disopyramide along or with beta-blocker and/or a calcium channel blocker and, to date, no excess of adverse events in this specific subgroup have been observed.

The design of EXPLORER-HCM generally appeared appropriate. The duration of the screening period, up to 35 days, is appropriate. In the randomized, double-blind treatment period of 30 weeks, eligible patients started with 5 mg mavacamten or matching placebo (1:1 randomization). At Week 6, the mavacamten dose could be down-titrated based on mavacamten plasma concentration and echocardiography responses on week 4, i.e. assessment for an early response. At Week 8 and 14 the dose could be up-titrated, down-titrated, or remain unchanged based on mavacamten plasma concentration and echocardiography responses on Week 6 and 12.

The primary endpoint was a composite functional response at Week 30, defined as achieving: 1. an improvement of ≥1.5 mL/kg/min in pVO_2max as determined by CPET and a reduction of ≥1 NYHA class or 2. an improvement of ≥3.0 mL/kg/min in pVO_2max with no worsening in NYHA class. The applicant argued that the combined interrogation of these two parameters provides complementary assessments of the impact of treatment on myocardial function (pVO_2max) and symptomatic burden (NYHA class) and that requiring an NYHA class improvement at the lower pVO_2max threshold provided an increased level of stringency to support clinical relevance. According to the applicant, the combination as a composite endpoint is supported by the fact that both measures are independent prognostic variables in HCM and allow an integrated assessment of both benefits on the functional and symptomatic limitations of oHCM patients. However, the Rapporteur considers that neither exercise capacity nor NYHA class are validated surrogates for morbidity/mortality in the context of oHCM treatment. According to the EMA Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure (CPMP/EWP/235/95, Rev.2), exercise capacity may be acceptable as a primary efficacy endpoint, in case the result is supported by secondary endpoints that meaningfully contribute to the understanding of the clinical relevance of the effect (e.g. hospitalization for heart failure, syncope, quality of life) and the cardiovascular safety profile of the product can be adequately characterised. As such, pVO_2max would be considered acceptable as a primary efficacy endpoint, as also previously mentioned in the 2017 CHMP scientific advice. However, the composite primary endpoint, which is based on pVO_2max and NYHA class, is difficult to interpret. The functional capacity component of the endpoint refers to thresholds for increase in pVO_2max, of which the relevance is not fully justified in the submitted dossier. The NYHA component of the endpoints is suitable as a secondary endpoint or in support of a functional endpoint but usually not as a component of the primary endpoint (see EMA Guideline; CPMP/EWP/235/95, Rev.2). In this respect, the focus in this application was on the data of the individual component pVO_2max (which was assessed as a secondary endpoint) rather than on the responder definition in the composite primary endpoint. In addition to pVO_2max and NYHA class, other relevant key secondary endpoints are included, such as a change from baseline to Week 30 in post-exercise LVOT peak gradient and patient-reported outcomes (Kansas City Cardiomyopathy Questionnaire (KCCQ-23 CSS) and hypertrophic cardiomyopathy symptom questionnaire (HCMSQ SoB). Additionally, exploratory endpoints included absolute values and changes from baseline in multiple CPET and echocardiography parameters and cardiac biomarkers. Moreover, a cardiac magnetic resonance (CMR) substudy has been included in order to assess the change from baseline to Week 30 in left ventricular mass index (LVMI) and exploratory endpoints, including changes

in left atrial (LA) volume and LV wall thickness, volume, and function, in order to adequately evaluate the cardiac structure and function, which is considered appropriate.

The planned sample size of 220 subjects (1:1 ratio or 110 subjects per treatment group) was chosen to provide up to 96% power to detect the superiority of mavacamten in improving pVO_2max and NYHA functional class relative to placebo with a type I error (overall 2-sided alpha) of 0.05. The power calculation was derived assuming a 25% difference between mavacamten and placebo in clinical response. The clinical response rate for the mavacamten group was assumed to be 50% based on PIONEER-HCM and for placebo at 25%. Participants who terminate early or cannot be assessed for the clinical response at the end of 30-week dosing period will be considered as non-responders. The sample size calculation was based on a 2-sided Cochran-Mantel-Haenszel (CMH) test for stratified categorical data. The study did not include sample-size re-estimation based on interim analysis.

The randomisation and blinding procedures are acceptable.

The Cochran-Mantel-Haenszel (CMH) test for stratified categorical data was used for the statistical analysis of the primary endpoint. That is to test the statistical significance of the association between clinical response status (responders vs non-responders) and treatment group (mavacamten vs placebo). The analysis of the primary efficacy endpoint was stratified for all the stratification factors which were used in the randomization procedure except for consent for the CMR substudy. This is considered acceptable. A composite strategy was used to handle missing pVO_2max data, according to which participants who dropped-out of the study were considered as non-responders. Missing NYHA class measurements were imputed using LOCF. The handling of intercurrent events is considered acceptable. Components of the composite primary endpoint were also assessed individually. This is endorsed and considered necessary, as explained above. The overall type-I error rate was controlled by applying a hierarchical test strategy. This is considered acceptable. The CMH test was also used to assess the categorical secondary endpoint (proportion of subjects who had at least 1 class of improvement from baseline in NYHA class) between the mavacamten and placebo groups. This is considered acceptable. Between-group comparisons of the continuous secondary endpoints were based on analysis of covariance (ANCOVA) for LVOT gradient and pVO_2max and based on a mixed model for repeated measures (MMRM) for KCCQ-23 CSS and HCMSQ SoB domain score. These methods are considered acceptable.

- *Study MYK-461-017 (VALOR-HCM)*

MYK-461-017 is an ongoing Phase 3, randomized, double-blind, placebo-controlled, multicenter study of mavacamten vs. placebo in adults with symptomatic oHCM who met 2011 ACCF/AHA guideline criteria for SRT and have been referred for an SRT procedure within the past 12 months in the USA. As of 07 February 2022 (the clinical cut-off data of the primary CRS), all subjects participating in the study completed the study through Week 16 and, as such, the primary analysis was conducted.

The inclusion criteria/exclusion criteria are considered appropriate. Key inclusion criteria included diagnosis with oHCM defined by 1) unexplained LV hypertrophy with nondilated ventricular chambers in the absence of other cardiac (e.g., hypertension, aortic stenosis) or systemic disease and 2) with maximal LV wall thickness ≥15 mm (or ≥13 mm with a positive family history of HCM) and the patient should meet ACCF/AHA 2011 guideline recommendations for invasive SRT therapies. In the AHA guideline, patients eligible for invasive therapies should have a) severe dyspnoea or chest pain (usually NYHA Class III/IV) or occasionally other exertional symptoms (such as syncope or near syncope) that interfere with every day activity or quality of life despite optimal medical therapy; b) dynamic LVOT gradient at rest or with physiologic provocation ≥50 mmHg associated with septal hypertrophy and SAM of the mitral valve; c) targeted anterior septal thickness sufficient to perform the procedure safely

and effectively in the judgement of the individual operator. The requirements are generally in line with the ESC guideline (2014), which states that invasive treatment to reduce obstructive LVOT should be considered in a patient with a resting of maximum LVOT gradient ≥50 mmHg, moderate-to-severe-symptoms (NYHA III-IV) and/or recurrent exertional syncope in spite of maximally tolerated drug therapy.

The design of VALOR-HCM generally appeared appropriate. After the screening period of up to two days, eligible patients started with 5 mg mavacamten or a matching placebo (1:1 randomization) once daily for 16 weeks (placebo-controlled dosing or double-blind period). At Week 4, the mavacamten dose could be down-titrated based on the echocardiographic response, e.g. VLVOT <30 mmHg and up-titrated at Week 8 and 12 to a maximum dose of 15 mg based on LVEF ≥50% and VLVOT ≥30 mmHg. After 16 weeks, subjects in the mavacamten group continued blinded mavacamten treatment, whereas subjects in the placebo group started with 5 mg mavacamten (blinded dose) once daily from Week 16 to 32 (active-controlled dosing period). The criteria for down- or up-titration were similar as the placebo-controlled dosing period, which is appropriate. In the placebo-controlled period the study drug and dose were blinded and in the active-controlled period the dose will be blinded. This approach of blinding is endorsed since it prevents observer bias. Furthermore, if at any visit the patients LVEF is <50%, the treatment with mavacamten should be interrupted for 2-4 weeks. If LVEF returns to ≥50%, dosing resumed at one lower dose strength.

The primary endpoint was the composite of a patient's decision to proceed with SRT or eligibility for SRT according to the ACCF/AHA 2011 guidelines after 16 weeks of treatment, which is considered a more robust ("hard") clinical endpoint compared with pVO_2max in the EXPLORER-HCM, since SRT is clinically relevant to patients as it is a highly invasive surgery associated with significant consequential risk. Secondary endpoints included changes in post-exercise LVOT gradient, NYHA FC, KCCQ-23 CSS and cardiac biomarkers, NT-proBNP and cardiac troponin I, to further evaluate the effect of mavacamten, which is considered appropriate. Additionally, exploratory endpoints included the need for SRT in a long-term follow-up period (Weeks 32, 56, 80, and 128), the need for SRT as determined by the investigator, and haemodynamic parameters (LV filling pressures, left atrium size, accelerometry etc).

Efficacy data and additional analyses

- *Study MYK-461-005 (EXPLORER-HCM)*

In the pivotal study, 251 subjects (123 subjects to mavacamten and 128 subjects to placebo) were randomized, and all received at least 1 dose of the study drug. The percentage of subjects who completed treatment was high (97.2%) and approximately similar in the mavacamten and placebo group (96.7% and 97.7%, respectively). A total of 67 subjects (31 subjects (25.2%) in the mavacamten and 36 subjects (28.1%) in the placebo group) who had their Week 38/end of study visit via telephone communication rather than on site due to the COVID-19 pandemic were characterized as having discontinued the study due to "Other". Consequently, the percentage of subjects who completed the study was 71.5% and 70.3% in the mavacamten and placebo group, respectively. Discontinuation of study rates other than due to the COVID-19 pandemic were very low (2.4%), with 2 subjects due to AEs, 1 due to death, 2 subject withdrawals, and 1 subject lost to follow-up.

Thirteen subjects receiving mavacamten had dose reductions due to mavacamten plasma concentrations between 700 and 1000 ng/ml, including 8 subjects with dose reductions from 10 mg to 5 mg and 5 subjects from 5 to 2.5 mg. One subject with consecutive concentration values ≥700 ng/mL had 2 dose reductions: from 5 mg to 2.5 mg and from 2.5 mg to placebo. These data demonstrate that

the starting dose of 5 mg is well tolerated considering that only 5 subjects (4.1%) are down-titrated to 2.5 mg or placebo.

Dose-increases were allowed at Week 8 and 14 based on plasma mavacamten and LVEF and LVOT assessments at Week 6 and Week 12, respectively. Results demonstrated that the majority of subjects (~50%) remained on the mavacamten starting dose of 5 mg throughout the 30 weeks treatment period. Forty subjects (32.5%) received 10 mg, and only 13 subjects (10.6%) received 15 mg at the end of the treatment period. These data indicate that the overall exposure to the highest dose (15 mg) is limited both in terms of the number of patients (n=13) and in terms of duration of exposure (week 14 till week 30, i.e. 16 weeks). However, the data of the EXPLORER-LTE cohort showed that a substantial percentage of patients received and tolerated the highest 15 mg once daily dose (~15%) up to at least week 108.

Important protocol deviations (IPD) were categorized depending on whether or not they were considered related to the COVID-19 pandemic and generally well balanced between both groups.

This study was a multicentre study (n=68). Considering that approximately half of the subjects (51.0%) were from Europe, the population is sufficiently representative for Europe.

The recruited patients reflect a population of oHCM regarding demographics, comorbidities and guideline-directed medical therapies for oHCM, which are generally well distributed across the two treatments, although some exceptions are observed. The majority of subjects were male (59.4%), with a lower percentage of males in the mavacamten group compared with the placebo group (53.7% and 64.8 %, respectively). Considering that subgroup analysis with respect to gender showed a consistent effect on the composite primary endpoint, it is anticipated that this disbalance has not affected the outcome of the study. The majority of subjects is white (91.2%), whereas, consequently, the non-white population is underrepresented. However, despite variations in disease presentation, genotypic abnormalities and phenotypic expression of LVH are similar in white and non-white populations. Further, in all clinical studies, only 17/263 (6.5%) patients dosed with mavacamten were aged 75 years or older, i.e. also this population is under-represented. Nevertheless, based on literature, phenotypic features of oHCM, clinical managements and recommended treatment are suggested similar across different age groups, and the effect of mavacamten would be similar across various age groups.

The mean baseline NT-proBNP was higher in the mavacamten groups compared with the placebo group (1516 ng/L and 1050 ng/L, respectively). Similarly, although less evident, the percentage of patients with NYHA class III was slightly higher in the mavacamten group than the placebo group (28.5% and 25.8%, respectively). Additionally, a disbalance has also been observed with respect to HCM genotype. Several additional ad hoc analyses had been conducted to demonstrate that the imbalances in patient characteristics at baseline in NT-proBNP and HCM genotype did not affect the treatment benefit with mavacamten. Moreover, the baseline pVO_2max is slightly higher in the placebo group compared with the mavacamten group (mean [SD] 19.9 [4.91]) vs (18.9 [4.86] mL/kg/min, respectively). Nevertheless, the analysis for pVO_2max did include baseline values as a covariate, as specified in the SAP of the pivotal Phase 3 study. Furthermore, it has been shown that the coefficient of change from baseline at Week 30 vs baseline pVO_2 is 0.12 indicating that for every 1 unit increase in baseline pVO_2 the expected improvement in pVO_2 would be 0.12 lower, indicating that the treatment effect on pVO_2 improvement was more prominent that any effect of baseline pVO2. Based on above, it can be concluded that the disbalances in patients' characteristics at baseline did not have a relevant impact on the outcome of the study.

In line with the inclusion criteria, patients with NYHA class IV were not included, which has been reflected in the currently proposed indication, i.e. symptomatic oHCM (NYHA class II-III).

The proportion of subjects with each CYP2C19 metabolizer phenotype was similar across the treatment groups. However, there were few CYP2C19 poor metabolizers (PM) are included in the study (n=5 (2.0%) with 2 subjects (1.6%) in the mavacamten group and 3 subjects (2.3%) in the placebo group). Therefore, CYP2C19 PM has been included as missing information in the summary of safety concerns of the RMP. The majority of subjects were on background HCM therapy at baseline, with 75.3% of the subjects using beta-blockers and 16.7% of the subjects using calcium channel blockers. Some subjects (n=20, 8.0%) did receive neither beta-blockers nor calcium channel blockers.

Baseline values for echocardiography parameters were generally similar between both treatment groups. At baseline, enrolled subjects showed the expected characteristics of oHCM; Subjects were hypertrophic (mean LV maximum wall thickness 20 mm), hypercontractile (mean LVEF 74%) and progressively obstructed LVOT both at rest to provocation (mean resting LVOT gradients approximately 50 mmHg and increasing to approximately 85 mmHg after exercise). Furthermore, the most common symptoms related to HCM within the past 12 months were shortness of breath (90.4%), followed by fatigue (70.1%), chest pain and palpitations (45.4% each). Fewer subjects in the mavacamten group compared with the placebo group had a history of atrial fibrillation (9.8% vs 18.0%) (see safety for further discussion). Nevertheless, the percentage of subjects with a history of non-sustained ventricular tachycardia (NSVT), an important complication of HCM, was slightly higher for the mavacamten group compared with the placebo group (17.1% vs 12.5%, respectively). The percentage of patients with a history of septal reduction therapy (SRT) was 7.6% (8.9% and 6.3% in the mavacamten and placebo group, respectively).

Treatment with mavacamten resulted in a higher percentage of subjects achieving the composite primary endpoint, defined as achieving: 1. an improvement of ≥1.5 mL/kg/min in pVO_2max as determined by CPET and a reduction of ≥1 NYHA class or 2. an improvement of ≥3.0 mL/kg/min in pVO_2max with no worsening in NYHA class, compared with placebo (36.6% vs 17.2%, respectively; treatment difference: 19.4%, 95% CI: 8.67, 30.13; p=0.0005). Additionally, the percentage of subjects meeting both primary endpoint components (at least 3·0 mL/kg per min pVO_2max increase and at least one NYHA class improvement) was higher for the mavacamten group compared with the placebo group (20.3% vs 7.8%, respectively; treatment difference: 12.5%, 95% CI: 4.02, 21.01). Nevertheless, it should be noted that the majority of the mavacamten group (63.4%) did not achieve the composite primary endpoint, i.e. non-responders. As mentioned earlier, exercise capacity in terms of pVO_2max is acceptable as a primary efficacy endpoint; however, the composite primary endpoint, which is based on pVO_2max and NYHA class, is difficult to interpret and not adequately justified. As such, the focus in order to assess the B/R was mainly on the data of the individual component pVO_2max, which was the second sequentially tested secondary endpoint in this study (please see below, secondary endpoints).

Further, subgroup analyses with respect to age, gender, BMI, LVEF at baseline, NYHA class, type of exercise testing, NT-proBNP at baseline, and HCM genotype generally showed consistent results. However, a heterogeneity of effect was observed with respect to beta-blocker usage at baseline; Subjects who were not using beta-blocker showed a greater magnitude of the treatment effect for the primary composite endpoint compared with subjects who were using beta-blockers (between-group difference 52.6%; 95% CI: 32.9, 72.2 vs between-group difference 8.7%; 95% CI: -3.6, 21.1, respectively). This difference is the result of the blunting effect of beta-blockers on cardiopulmonary exercise testing (CPET) performance, which is reflected by the lower baseline mean peak heart rate, i.e. 118 beats/min vs 138 beats/min, and lower baseline mean pVO_2max (19.0 ml/kg/min vs 20.5 ml/kg/min) during exercise for subjects using beta-blockers compared with subjects not using beta-blockers, respectively. Moreover, the change in VE/VO2 slope, a heart rate independent parameter of CPET, showed similar improvements in both treatment groups, regardless of beta-blocker use (treatment difference of -2.9 and -2.6 for subjects using beta-blockers compared with subjects not

using beta-blockers, respectively). Additionally, post-hoc subgroup analyses by beta-blocker use for the measurement of patient symptoms (NYHA class), health status (KCCQ-23), cardiac structure (LVOT gradient, LVEF, LAVI, and LVMI), and cardiac biomarkers (NT-proBNP and Hs-cTn1) also showed approximately similar improvements in both treatment groups, regardless of beta-blocker use. Nevertheless, the main evidence for similar efficacy in patients regardless of their beta-blocker use comes from the VALOR-HCM study, which used a more robust ("hard") clinical endpoint, i.e. the composite of a patient decision to proceed with septal reduction therapy (SRT) or eligibility for SRT according to the ACCF/AHA 2011 guidelines after 16 weeks of treatment. A beta-blocker subgroup analysis of VALOR-HCM data showed similar improvements in SRT eligibility, regardless of beta-blocker use (treatment difference: 52.41% beta-blocker no vs 61.71% beta-blocker yes). Therefore, it can be concluded, that the totality of evidence demonstrates similar efficacy of mavacamten in oHCM patients regardless of their beta-blocker status.

Treatment with mavacamten resulted in significant improvements compared to placebo for all secondary endpoints, including post-exercise LVOT peak gradient, pVO_2max, KCCQ-23 CSS, and HCMSQ SoB domain score.

Peak VO_2max, which was the second sequentially tested secondary endpoint in this study (after LVOT), is considered the most important efficacy endpoint. Mavacamten demonstrated a significant increase in pVO_2max of 1.4 ml/kg/min compared with placebo (1.4 ml/kg/min vs -0.05 ml/kg/min, respectively; 95% CI: 0.59, 2.12; p=0.0006). This corresponds to an absolute mean change in pVO_2max of 18.9 ml/kg/min at baseline to 20.4 ml/kg/min at week 30. In order to justify that this increase in pVO_2max of 1.4 ml/kg/min compared to placebo is clinically relevant, the applicant referred to the Heart Failure and a Controlled Trial Investigating Outcome of Exercise Training (HF-ACTION) trial. The HF-ACTION study was a multicenter clinical trial designed to study the effects of exercise training on mortality and morbidity in 23331 patients with NYHA class II-IV chronic systolic HF receiving guideline-based optimal medical therapy. The results of this trial showed that improvements in pVO_2max correlates with improved clinical outcomes (Swank AM, 2012): every 6% increase in pVO_2max (0.9 mL/kg/min) adjusted for other significant predictors, was associated with a 5% lower risk of the primary endpoint (hazard ratio=0.95; CI=0.93-0.98; P<0.001) – time to all-cause mortality or all-cause hospitalization; a 4% lower risk of the secondary end point of time to cardiovascular mortality or cardiovascular hospitalization (hazard ratio=0.96; CI=0.94-0.99; P<0.001); an 8% lower risk of cardiovascular mortality or heart failure hospitalization (hazard ratio=0.92; CI=0.88-0.96; P<0.001); and a 7% lower all-cause mortality (hazard ratio=0.93; CI=0.90-0.97; P<0.001). The HF-ACTION is suggested the largest study to address whether a change in pVO_2max is related to mortality and morbidity in patients with chronic HF, however, the study had several limitations. First, the exercise intervention was not blinded to patients and site investigator due to the nature of the intervention, however, all cardiopulmonary exercise (CPX) tests were reviewed by blinded experts from a core laboratory. Secondly, almost 30% of the randomized subjects were excluded from the analyses because they either did not have a baseline or 3-month CPX test or experienced a primary outcome before the 3-month test, which may could have biased the outcome. Furthermore, it remains uncertain whether the results of the HF-ACTION study can be directly extrapolated to the EXPLORER-HCM study since the population is different; The HF-ACTION trial enrolled a broader HF population, however, with reduced LVEF (≤ 35%), whereas the EXPLORER study included patients with obstructive HCM with normal LVEF (> 55%). Additionally, the subjects enrolled in the HF-ACTION study received exercise as intervention vs. mavacamten in EXPLORER-HCM. Exercise positively affects the body in many different ways, which may have contributed to the improved clinical outcome observed in the HF-ACTION trial. After all, the improvement in pVO_2max after exercise training was relatively modest (0.6 ml/kg/min vs 0.2 ml/kg/min for usual care alone).

The most important support for the clinical relevance of the effect on pVO_2max observed in the EXPLORER-HCM study can be derived from the ongoing VALOR-HCM study (see below).

The effect of mavacamten on exercise capacity (pVO_2max) was supported by a significant reduction in post-exercise LVOT gradient of -35 mmHg in the mavacamten group compared to placebo (-47 mmHg vs -10 mmHg; 95% CI: -43.2, -28.1; p<0.0001). This corresponds to an absolute mean change in post-exercise LVOT gradient from 86 mmHg at baseline to 38 mmHg at week 30, which is below the level of consideration for septal reduction therapy (SRT) of ≥50 mmHg but still above the ≥30 mmHg criterion that defines obstruction in HCM patients. With respect to Valsalva LVOT gradient, an effect on this parameter was already observed at Week 4, decreased more gradually from Week 4 to Week 18 and stabilized from Week 18 to Week 30. The absolute change from baseline to Week 30 was -49 mmHg in the mavacamten group and -12 mmHg in the placebo group. Similar effects for the changes from baseline to Week 30 were found for resting LVOT gradient with -39 mmHg and -6 mmHg for the mavacamten and the placebo group, respectively. The effects returned to baseline following 8 weeks of study drug washout, indicating that the effect on resting and Valsalva LVOT peak gradient is reversible.

Relief of symptoms was further demonstrated by a higher percentage of subjects who had a ⩾1 class improvement from baseline in NYHA class in the mavacamten group compared with the placebo group (65.0% mavacamten vs 31.3% placebo; treatment difference 33.8, 95% CI: 22.15, 45.43; p <0.0001). Only one subject worsened in NYHA class (from NYHA class II to class III). Moreover, mavacamten treatment compared with placebo was also associated with greater improvements in health status measured by KCCQ-23 CSS (mean (SD) of 13.6 (14.42) vs 4.2 (13.68), 95% CI: 5.46, 12.66; p<0.0001) and HCMSQ SoB score (mean (SD) of -2.8 (2.68) vs -0.9 (2.41), 95% CI: -2.40, -1.20; p<0.0001). Nevertheless, the improvements in KCCQ-23 (between-group treatment difference: 9.1; p<0.0001) and HCMSQ SoB (between-group treatment difference: -1.8 ; p<0.0001) were both just below the clinically meaningful within-patient change threshold of increase of ⩾10 and decrease ≥ 2.5 points, respectively. These results question the clinical relevance of treatment with mavacamten. Responders using these clinically meaningful within-patient change thresholds for KCCQ-23 and HCMSQ SoB were 53.9% vs 33.8% (treatment difference: 20.1%) (increase ⩾10 points mavacamten vs. placebo) and 50.0% vs. 21.3% (treatment difference: 28.7%%) (decrease ≥ 2.5 points mavacamten vs. placebo), respectively.

With respect to exploratory endpoints, improvement in exercise performance and cardiac output was further supported by improvement in peak VE/VCO_2, VE/VCO_2 slope, peak circulatory power, ventilatory power, peak MET, percent predicted VO_2 and ventilatory threshold as measured by cardiopulmonary testing. Furthermore, consistent with the MoA of mavacamten, which causes reduced contractility, treatment with mavacamten resulted in a slight increase in left ventricular end-systolic volume index (LVESVI). Further effects of mavacamten were reductions in the percentage of subjects with systolic anterior motion (SAM) of the mitral valve and mitral regurgitation, E/e', and LAVI, suggesting improvements in LV filling during diastole, i.e. improved diastolic function. No differences were observed with respect to LV stroke volume (LVSV), heart rate, and cardiac output, which is reassuring since these are important indicators of cardiac function. Moreover, treatment with mavacamten resulted in a reduction in NT-proBNP and cardiac troponin, indicating a reduction in LV wall stress and myocardial injury. At week 38, following 8 weeks of study drug washout, NT-proBNP levels returned to baseline for the mavacamten, indicating that this effect is reversible.

LVEF was measured to ensure subject safety/tolerability. Subjects in the mavacamten group showed a small decrease in LVEF (-4% [7.7%]) during 30 weeks of treatment compared with the placebo group (-4% vs -0.01%), which is consistent with the mavacamten mechanism of action.

The pivotal study included a cardiac magnetic resonance (CMR) substudy to assess the change from baseline to Week 30 in the left ventricular mass index (LVMI) (primary endpoint). Treatment with mavacamten resulted in a favourable effect on cardiac remodelling as shown by a reduction in the LV mass index (mean difference -15.8 g/m^2; 95% CI:-22.6, -9.0; p<0.0001), and a reduction in the exploratory endpoints of LV maximal wall thickness (mean difference -2.4 mm; 95% CI: -3.9, -0.9; p <0.0079), and in left atrial volume index over the 30-week treatment period. At the same time, myocardial contraction fraction and contractile fraction (stroke volume/LV mass ratio), which are load-independent measures of LV pump reserve, were maintained, which is reassuring.

- *Study MYK-461-017 (VALOR-HCM)*

In this study, 112 subjects (56 subjects to each arm) were randomized of which 111 received at least 1 dose of the study drug. The study is still ongoing, and as of 07 February 2022, all subjects participating in the study completed the study through Week 16 (primary analysis timepoint). The percentage of subjects who completed 16 weeks of treatment (double-blind period) was high (99.1%) and similar between the mavacamten and placebo group (100.0% and 98.2%, respectively).

Twelve subjects (21.4%) in the mavacamten group had a dose reduction to 2.5mg, indicating that a relatively high percentage could not tolerate the 5 mg dose. Nevertheless, considering that no subjects in the mavacamten group discontinued treatment in the double-blind period, indicates that the lower 2.5 mg is well tolerated by these subjects. The most frequent dose received was 10 mg (33.9%) followed by 5 mg (23.2%) and 15 mg (21.4%).

Important protocol deviations (IPD) were generally well balanced between both groups (25.0% and 26.8% in the mavacamten and placebo group, respectively). Furthermore, there was minimal impact of the COVID-19 pandemic.

This study was a multicentre study (n=19) conducted in the USA. Consequently, all subjects were from the USA. A post-hoc analysis has been conducted (see below) which showed that consistent results in terms of proportion of SRT eligibility, LVOT gradients decrease, and improvements in NYHA class, KCCQ-23 CSS, and NT-proBNP were found between the VALOR-HCM study conducted in the USA and EXPLORER-HCM study conducted worldwide of which 50% of the subjects were enrolled in Europe. Based on these findings, it might be acceptable to extrapolate the results of the VALOR-HCM study to the European population.

The recruited patients reflect a population of oHCM regarding demographics, comorbidities and guideline-directed medical therapies for oHCM, which are generally well distributed across the two treatments, although a few exceptions are observed. The mean age was 60.3 years and halve of the subjects were male (50.9%). At baseline, the majority of subjects had NYHA Class III (92.0%) and the median NT-proBNP level was 743 ng/L and the median cardiac Troponin I was 14.7 ng/L. A slightly higher proportion of subjects in the mavacamten group had atrial fibrillation, a known complication of HCM, compared with the placebo group (19.6% vs 14.5 %, respectively) (see safety for further discussion). Furthermore, a slightly higher proportion of subjects in the mavacamten group received beta-blocker agents at baseline compared with the placebo group (78.6% vs 69.1%, respectively). However, on the contrary, a slightly lower proportion of subjects in the mavacamten group received calcium channel blockers compared with the placebo group (25.0% vs 38.2%, respectively). This indicates that both groups received comparable intensive HCM therapy. With respect to CYP2C19 metabolizer phenotype, the majority of subjects were rapid metabolizers (28.6%), normal metabolizers (27.7%) or intermediate metabolizers (22.3%). Similarly as in the EXPLORER-HCM study, only few poor metabolizers were included in the VALOR-HCM study (n=2 in the mavacamten group).

Therefore, CYP2C19 PM has been included as missing information in the summary of safety concerns of the RMP.

Treatment with mavacamten resulted in a substantially lower proportion of subjects meeting the primary endpoint of decided to proceed with SRT or remained SRT guideline eligible (17.9% (10/56) vs 76.8% (43/56) for placebo; treatment difference (95% CI): 58.93% (43.99, 73.87), p<0.0001). Since only two patients in each treatment group underwent SRT, the primary endpoint was mainly driven by the proportion of subjects who met guideline criteria for SRT (14.3% (8/56) vs. 69.6% (39/56). Additionally, 2 subjects in the placebo group vs non in the mavacamten group had a SRT status not evaluable.

The question is whether the overall positive, beneficial results of the VALOR-HCM study can be extrapolated to the entire target population of the EXPLORER-HCM study, including the less compromised NYHA class II subpopulation. In this respect, the applicant has adequately justified the extrapolation based on 4 aspects: 1) *Overlapping study populations*. Despite a different distribution in NYHA class (NYHA class III 92% vs. 27% for VALOR-HCM and EXPLORER-HCM, respectively), the study population in the VALOR-HCM and EXPLORER-HCM were generally comparable including a similar level of obstruction at baseline (mean (SD) resting, Valsalva and post-exercise LVOT gradients of 49 (30.9), 76 (30.2), and 84 (35.8) mmHg in the VALOR-HCM study vs 51 (31.9), 74 (32.0) and 84 (35.7) in the EXPLORER-HCM study, respectively), a similar percentage of subjects using beta-blockers (BB) as concomitant medication (75% were on BB monotherapy or combination therapy (BB with CCB and/or disopyramide) in the VALOR-HCM study vs 75.3% on BB monotherapy in the EXPLORER-HCM study), a similar duration of oHCM (5.4 vs 5.5 years median respectively) and a similar level of NT-proBNP at baseline (740 vs 710 ng/L median, respectively); 2) *Consistent results for endpoints assessed in both studies*. The results from secondary and exploratory endpoints were consistent across both studies, even though the majority of subjects in the EXPLORER-HCM study were NYHA class II (72.9% versus 0.9% in the VALOR-HCM study). More specifically, the study populations of the VALOR-HCM and the EXPLORER-HCM had a comparable level of LVOT obstruction at baseline and magnitude of treatment effect regarding LVOT gradient decrease (-37 vs -36 mmHg, respectively) and showed approximately similar improvements in NYHA class (improved ≥1: 41 vs 34 %,), KCCQ-23 CSS (9.5 vs 9.1), and NT-proBNP (0.33 vs 0.20 GM ratio to BL). Moreover, within the EXPLORER-HCM study, consistent results were seen for key efficacy endpoints regardless of NYHA class, including LVOT gradient (-38.4 vs -33.0 mmHg for Class II and Class III respectively), pVO_2 (1.5 vs 1.33 mL/kg/min, respectively), NYHA class (improved ≥1: 34 vs 32 %, respectively), and KCCQ-CSS (10 vs 7, respectively).; 3) *Consistent results on septal reduction therapy eligibility*. A post-hoc analysis has been conducted which showed that, consistent with the VALOR-HCM data, in the EXPLORER-HCM of the patients who were NYHA Class III (n=68), a lower percentage of patients in the mavacamten group compared with the placebo group remained SRT eligible at week 30 (3/35 (8.6%) vs 13/33 (39.4%), respectively). Although the magnitude of the treatment difference is smaller than that observed in the VALOR-HCM study, the results are directionally consistent. Based on the data described above, it is considered acceptable to extrapolate the clinically relevant results of the VALOR-HCM study to oHCM patients who were NYHA class III in the EXPLORER-HCM study. Regarding the NYHA Class II subpopulation of the EXPLORER-HCM study, a total of 183 subjects were NYHA Class II and were not eligible for SRT, although their level of LVOT obstruction ≥50 mmHg places them at risk for progression from Class II to Class III. Prespecified exploratory analysis in the entire EXPLORER-HCM study, of which the majority was NYHA Class II, showed that 74% on mavacamten vs 21% on placebo had post-exercise LVOT gradients <50 mmHg (below SRT eligibility criteria). Additionally, results of the EXPLORER-LTE cohort of the long-term extension (MYK-461-007) showed durable reductions in Valsalva LVOT gradient and NYHA class below the threshold for SRT in the majority of participants. Therefore, it is agreed with the applicant that these findings indicate that also for the NYHA Class II population, reducing the level of LVOT obstruction <50 mmHg and maintaining their NYHA class below III with mavacamten treatment is

important in preventing patients from progressing to SRT eligibility, which is considered clinically relevant; 4) *Comparable safety profile*. It is acknowledged that compared to the EXPLORER-HCM safety results, no new safety signals with mavacamten treatment were seen in the VALOR-HCM study. Based on the above, it is acknowledged that data from EXPLORER-HCM and VALOR-HCM demonstrate that mavacamten treatment results in clinically relevant improvements across the entire population of symptomatic NYHA Class II-III oHCM patients.

Further subgroup analyses of the primary endpoint for VALOR-HCH with respect to age, baseline resting LVOT gradient, duration since oHCM diagnosis, beta-blocker use at baseline, number of background HCM medication and baseline NT-proBNP showed consistent results. However, heterogeneity of effect was observed with respect to gender (75.4% for males vs. 41.9% in females), BMI, (71.5% for BMI <30 vs 42.7% for BMI ≥30) and calcium channel blockers (69.3% for N vs 38.3% for Y), but all treatment effects were considered clinically relevant. Moreover, the number of subjects receiving calcium channel blocker were relatively low (n=16 vs 23 in the mavacamten and placebo, respectively), and should therefore be interpreted with caution.

Regarding long-term follow-up, as of the 07-February-2022 data cut, 71 subjects were randomized at least 32 weeks (38 subjects in the mavacamten group and 33 in the placebo group). After the Week 16 assessments, subjects in the mavacamten group continued blinded mavacamten administration on the dose they were receiving at Week 16, and subjects in the placebo group began dosing with mavacamten 5mg. In the previous placebo group, 2 out of 33 (6.1%) subjects with Week 32 data proceeded to SRT, and 3 out of 33 (9.1%) subjects remain SRT eligible. These data is similar as those observed in the mavacamten group in the double-blind period. In the previous mavacamten group, 2 out of 38 (5.3%) subjects have proceeded to SRT and 2 out of 38 (5.3%) are SRT guideline eligible, which suggest maintenance of treatment effect or even increased magnitude of effect at Week 32.

Furthermore, mavacamten treatment resulted in significant improvements compared to placebo on secondary endpoints of post-exercise LVOT gradient (treatment difference (95% CI): -37.2 (-48.08, -26.24) mmHg; p<0.0001), ≥1 NYHA class improvement (treatment difference (95% CI): 41.07 (24.48, 57.66); p<0.001), improvement in KCCQ- 23 CSS (treatment difference (95% CI) 9.45 (4.868, 14.041) points; p<0.0001) and NT-proBNP and cardiac troponin I between groups geometric mean ratio, 0.33 (0.266, 0.421) and 0.53 (0.406, 0.700); both p<0.0001). Maintenance of effect after 32 weeks of treatment has also been demonstrated for these secondary endpoints.

With respect to exploratory endpoints using transthoracic echocardiography, the effect on these endpoints seen after 16 weeks in the VALOR-HCM study was consistent with what was observed after 30 weeks of treatment in less severe oHCM patients in the EXPLORER-HCM study.

Supportive data are obtained from the ongoing long-term extension studies MAVA-LTE (Study MYK-461-007; EXPLORER-LTE cohort) and PIONEER-OLE (Study MYK-461-008).

The MAVA-LTE study (Study MYK-461-007) is an ongoing Phase II/III, dose-blinded, 5-years long-term extension (LTE) study to evaluate the safety, and tolerability of mavacamten in subjects with symptomatic HCM who completed the pivotal Phase 3 MYK-461-005 (EXPLORER-HCM) study through Week 38 (EXPLORER-LTE Cohort). After the washout period (minimal 8 weeks) of the parent study, subjects enrolled in this LTE started with 5 mg mavacamten. The LTE study was designed as a dose-blinded study as it was being run in parallel to the parent study and evaluating the safety and utility of a clinically guided dose titration protocol. At week 4, 8, and 12 the dose could be adjusted based on Valsalva LVOT gradient and LVEF, and the dose could be adjusted based on post-exercise LVOT gradient and LVEF at Week 24. At any visit after Week 24, if the site-read LVOT gradient with Valsalva manoeuvre was > 30 mmHg and LVEF ≥50%, then a dose increase to a maximum of 15 mg could be considered after discussion with the Medical Monitor. At baseline of the LTE study, the mean LVEF (74%), mean resting LVOT gradient (48 mmHg) and mean Valsalva LVOT gradient (69 mmHg) were

approximately similar compared with the baseline of the parent study (74%, 51 mmHg, and 73 mmHg, respectively). As of the latest data cut-off of 31 August 2021, there were a total of 231 subjects enrolled, of which the majority (88.8%) had completed mavacamten treatment through at least week 48 and 14.7% of the subjects reached week 96. The LTE study showed that mavacamten was well tolerated and remained stable from week 24 up to week 96, with the majority (~55%) of the patients on 5 or 10 mg and approximately ~15 % on the highest daily dose of 15 mg. pVO_2max, which is considered the most relevant efficacy endpoint in support of the indication, has only been assessed in the parent study EXPLORER-HCM and not in this LTE study; as such, maintenance of effect on pVO_2max has not been demonstrated. As of the cut-off date of 31 August 2021, improvements in LVOT gradients in the EXPLORER-LTE cohort of the MAVA-LTE study were consistent with those in the parent study; Mavacamten demonstrated a reduction in resting and Valsalva LVOT gradient of -35.6 mmHg and -45.3 mmHg from LTE baseline to Week 48. Post-exercise LVOT gradient was not assessed at baseline of the MAVA-LTE study; however, an exercise test was performed at Week 24. The mean post-exercise gradient was 42 mmHg, which is approximately comparable to the post-exercise LVOT gradient at Week 30 of 38 mmHg in the mavacamten group in the parent study. Improvements in NYHA class were approximately consistent to those observed in the parent study. Furthermore, consistent with the parent study, mavacamten resulted in a slight increase in LVESVI, due to reduced contractility and decreases in the percentage of subjects with systolic anterior motion (SAM) of the mitral valve and mitral regurgitation and decreases in E/e', LAVI, indicating improved diastolic function. Moreover, mavacamten resulted in a small favourable effect on cardiac remodelling (measured by TTE), as shown by small reductions in LVMI. With respect to safety, LVEF remained stable through 96 weeks of continuous mavacamten treatment remaining at approximately 65%, which is reassuring. Overall, the results demonstrated that subjects receiving mavacamten in this LTE study continue to experience therapeutic benefit generally consistent with that achieved in the parent with respect to LVOT gradient, NYHA class, and other TTE parameters. However, maintenance of effect on pVO_2max has not been demonstrated as this has not been assessed in this LTE.

Study MYK-461-008 is an ongoing Phase II, open-label, 5-years long-term extension (LTE) study to evaluate the safety, tolerability of mavacamten in subjects with symptomatic HCM who completed the 16-week PIONEER-HCM study (MYK0461-004). Individualized target doses, which were based on maintaining a study drug plasma concentration between approximately 250 ng/mL and 500 ng/mL were determined for each subject prior to the start of the study. Due to these individualized target doses based on mavacamten plasma levels, which were slightly lower compared to the levels achieved in the pivotal study, the supportive value of this study is considered limited. Overall, consistent with the parent study (and other clinical studies such as pivotal EXPLORER-HCM and EXPLORER-LTE cohort in MAVE-LTE studies), mavacamten resulted in beneficial effects as shown by reductions in resting, Valsalva and post-exercise LVOT gradient from baseline to Week 144, improvements in NYHA class and KCCQ scores. Additionally, also consistent with other clinical studies, modest mean changes in LVEF were observed and LVEF was maintained above 50% in all subjects throughout the observation period.

2.5.7. Conclusions on the clinical efficacy

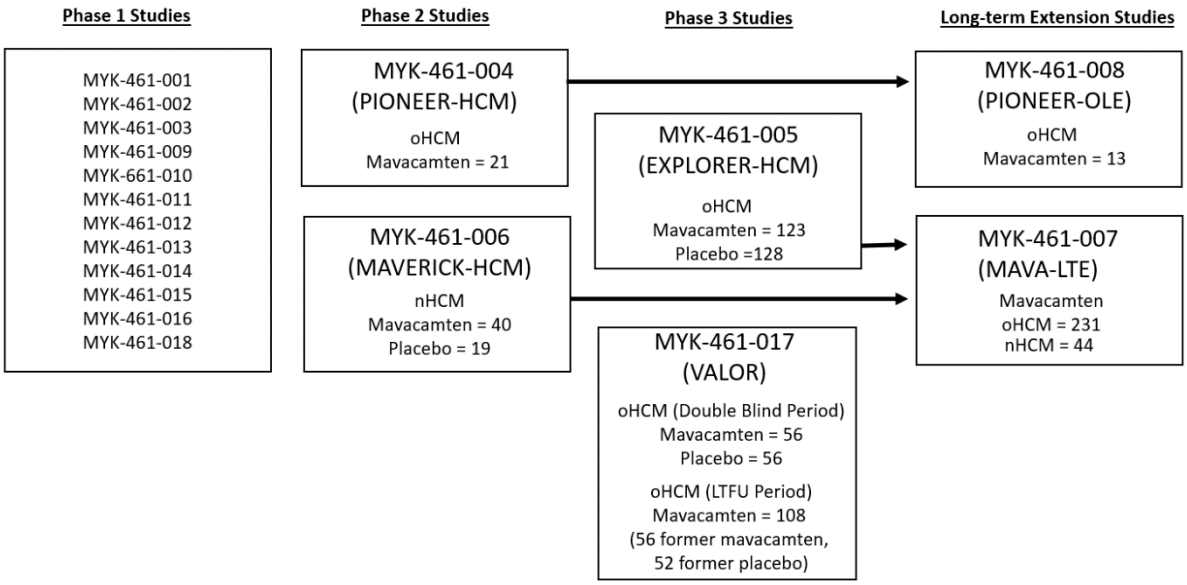
Mavacamten resulted in clinically relevant improvements in exercise capacity (pVO_2max) and prevented patients from (progressing to) septal reduction therapy eligibility across the entire population of symptomatic NYHA Class II-III oHCM patients. These improvements were further supported by improvements in LVOT gradient, NYHA class, patient-reported outcomes, and cardiac function and structure.

2.5.8. Clinical safety

Clinical safety data supporting the application are presented as integrated analyses of pooled safety data from five clinical studies with a cut-off date of 31 August 2021 (Figure 43). These studies include:

- One pivotal phase 3 double-blind, placebo-controlled study (MYK-461-005) in subjects with oHCM.
- Two phase 2 proof-of-concept studies in subjects with oHCM and nHCM (MYK-461-004 and MYK-461-006, respectively).
- Two ongoing extension studies (MYK-461-007 and MYK-461-008) in patients previously enrolled in the pivotal phase 3 study and the phase 2 studies.

Figure 43. Mavacamten clinical development program



LTE = long-term extension; nHCM = nonobstructive hypertrophic cardiomyopathy; oHCM = obstructive hypertrophic cardiomyopathy; MAVA = mavacamten; OLE = open-label extension

For the studies MYK-461-004 and -005 the evaluation of the safety and tolerability of mavacamten, including CV effects, was one of the secondary endpoints. For MYK-461-006, this was a primary endpoint. For studies MYK-461-007 and -008, evaluation of the long-term safety and tolerability, including CV effects, of mavacamten was the primary endpoint.

VALOR-HCM study (MYK-461-017)

All safety data for the ongoing VALOR-HCM study (MYK-461-017) up to a cut-off date of 7 February 2022 are presented. These data are presented and assessed separately in addition to the integrated analyses of pooled safety data from the five earlier mentioned clinical studies and include the primary analysis of the double-blind period (Day 1 to Week 16) in subjects treated with either mavacamten (N = 56) or placebo (N = 55), and data from all mavacamten exposure (N = 108) through Week 80.

Integrated populations

The integrated populations for the analyses are designated as the following:

- All-Mava (N=314): subjects in the five studies who received at least one dose of mavacamten (All-Mava oHCM; N=260) and nHCM (All-Mava nHCM; N=54).
- RCT-Mava (N= 162): subjects from the two randomized, double-blind, placebo-controlled studies (Study MYK-461-005 and Study MYK-461-006) who were treated with mavacamten (RCT-Mava oHCM; N= 123) and nHCM (RCT-Mava nHCM; N= 39).
- RCT-Placebo (N= 147): subjects from the two randomized, double-blind, placebo-controlled studies (Study MYK-461-005 and Study MYK-461-006) who received only placebo (RCT-Placebo oHCM; N= 128) and nHCM (RCT-Placebo nHCM; N= 19).

2.5.8.1. Patient exposure

Duration of exposure in the integrated analyses

Due to study the design, the maximum possible length of treatment time for subjects participating in the pivotal Study MYK-461-005 was 30 weeks (a 30-week treatment period). In the RCT-Mava oHCM treatment group (i.e. mavacamten-treated subjects in the pivotal Phase 3 Study MYK-461-005), 98.4% and 97.6% of subjects completed at least 3 and 6 months of mavacamten treatment, respectively, with a median duration of exposure of 7.0 months. Total exposure was 70.87 patient-years (850.46 patient months; Table 48).

Table 48. Duration of exposure in the integrated studies

	All-Mava combined N = 314 n (%)	oHCM		nHCM	
		RCT-Mava N = 123 n (%)	RCT-Placebo N = 128 n (%)	RCT-Mava N = 39 n (%)	RCT-Placebo N = 19 n (%)
Total patient-months of exposure	6330.87	850.46	882.56	143.70	72.28
Total patient-years of exposure	527.57	70.87	73.55	11.98	6.02
Duration of Exposure (Months)					
N	314	123	128	39	19
Duration of Exposure					
≤ 3 months	18 (5.7)	2 (1.6)	1 (0.8)	4 (10.3)	0
> 3-6 months	11 (3.5)	1 (0.8)	2 (1.6)	35 (89.7)[b]	19 (100.0)[b]
> 6-12 months	29 (9.2)	120 (97.6)[b]	125 (97.7)[b]	0	0
> 12-18 months	58 (18.5)	0	0	0	0
> 18-24 months	86 (27.4)	0	0	0	0
> 24-30 months	74 (23.6)	0	0	0	0
> 30 months	38 (12.1)	0	0	0	0

a Duration of exposure is defined as (last dose date – first dose date + 1 day) within a single study, regardless of intermittent discontinuations. Adjusted duration of exposure excludes the time off drug due to temporary interruptions. b Based on study design, the maximum planned length of treatment time for RCT-Mava oHCM and RCT-Placebo oHCM was approximately 7 months, and the maximum planned length of treatment time for RCT-Mava nHCM and RCT-Placebo nHCM was approximately 4 months. c duration of exposure includes duration of exposure from parent + extension studies for individual subjects and does not include the time between parent and extension studies.

VALOR-HCM study (MYK-461-017) - double-blind period

All subjects completed the 16-week placebo control period except for the 2 placebo subjects who discontinued the study and the 4 (2 in each arm) subjects who went to SRT prior to Week 16. The mean (SD) duration of exposure was 17.0 (2.13) weeks for subjects who received mavacamten and 16.5 (2.85) weeks for subjects who received placebo.

VALOR-HCM study (MYK-461-017) - long-term follow-up

Overall, the mean (SD) duration of exposure was 32.59 (20.012) weeks for all the subjects (n=108) who received mavacamten during the DB period and LTFU. Nearly half of subjects have had 32 weeks of mavacamten exposure at time of this data cutoff (Table 49).

Table 49. Counts of Subjects with a Certain Duration of Mavacamten Exposure - Long-Term Follow-up.

	Duration of Mavacamten Exposure				
	16 Weeks	**32 Weeks**	**44 Weeks**	**56 Weeks**	**68 Weeks**
Previous Mavacamten (N=56)	55 (98.2)	37 (66.1)	26 (46.4)	13 (23.2)	5 (8.9)
Previous Placebo (N=52)	31 (59.6)	16 (30.8)	7 (13.5)	1 (1.9)	0
Total Mavacamten (N=108)	86 (79.6)	53 (49.1)	33 (30.6)	14 (13.0)	5 (4.6)

Duration of exposure is calculated as the planned duration of exposure from start of mavacamten treatment to end of treatment (or data cutoff date).

Average and Cumulative Dose Exposure

A summary of average daily and cumulative study treatment exposure is provided in Table 50 below.

Table 50. Average daily and cumulative study treatment exposure in the safety database

	All-Mava combined N = 314 n (%)	oHCM		nHCM	
		RCT-Mava N = 123 n (%)	RCT-Placebo N = 128 n (%)	RCT-Mava N = 39 n (%)	RCT-Placebo N = 19 n (%)
Average Daily Dose (mg)[a]					
N	314	123	128	39	19
Mean ±SD	6.89 (3.465)	6.69 (2.242)	0.00 (0.000)	6.81 (2.517)	0.00 (0.000)
Median	5.68	5.78	0.00	5.42	0.00
Q1, Q3	4.18, 9.20	4.97, 8.46	0.00, 0.00	4.91, 8.31	0.00, 0.00
Min, Max	2.2, 15.1	2.2, 11.6	0.0, 0.0	2.3, 11.8	0.0, 0.0
Actual Cumulative Dose (mg)					
N	314	123	128	39	19
Mean ±SD	4257.4 (3262.73)	1410.9 (508.65)	0.0 (0.00)	760.6 (300.72)	0.0 (0.00)
Median	3491.3	1210.0	0.0	620.0	0.0
Q1, Q3	1830.0, 5660.0	1055.0, 1800.0	0.0, 0.0	550.0, 980.0	0.0, 0.0
Min, Max	60, 17285	60, 2510	0, 0	255, 1360	0, 0

Abbreviations: HCM = hypertrophic cardiomyopathy; Mava = mavacamten; Max = maximum; Min = minimum; oHCM = obstructive hypertrophic cardiomyopathy; nHCM = non-obstructive hypertrophic cardiomyopathy; Q = quartile; SD = standard deviation. [a] Average daily dose is defined as the cumulative dose of study drug divided by the duration of exposure. NC=not calculable.

VALOR-HCM study (MYK-461-017) – double-blind period

The most frequent dose received was 10 mg. Other doses were evenly distributed during the double-blind period at Week 16 (Table 51).

Table 51. Summary of Dose Levels at Week 16 - Safety Analysis Population (Double-Blind Period VALOR Study)

Last Dose Level (mg)	**Mavacamten N = 56 n (%)**
2.5	12 (21.4)
5	13 (23.2)
10	19 (33.9)
15	12 (21.4)

The dose levels during long-term follow-up are presented in the table below. The most frequent dose received was 10 mg.

Table 52. Summary of mavacamten dose levels- Long-term follow up

	During the 56 Weeks of Treatment[a]										
Last Dose Level (mg)	**Overall Mavacamten Group N = 108**										
	Weeks of Mavacamten Exposure, n (%)										
	Day 1	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**44**	**56**
2.5	0	42 (38.9)	23 (21.3)	17 (15.7)	16 (14.8)	12 (11.1)	11 (10.2)	11 (10.2)	12 (11.1)	7 (6.5)	1 (0.9)
5	108 (100.0)	54 (50.0)	29 (26.9)	21 (19.4)	19 (17.6)	8 (7.4)	10 (9.3)	9 (8.3)	12 (11.1)	6 (5.6)	4 (3.7)
10	0	0	39 (36.1)	33 (30.6)	30 (27.8)	15 (13.9)	13 (12.0)	11 (10.2)	19 (17.6)	12 (11.1)	4 (3.7)
15	0	0	0	17 (15.7)	12 (11.1)	9 (8.3)	7 (6.5)	6 (5.6)	8 (7.4)	6 (5.6)	5 (4.6)
Missing	0	12 (11.1)	17 (15.7)	20 (18.5)	31 (28.7)	64 (59.3)	67 (62.0)	71 (65.7)	57 (52.8)	77 (71.3)	94 (87.0)

Source: Table 14.1.5.4 and Table 14.1.5.5 in the CV027006 Primary CSR

[a] Only the dose level observed at scheduled visits are summarized. Unscheduled visits are not shown. The data was collected from Day 1 until EOT for mavacamten treatment and from Week 16 until EOT for placebo to mavacamten treatment.

The missing dose data at a visit are due to (1) early treatment termination; (2) drug interruption; (3) no bottle dispensed on the scheduled visit but on an unscheduled visit; or (4) pill counts indicated no pills taken from the bottle. (5) subjects that have not reached that visit yet.

Time interval between treatment in parent and extension studies

Subjects who completed treatment in the parent studies (mavacamten or placebo) had a washout/follow-up period prior to enrolling and being exposed again to study treatment in the extension studies (mavacamten).

The mean time from last dose in the pivotal study MYK-461-005 for subjects in the mavacamten arm until the first dose in extension study MYK-461-007 was 15.7 weeks (total 115 subjects), and the mean time from last dose in the supporting study MYK-461-004 until the first dose in extension study MYK-461-008 was 53.3 weeks (total 13 subjects)(Table 53).

Table 53. Duration of treatment interval between parent and extension studies

	Treatment Group in Parent Study		
	Mavacamten (Active)	Placebo	Overall
Time from last dose in Study MYK-461-005 to first dose in Study MYK-461-007 (Weeks)			
N	115	116	231
Mean (SD)	15.66 (8.794)	18.15 (10.565)	16.91 (9.783)
Median	11.86	13.64	12.00
Q1, Q3	9.57, 21.86	9.86, 23.93	9.86, 22.14
Min, Max	1.7, 54.0	7.7, 59.6	1.7, 59.6

	Treatment Group in Parent Study		
	Mavacamten (Active)	Placebo	Overall
Time from last dose in Study MYK-461-006 to first dose in Study MYK-461-007 (Weeks)			
N	29	15	44
Mean (SD)	17.40 (15.649)	11.83 (4.707)	15.50 (13.184)
Median	12.57	10.29	11.93
Q1, Q3	10.86, 19.14	8.71, 12.43	10.00, 15.86
Min, Max	9.4, 92.4	7.6, 25.0	7.6, 92.4
Time from last dose in Study MYK-461-004 to first dose in Study MYK-461-008 (Weeks)			
N	13	NA	13
Mean (SD)	53.30 (15.704)	NA (NA)	53.30 (15.704)
Median	52.57	NA	52.57
Q1, Q3	38.29, 63.00	NA, NA	38.29, 63.00
Min, Max	30.9, 76.3	NA, NA	30.9, 76.3

Abbreviations: Max = maximum; Min = minimum; NA = not applicable; Q = quartile; SD = standard deviation.

Duration of exposure >1 year in the same study

As only the extension studies had a duration > 1 year, these data for exposure to study drug within a single study are derived only from Studies MYK-461-007 and MYK-461-008.

A total of 245 subjects (207 subjects with oHCM and 38 subjects with nHCM) qualified for a > 1-year duration of exposure in a single study as of the data cut-off. Of the 245 mavacamten-exposed subjects, 100%, 59%, and 25% of subjects completed at least 12, 18, and 24 months of mavacamten treatment, respectively, with a median duration of exposure of 19 months (range 12.0 to 39.8 months)(Table 54). The median average daily dose was 5.45 mg. Total exposure in this analysis was 407 patient-years.

Table 54. Summary of drug exposure > 1 year for subjects in the same study.

	All-Mava (oHCM and nHCM) (N = 245) n (%)	All-Mava (oHCM) (N = 207) n (%)	All Mava (nHCM) (N = 38) n, (%)
Total patient-months of continuous exposure	4885.42	3897.30	988.12
Total patient years of continuous exposure	407.12	324.77	82.34
Duration of continuous exposure[a] (months)			
N	245	207	38
Mean (SD)	19.94 (6.451)	18.83 (6.226)	26.00 (3.729)
Median	19.02	18.23	25.30
Q1, Q3	14.09, 23.95	14.00, 21.42	24.11, 27.60
Min, Max	12.0, 39.8	12.0, 39.8	16.6, 34.9
Duration of continuous exposure			
> 12-18 months	101 (41.2)	100 (48.3)	1 (2.6)
> 18-24 months	83 (33.9)	75 (36.2)	8 (21.1)
> 24-30 months	42 (17.1)	20 (9.7)	22 (57.9)
> 30 months	19 (7.8)	12 (5.8)	7 (18.4)
Cumulative duration of continuous exposure			
> 12 months	245 (100.0)	207 (100.0)	38 (100.0)
> 18 months	144 (58.8)	107 (51.7)	37 (97.4)
> 24 months	61 (24.9)	32 (15.5)	29 (76.3)
> 30 months	19 (7.8)	12 (5.8)	7 (18.4)
Average daily dose (mg)			
N	245	207	38
Mean (SD)	6.94 (3.826)	6.81 (3.835)	7.63 (3.750)
Median	5.45	5.49	5.13
Q1, Q3	3.90, 9.46	2.84, 9.42	4.98, 10.00
Min, Max	2.2, 15.0	2.2, 14.8	2.5, 15.0

Impact of COVID-19 on the collection of safety data

The impact of the COVID-19 pandemic on safety data collection for the pivotal Phase 3 study MYK-461-005 resulted in subjects unable to attend onsite visits for their Week 38/end of study visit. These subjects were allowed to complete assessment visits via telephone contact. A total of 67 subjects completed their Week 38/end of study visit via a telephone conversation with study site personnel to monitor AEs and concomitant medications and assess NYHA class, but many of the protocol-specified assessments were not performed. Missed assessments were included as important protocol deviation categories of study procedures/assessments and/or missing endpoint assessments as described in the CSR. This was the case for 27.1% of subjects, including 25.2% (31 of 123 subjects) in the mavacamten group and 28.9% (37 of 128 subjects) in the placebo group.

The impact of the COVID-19 pandemic on the extension MYK-461-007 study resulted in dose interruptions or missed clinic visits. For subjects already enrolled in the MYK-461-007 study, missed visits that occurred during the dose titration period (ie, initial 12 weeks of the study), presented a potential safety issue necessitating treatment discontinuation for those who were unable to complete the required safety monitoring assessments due to the COVID-19 pandemic. These subjects were discontinued from the study but were allowed to rescreen and restart the study when access to the clinic was possible, resulting in 2 treatment periods for these subjects: a pre-pandemic period and a re-enrollment period. In total, 28 subjects re-enrolled in the study and started treatment again. Among these, the majority (24 [10.4%] subjects) had a dose interruption due to COVID-19, and 4 subjects had to discontinue study treatment for other reasons (2 subjects met stopping criteria and 2 reported an adverse event.

VALOR-HCM study (MYK-461-017) – double-blind period

This study started screening potential subjects in June 2020 and the first subject was randomized on 29-Jul-2020, which occurred during the global COVID-19 pandemic. There was minimal impact to the study conduct due to COVID-19 pandemic over the past two years.

A COVID-19 Risk Assessment Plan was implemented to identify potential risks and mitigation strategies. AE's and protocol deviations pertaining to COVID-19 were assessed and reported per FDA issued guidance. There were two subjects that were unable to complete a study visit within window due to COVID-19 infection (Week 12 and Week 32). Additionally, one subject was hospitalized with COVID-19 and had a delay in week 16 study visit, but the visit was completed within the allowed window.

Virtual/remote Site Initiation Visits (SIV) and interim monitoring visits were performed in lieu of in-person visits as needed due to country and site restrictions, as indicated in the SMP.

Overall, COVID-19 did not impact the overall quality or outcome of the study.

One subject in the mavacamten group had acute COVID-19 infection. There were no dose interruptions or delays due to COVID-19.

2.5.8.2. Adverse events

All adverse events

Table 55 provides a summary of AEs reported for all mavacamten-treated subjects in the integrated analyses (All-Mava combined, includes subjects with oHCM and subjects with nHCM).

Table 55. Overall summary of adverse events (safety population).

	All-Mava combined N = 314 n (%)	oHCM		nHCM	
		RCT-Mava N = 123 n (%)	RCT-Placebo N = 128 n (%)	RCT-Mava N = 39 n (%)	RCT-Placebo N = 19 n (%)
At least 1 AE	291 (92.7)	108 (87.8)	104 (81.3)	35 (89.7)	13 (68.4)
Grade 1	102 (32.5)	53 (43.1)	48 (37.5)	19 (48.7)	7 (36.8)
Grade 2	141 (44.9)	43 (35.0)	42 (32.8)	14 (35.9)	5 (26.3)
Grade 3	42 (13.4)	11 (8.9)	13 (10.2)	2 (5.1)	1 (5.3)
Grade 4	3 (1.0)	1 (0.8)	0	0	0
Grade 5	3 (1.0)	0	1 (0.8)	0	0
Grade ≥3	48 (15.3)	12 (9.8)	14 (10.9)	2 (5.1)	1 (5.3)
At least 1 serious AE (SAE)	58 (18.5)	14 (11.4)	12 (9.4)	4 (10.3)	4 (21.1)
At least 1 drug-related AE	86 (27.4)	19 (15.4)	18 (14.1)	13 (33.3)	1 (5.3)
At least 1 AE leading to study discontinuation [a,b]	12 (3.8)	2 (1.6)	1 (0.8)	0	0
At least 1 AE leading to permanent treatment discontinuation	17 (5.4)	2 (1.6)	0	3 (7.7)	0
At least 1 AE leading to drug interruptions	28 (8.9)	3 (2.4)	6 (4.7)	2 (5.1)	0
At least 1 AE leading to death	3 (1.0)	0	1 (0.8)	0	0

Abbreviations: AE = adverse event; Mava = mavacamten; nHCM = non-obstructive hypertrophic cardiomyopathy; oHCM = obstructive hypertrophic cardiomyopathy; RCT = randomized controlled trial; SAE = serious adverse event. Data presented in this table are treatment emergent.

Subject with TEAE leading to study discontinuation may have reasons other than Adverse Event entered as reason for study discontinuation under disposition (eg, Death, Stopping criteria met, or Other).
3 MYK-461-007 subjects with AE leading to study discontinuation did not permanently discontinue the study per disposition.

VALOR study (MYK-461-017) – double-blind period and long-term follow-up

A summary of the overall adverse events that occurred during the double-blind period and long-term follow-up is provided in Table 56.

Table 56. Overall Adverse Event Summary – VALOR study

	Double-Blind[a]		**Long-Term Follow-Up[b]**
Number of Subjects with	**Mavacamten N = 56 n (%)**	**Placebo N = 55 n (%)**	**Overall Mavacamten N = 108 n (%)**
At least 1 AE leading to death	0	0	1 (0.9)
At least 1 on treatment SAE	3 (5.4)	1 (1.8)	9 (8.3)
At least 1 study drug-related AE	9 (16.1)	9 (16.4)	17 (15.7)
At least 1 AE leading to study discontinuation	0	0	1 (0.9)
At least 1 AE leading to permanent treatment discontinuation	0	0	2 (1.9)
At least 1 AE leading to drug interruptions	4 (7.1)	1 (1.8)	5 (4.6)

Common Adverse Events

A summary of common adverse events is provided in Table 57 below.

Regardless of treatment group or indication, the majority of subjects experienced at least 1 AE (RCT-Mava oHCM 87.8%, RCT-Placebo oHCM 81.3%; RCT-Mava nHCM 89.7%, RCT-Placebo nHCM 68.4%All-Mava combined 92.7%).

In the All-Mava combined population AEs most frequently occurred were dizziness (19.7%), fatigue (15.6%), nasopharyngitis (15.0%), headache (14.6%), dyspnoea (13.4%), atrial fibrillation (12.1%), hypertension (11.1%) and upper respiratory tract infection (10.2%).

When evaluated by individual PT, in the oHCM indication the most frequently reported AEs in the pivotal Study MYK-461-005 were dizziness (21.1% in RCT-Mava oHCM vs. 13.3% in RCT-Placebo oHCM), dyspnoea (14.6% vs. 10.2%), headache (12.2% vs. 7.8%), and nasopharyngitis (12.2% vs. 14.8%).

In the nHCM indication, the most frequently reported AEs were dizziness (17.9% in RCT-Mava nHCM vs. 5.3% in RCT-Placebo nHCM), palpitations (15.4% vs. 15.8%), fatigue (12.8% vs. 15.8%), nasopharyngitis (10.3% vs. 10.5%), dyspnea (10.3% vs. 15.8%), nausea (10.3% vs. 10.5%), upper respiratory tract infection (10.3% vs. 0), and constipation (10.3% vs. 0).

Additionally, across the integrated analyses the Grade ≥3 AEs reported in >1 mavacamten-treated subject across the integrated analyses were atrial fibrillation (RCT-Mava oHCM vs. RCT-Placebo oHCM, All-Mava combined Grade ≥3: 2.4% vs. 3.1%, 3.2%), cardiac failure (Grade ≥3: 0.8% vs. 0, 1.3%), syncope (Grade ≥3: 2.4% vs. 0.8%, 1.0%), systolic dysfunction (Grade ≥3: 1.2% vs. 0, 0.6%), and bile duct obstruction (Grade ≥3: 0 vs. 0, 0.6%). These AEs are further discussed below.

Table 57. Subject incidence of common adverse events by preferred term in ≥5% of subjects in any treatment group.

Preferred Term	All-Mava combined N = 314 n (%)		oHCM				nHCM			
			RCT-Mava N = 123 n (%)		RCT-Placebo N = 128 n (%)		RCT-Mava N = 39 n (%)		RCT-Placebo N = 19 n (%)	
	All Grades	Grade **≥3**	All Grades	Grade **≥3**	All Grades	Grade **≥3**	All Grades	Grade **≥3**	All Grades	Grade **≥3**
At least 1 AE	291 (92.7)	48 (15.3)	108 (87.8)	12 (9.8)	104 (81.3)	14 (10.9)	35 (89.7)	2 (5.1)	13 (68.4)	1 (5.3)
Dizziness	62 (19.7)	1 (0.3)	26 (21.1)	1 (0.8)	17 (13.3)	0	7 (17.9)	0	1 (5.3)	0
Fatigue	49 (15.6)	1 (0.3)	7 (5.7)	0	7 (5.5)	0	5 (12.8)	0	3 (15.8)	0
Nasopharyngitis	47 (15.0)	0	15 (12.2)	0	19 (14.8)	0	4 (10.3)	0	2 (10.5)	0
Headache	46 (14.6)	0	15 (12.2)	0	10 (7.8)	0	3 (7.7)	0	1 (5.3)	0
Dyspnoea	42 (13.4)	1 (0.3)	18 (14.6)	0	13 (10.2)	0	4 (10.3)	0	3 (15.8)	0
Atrial fibrillation	38 (12.1)	10 (3.2)	10 (8.1)	3 (2.4)	10 (7.8)	4 (3.1)	3 (7.7)	1 (2.6)	1 (5.3)	1 (5.3)
Hypertension	35 (11.1)	0	6 (4.9)	0	4 (3.1)	0	0	0	0	0
Upper respiratory tract infection	32 (10.2)	0	10 (8.1)	0	6 (4.7)	0	4 (10.3)	0	0	0
Back pain	30 (9.6)	0	10 (8.1)	0	8 (6.3)	0	2 (5.1)	0	0	0
Palpitations	28 (8.9)	0	7 (5.7)	0	10 (7.8)	0	6 (15.4)	0	3 (15.8)	0
Cough	24 (7.6)	0	10 (8.1)	0	4 (3.1)	0	2 (5.1)	0	0	0
Nausea	21 (6.7)	0	4 (3.3)	0	4 (3.1)	0	4 (10.3)	0	2 (10.5)	0
Oedema peripheral	20 (6.4)	0	6 (4.9)	0	3 (2.3)	0	1 (2.6)	0	0	0

Preferred Term	All-Mava combined N = 314 n (%)		oHCM				nHCM			
			RCT-Mava N = 123 n (%)		RCT-Placebo N = 128 n (%)		RCT-Mava N = 39 n (%)		RCT-Placebo N = 19 n (%)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Pain in extremity	20 (6.4)	0	2 (1.6)	0	3 (2.3)	0	0	0	0	0
Diarrhoea	19 (6.1)	0	5 (4.1)	0	7 (5.5)	0	3 (7.7)	0	0	0
Urinary tract infection	19 (6.1)	1 (0.3)	6 (4.9)	0	5 (3.9)	1 (0.8)	1 (2.6)	0	0	0
Arthralgia	19 (6.1)	0	7 (5.7)	0	2 (1.6)	0	0	0	0	0
Fall	18 (5.7)	0	5 (4.1)	0	3 (2.3)	0	3 (7.7)	0	0	0
Constipation	16 (5.1)	0	2 (1.6)	0	2 (1.6)	0	4 (10.3)	0	0	0
Ventricular tachycardia	16 (5.1)	0	2 (1.6)	0	2 (1.6)	1 (0.8)	1 (2.6)	0	1 (5.3)	0

Abbreviations: AE = adverse event; Mava = mavacamten; nHCM = non-obstructive hypertrophic cardiomyopathy; NR = not reported; oHCM = obstructive hypertrophic cardiomyopathy; RCT = randomized controlled trial. Data presented in this table are treatment emergent. Safety Population includes all subjects who received at least 1 dose of study drug.

VALOR study (MYK-461-017) – double-blind period and long-term follow-up

A summary of the most common adverse events (5%) that occurred during the double-blind period and long-term follow-up is provided in Table 58 and Table 59. In the DB period the most frequently reported AEs (≥5%) were fatigue (8.9% vs 3.6% for mavacamten and placebo, respectively), atrial fibrillation (7.1% vs 0), nausea (7.1% vs 1.8%), dizziness (7.1% vs 5.5%), dyspnea (7.1% vs 5.5%), rash (7.1% vs 0%), urinary tract infection (5.4% vs 1.8%), and hypertension (5.4% vs 3.6%).

Table 58. Common AEs in ≥5% of subjects in any treatment group – DB period of VALOR study

	Double-Blind[C]	
Number of Subjects with	**Mavacamten N = 56 n (%)**	**Placebo N = 55 n (%)**
At least 1 on treatment AE	41 (73.2)	34 (61.8)
Cardiac disorders	10 (17.9)	6 (10.9)
Atrial fibrillation	4 (7.1)	0
Palpitations	2 (3.6)	2 (3.6)
Ventricular Tachycardia	0	5 (9.1)
Gastrointestinal disorders	12 (21.4)	7 (12.7)
Nausea	4 (7.1)	1 (1.8)
General disorders and administration site conditions	9 (16.1)	6 (10.9)
Fatigue	5 (8.9)	2 (3.6)
Infections and infestations	6 (10.7)	8 (14.5)
Urinary tract infection	3 (5.4)	1 (1.8)
Nervous system disorders	10 (17.9)	9 (16.4)
Dizziness	4 (7.1)	3 (5.5)

	Double-Blind[C]	
Number of Subjects with	**Mavacamten N = 56 n (%)**	**Placebo N = 55 n (%)**
Headache	2 (3.6)	5 (9.1)
Respiratory, thoracic and mediastinal disorders	6 (10.7)	5 (9.1)
Dyspnea	4 (7.1)	3 (5.5)
Skin and subcutaneous tissue disorders	9 (16.1)	5 (9.1)
Rash	4 (7.1)	0
Vascular disorders	6 (10.7)	3 (5.5)
Hypertension	3 (5.4)	2 (3.6)
At least 1 on treatment AESI	0	0
At least 1 on treatment AECI	24 (42.9)	12 (21.8)
OAEI		
At least 1 on treatment OAEI	0	5 (9.1)

Abbreviations: AE = adverse event; AECI - adverse event of clinical interest; COID-19 = coronavirus disease 2019; OAEI = other adverse event of interest; SAE = serious adverse event.

[a] DB data was collected from Day 1 of mavacamten treatment until Week 16

[b] LTFU data was collected from Day 1 of mavacamten treatment until EOT for mavacamten treatment group and from Week 16 until EOT for placebo to mavacamten treatment group

Table 59. VALOR - Summary of On-Treatment Adverse Events ≥5% in Either Treatment Group - Long-Term Follow-Up Period

System Organ Class Preferred Term	**Previous Mavacamten N = 56 n (%)**	**Previous Placebo N = 52 n (%)**	**Total Mavacamten N = 108 n (%)**
Total number of TEAEs	239	108	347
Number of Subjects with at Least One TEAE	49 (87.5)	32 (61.5)	81 (75.0)
Cardiac disorders	14 (25.0)	4 (7.7)	18 (16.7)
Atrial Fibrillation	5 (8.9)	2 (3.8)	7 (6.5)
Palpitations	5 (8.9)	2 (3.8)	7 (6.5)
Bradycardia	4 (7.1)	0	4 (3.7)
Gastrointestinal disorders	17 (30.4)	5 (9.6)	22 (20.4)
Nausea	5 (8.9)	0	5 (4.6)
Constipation	3 (5.4)	2 (3.8)	5 (4.6)
General disorders and administration site conditions	16 (28.6)	6 (11.5)	22 (20.4)
Fatigue	8 (14.3)	2 (3.8)	10 (9.3)
Chest pain	4 (7.1)	0	4 (3.7)
Infections and infestations	14 (25.0)	9 (17.3)	23 (21.3)
COVID-19	4 (7.1)	2 (3.8)	6 (5.6)

System Organ Class Preferred Term	Previous Mavacamten N = 56 n (%)	Previous Placebo N = 52 n (%)	Total Mavacamten N = 108 n (%)
Urinary tract infection	3 (5.4)	2 (3.8)	5 (4.6)
Investigations	15 (26.8)	4 (7.7)	19 (17.6)
Ejection fraction decreased	3 (5.4)	2 (3.8)	5 (4.6)
SARS-CoV-2 test positive	3 (5.4)	1 (1.9)	4 (3.7)
Musculoskeletal and connective tissue disorders	15 (26.8)	4 (7.7)	19 (17.6)
Arthralgia	5 (8.9)	2 (3.8)	7 (6.5)
Nervous system disorders	17 (30.4)	9 (17.3)	26 (24.1)
Dizziness	5 (8.9)	4 (7.7)	9 (8.3)
Dizziness postural	3 (5.4)	0	3 (2.8)
Headache	3 (5.4)	5 (9.6)	8 (7.4)
Respiratory, thoracic and mediastinal disorders	12 (21.4)	8 (15.4)	20 (18.5)
Dyspnea	4 (7.1)	3 (5.8)	7 (6.5)
Dyspnea exertional	3 (5.4)	4 (7.7)	7 (6.5)
Skin and subcutaneous tissue disorders	14 (25.0)	2 (3.8)	16 (14.8)
Rash	4 (7.1)	0	4 (3.7)
Alopecia	3 (5.4)	0	3 (2.8)
Dermatitis contact	3 (5.4)	1 (1.9)	4 (3.7)
Vascular disorders	7 (12.5)	5 (9.6)	12 (11.1)
Hypertension	4 (7.1)	3 (5.8)	7 (6.5)

Additional details on the characterization of selected AEs

For the adverse drug selection process, data from the 2 Phase 3 placebo-controlled studies (EXPLORER-HCM through Week 38 and VALOR-HCM through Week 16 double-blind period) were pooled. Selection criteria for ADR consideration were based on the AE occurrence ≥5% (all causality) in mavacamten-treated subjects and ≥2% higher than subjects who received placebo (Table 60).

Table 60. Pooled Phase 3 Studies (MYK-461-005 and MYK-461-017) Subject Incidence of Treatment-Emergent Adverse Events by Preferred Term in ≥5% of Mavacamten-Treated Subjects and At Least 2% Higher Than Subjects Who Received Placebo

Preferred Term	RCT-Mava (N = 179)	RCT-Placebo (N = 183)
Dizziness	30 (16.8)	20 (10.9)
Dyspnea	22 (12.3)	16 (8.7)
Atrial fibrillation	15 (8.4)	10 (5.5)
Arthralgia	12 (6.7)	7 (3.8)
Cough	11 (6.1)	4 (2.2)
Upper respiratory tract infection	10 (5.6)	6 (3.3)

Abbreviations: Mava= mavacamten; RCT = randomized controlled trial.

Pooled data from 2 Phase 3 studies (MYK-461-005 through Week 38 and MYK-461-017 through Week 16 double-blind period)

Frequent TEAEs are those with ≥5% crude incidence in the Mavacamten arm. Adverse Events were coded using MedDRA, Version 24.0.PTs and are presented in order of descending frequency in the Mavacamten arm followed by Placebo arm.

Further analyses of upper respiratory tract infection, cough, and arthralgia showed no reasonable possibility of a causal relationship of the use of mavacamten and the event. They were not included as an ADR in the SmPC of mavacamten.

Dizziness

Integrated summary of safety analyses

In the EXPLORER-HCMl study, comparing the RCT-Mava oHCM with the RCT-Placebo oHCM treatment groups, dizziness as an individual term was observed in 21.1% vs. 13.3% of subjects.

Overall, in All-Mava combined, there were 62 subjects (19.7%) who experienced a total of 83 AEs of dizziness. Most dizziness AEs were non-serious and low grade (Grade 1 or 2), with the exception of a non-serious Grade 3 AE of dizziness that resolved on the same day, and a Grade 1 SAE of dizziness with hospital admission for neurologic and other workup but for which no aetiology was identified (the SAE, with onset on extension SD246 and resolution 17 days later, was considered not related by the investigator and no action was taken with study treatment). Of subjects who experienced dizziness, the majority of subjects experienced a single event (44 of 62 subjects), approximately a third of subjects experienced 2 dizziness events (16 of 62 subjects), and 1 subject each experienced 3 of dizziness and 1 subject experienced 4 events of dizziness. The mean time to the first onset of dizziness was 185.0 study days. The majority of dizziness events resolved (58 of 83 events, 69.9%), and the median duration of resolved events was 3.5 days. No dizziness events led to permanent discontinuation of study treatment, although for 1 subject, dizziness led to temporary interruption.

Dizziness was the most frequent AE reported in both arms of the pivotal Study MYK-461-005. As a result of the greater incidence of dizziness in RCT-Mava oHCM vs. RCT-Placebo oHCM subjects, dizziness is considered an ADR with use of mavacamten.

VALOR-HCM study (MYK-461-017) – double-blind period

Dizziness was considered an ADR due to imbalance and consistently higher incidence proportions (Table 61).

Table 61. VALOR On-treatment Adverse Events for Dizziness ADR determination - Double-Blind Period

Preferred Term	Mavacamten (N = 56) n (%)	Placebo (N = 55) n (%)
Dizziness	4 (7.1)	3 (5.5)
Balance disorder	1 (1.8)	0
Dizziness postural	1 (1.8)	0
Presyncope	1 (1.8)	0

Source: Table 14.3.2.2 in the CV027006 Primary CSR**Error! Bookmark not defined.**

Overall Pooled EXPLORER-HCM + VALOR-HCM

Overall, confirmed by the pooled Phase 3 studies, dizziness was the most frequently reported AE (16.8 vs 10.9 % in the pooled analysis of the 2 Phase 3 studies. Based on these data, dizziness is considered an adverse reaction for Section 4.8 of the SmPC.

Dyspnoea

Integrated summary of safety analyses

In the EXPLORER-HCM study, comparing the RCT-Mava oHCM with the RCT-Placebo oHCM treatment groups, the TEAE, dyspnoea, was observed in 14.6% vs. 10.2% of subjects. However, during the on-treatment period, dyspnoea events were balanced between mavacamten-treated subjects and subjects who received placebo (RCT-Mava combined vs. RCT-Placebo combined: 12 subjects [7.4%] vs. 12 subjects [8.2%]), while dizziness events were more frequently reported during the follow-up/washout period in mavacamten-treated subjects than subjects who received placebo (14 subjects vs. 4 subjects), suggesting that the observed imbalance was attributable to dyspnoea in mavacamten-treated subjects during the follow-up/washout period (after planned treatment completion), at a time when mavacamten plasma concentrations were decreasing and LVOT gradients were returning (increasing) back to baseline.

Overall, in All-Mava combined, there were 42 subjects (13.4%) who experienced AEs of dyspnoea. Most dyspnoea AEs were non-serious and low grade (Grade 1 or 2), with the exception of 1 subject in the extension MYK-461-007 study with a non-serious Grade 3 event considered not related to study treatment that resolved after 39 days without dose interruption. Of subjects who experienced dyspnoea, the majority of subjects experienced a single event (33 of 42 subjects, 78.6%), the remaining subjects experienced 2 dyspnoea events (6 of 42 subjects, 14.3%), and 3 subject experienced 3 events of dyspnoea. The mean time to the first onset of dyspnoea was 234.2 study days; approximately half of dyspnea events resolved (29 of 42 events, 53.7%) and the median duration of resolved events was 35.0 days. No dyspnoea events led to temporary interruption of study treatment. There was 1 subject for whom a Grade 2 AE of dyspnoea led to permanent discontinuation of study treatment; this subject received mavacamten 15 mg QD (the highest dose in the study, per protocol based on subject weight) in Part A of the proof-of-concept dose-ranging parent Study MYK-461-004, and the event of dyspnoea occurred in the context of an ongoing Grade 3 SAE of atrial fibrillation and a concurrent Grade 2 AE of cardiac failure.

In addition to characterization based on the individual event term, other similar reported events (based on ‘dyspnoea’ in the coded PT) were dyspnoea exertional, nocturnal dyspnoea, and dyspnoea paroxysmal nocturnal. Of these similar events, all were non-serious and low-grade (Grade 1 or 2) with the exception of a Grade 3 AE of nocturnal dyspnoea (the AE, with onset on extension SD643, was considered not related by the investigator and no action was taken with study treatment). However, for 1 subject a Grade 2 AE of dyspnoea paroxysmal nocturnal led to permanent discontinuation of study treatment on extension SD100; approximately 1 week prior, this subject had interrupted treatment due to a Grade 2 AE of atrial flutter, and within 1 week after the subject met protocol-specified criteria for mavacamten plasma concentration ≥1000 ng/mL and LVEF <50% and also had a non-serious Grade 1 AE of fall.

In summary, although in some cases dyspnoea or similar events were reported contemporaneous with clinical scenarios involving arrhythmias (atrial fibrillation or atrial flutter) and cardiac failure or LVEF reduction, overall analyses (including review of the pattern of dyspnoea events in the pivotal study) support that dyspnoea primarily represents a recurrence of symptoms of underlying disease after planned discontinuation of mavacamten.

VALOR-HCM study (MYK-461-017) - double blind period

During DB period, dyspnea was reported in 4 (7.1%) subjects in the mavacamten group and in 3 (5.5%) subjects in the placebo group.

Overall Pooled EXPLORER-HCM + VALOR-HCM

Overall, confirmed by the pooled Phase 3 studies, dyspnea was the most frequently reported AE (12.3 vs 8.7 % in the pooled analysis of the 2 Phase 3 studies Table 60. The applicant has accepted the CHMP recommendation to add dyspnea as an ADR, although there are confounding factors.

Headache

Integrated summary of safety analyses

In the EXPLORER-HCM study, comparing the RCT-Mava oHCM with the RCT-Placebo oHCM treatment groups, headache as an individual term was observed in 12.2% vs. 7.8% of subjects. In the randomized placebo-blinded studies, a relative association of headaches with beta-blocker use at baseline was observed (RCT-Mava combined vs. RCT-Placebo combined: headache in subjects with baseline beta-blocker use, 9.3% vs. 4.1%; headache in subjects without baseline beta-blocker use, 1.9% vs. 3.4%). Headache was not a result of the ADR selection criteria based on the pooled analysis of EXPLORER and VALOR.

Overall, in All-Mava combined, there were 46 subjects (14.6%) who experienced a total of 68 AEs of headache. All headache AEs were non-serious and low grade (Grade 1 or 2). Of subjects who experienced headache, the majority experienced a single event (33 of 46 subjects, 71.7%), approximately a quarter of subjects total experienced 2 or 3 events (8 or 4 subjects, respectively), and 1 subject experienced ≥5 events of headache. The mean time to first onset of headache was 186.0 study days. The majority of headache events resolved (65 of 68 events, 95.6%) and the median duration of resolved events was 3.0 days. No headache events led to permanent discontinuation of study treatment, but headache AEs led to temporary interruption of study treatment for 2 mavacamten-treated subjects in the integrated analysis, and for 1 subject in the RCT-Placebo oHCM treatment group a Grade 2 AE of headache led to treatment interruption of blinded placebo.

In addition to characterization based on the individual event term, other similar reported events (based on ‘headache’ or ‘migraine’ in the coded PT) were cluster headache, tension headache, sinus headache, migraine, and migraine with aura. Of these similar AEs, all were non-serious and low-grade. Across the integrated analyses, migraine was reported for 3 mavacamten-treated subjects and the remaining similar events occurred in ≤2 mavacamten subjects each, and none of these similar events led to permanent discontinuation or temporary interruption of study treatment.

Considering all mavacamten-treated subjects across the integrated analyses (All-Mava combined) with AEs of headache or similar events, after detailed review there was no apparent pattern identified for time to headache onset. In addition, no apparent correlation could be identified between the events and proximate mavacamten plasma trough concentrations. In some cases where the most proximate mavacamten plasma trough concentrations at AE onset differed from that at AE resolution due to the duration of the headache or similar event, mavacamten plasma trough concentrations were notably lower at AE onset than at resolution.

Overall, current data do not support headache as an on-treatment effect of mavacamten. Although a numerical imbalance of headache was observed between mavacamten-treated subjects and subjects who received placebo in the pivotal Study MYK-461-005, in detailed case review no pattern of onset was observed, and there was no apparent correlation with mavacamten plasma concentration.

VALOR-HCM study (MYK-461-017) - double blind period

During the DB period, headache was reported in 2 (3.6%) and 5 (9.1%) subjects in mavacamten and placebo groups, respectively.

Overall Pooled EXPLORER-HCM + VALOR-HCM

The applicant was requested to discuss inclusion of 'headache' as an ADR in section 4.8 of the SmPC. Although the imbalance was not seen in subjects without beta-blocker use, these numbers were small but a contributory role of mavacamten could not be completely excluded and therefore it was included as ADR.

However, based on evaluation of the recently available pooled analysis of Week 38 and Week 16 safety data of EXPLORER-HCM and VALOR-HCM. as well as results of the individual VALOR CSR, the applicant considers headache not to be an ADR.

In the VALOR-HCM study, headache was reported less in the mavacamten (RCT-Mava) group compared with placebo (RCT-placebo): 3.6% vs. 9.1%, respectively. In the pooled data-set of EXPLORER-HCM and VALOR-HCM, the imbalance between subjects treated with mavacamten (RCT-Mava) compared with placebo (RCT-placebo) is narrowed to 9.5% vs. 8.2%, respectively (Adhoc Table 1). The additional data suggest that mavacamten does not play a contributory role in causing headache, and that it is more likely associated with beta-blocker use in combination with mavacamten.

Syncope

Syncope as an ADR was not based on the criteria used to generate Table 60, but is included as an ADR based on a numerical imbalance in the EXPLORER-HCM study; however, the applicant considers that events of syncope are heavily confounded by other factors.

Integrated summary of safety analyses

In the EXPLORER-HCM study, comparing the RCT-Mava oHCM with the RCT-Placebo oHCM treatment groups, syncope as an individual term was observed in 5.7% (7 subjects) vs. 1.6% (2 subjects) for any grade and 2.4% (3 subjects) vs. 0.8% (1 subject) for Grade ≥3 AEs.

Among the 7 subjects in the mavacamten arm (RCT-Mava oHCM) who experienced syncope, 4 had medical history of syncope or presyncope and among the 2 subjects who received placebo (RCT-Placebo oHCM) who experienced syncope, both had medical history of syncope. Syncope, as a recurrent complication of oHCM is observed at times when the LVOT gradient is elevated and also occurs secondary to volume depletion (e.g. with use of diuretics) and with uncontrolled arrhythmias.

Overall, in All-Mava combined, there were 9 subjects (2.9%) who experienced any grade and 3 subjects (1.0%) who experienced Grade ≥3 AEs of syncope. Seven subjects in the RCT-Mava oHCM treatment group were discussed in the paragraph above, and the 2 additional subjects (with oHCM) experienced syncope AEs during long-term extension. Of the 9 mavacamten-treated subjects with syncope across the integrated analyses, 3 subjects experienced Grade 3 SAEs of syncope (all in the parent pivotal study), and the remaining 6 subjects experienced non-serious and low grade (Grade 1 or 2) AEs of syncope. Brief summaries of the 3 mavacamten-treated subjects with SAEs are provided below; for all 3 subjects, resting and Valsalva LVOT gradients were trending higher at the time of the SAEs based on proximate values before and after the events.

- 1 subject who had 2 reported Grade 3 SAEs of syncope, both attributed to metoprolol and underlying oHCM, that led to temporary interruption and permanent discontinuation of study treatment; proximate mavacamten plasma concentrations were <200 ng/mL

- 1 subject with a medical history of seizure, syncope, and collapse, who had a Grade 3 SAE of syncope attributed to underlying worsening oHCM and hypovolemia in the setting of a recent hike; proximate mavacamten plasma trough concentration was 32.4 ng/mL
- 1 subject with a medical history of syncope neurally mediated and with ongoing atrial fibrillation, who had a Grade 3 SAE of syncope 25 days after planned treatment completion according to study design; proximate mavacamten plasma trough concentrations were <450 ng/mL

Of the 4 mavacamten-treated subjects with non-serious and low-grade (Grade 1 or 2) AEs of syncope in the pivotal study, 2 occurred on-treatment (both subjects had proximate mavacamten plasma trough concentrations <200 ng/mL) and 2 occurred during the follow-up/washout period either 23 days or 40 days after planned treatment completion, a time when not only mavacamten plasma concentrations were decreasing, but also LVOT gradients were returning (increasing) back to baseline. Both subjects had end-of-treatment mavacamten plasma trough concentrations <400 ng/mL and end-of-study mavacamten plasma trough concentrations <40 ng/mL).

The 1 subject with syncope during long-term extension experienced 2 non-serious Grade 2 AEs of syncope (2 days apart from each other) that each resolved on the same day as onset with no action taken with study treatment. This subject had initiated a new concomitant mediation of bisoprolol approximately 3 weeks prior to the first syncope AE, and approximately 1 week after the second syncope AE met protocol-specified criteria for mavacamten concentration ≥1000 ng/mL at the same time bisoprolol was discontinued (reported vital signs were stable).

VALOR-HCM study (MYK-461-017) - double blind period

During the DB period, 1 subject (1.8%) in the mavacamten group and 0 subjects in placebo group experienced syncope.

Atrial fibrillation

Integrated summary of safety analyses

In EXPLORER-HCM (MYK-461-005), subject incidence of any grade events in the atrial fibrillation ECI category were generally similar, and of Grade ≥3 events were numerically lower, for the RCT-Mava oHCM treatment group than for the RCT-Placebo oHCM treatment group (any grade, 8.1% vs. 7.8%; Grade ≥3, 2.4% vs. 3.1%).

In the pooled analysis of the 2 Phase 3 studies AF was observed 8.4% for mavacamten and 5.5% in placebo. However, AF is not considered an ADR for the label as it is the most common arrhythmia encountered in HCM patients. It is well recognized that the prevalence of AF in HCM patients is approximately 20%

VALOR-HCM study (MYK-461-017) - double blind period

In this study, AF is not considered an ADR as it is the most common arrhythmia encountered in HCM patients and could arise under various circumstances unrelated to mavacamten treatment. It is well recognized that the prevalence of AF in HCM patients is approximately 20%18. Holter analyses at 16 weeks detected only 1 subject with AF in mavacamten treatment group and 2 subjects with AF in placebo group (see Section 2.7.4.7), although these episodes in the placebo group were not specifically reported as AEs. Overall, in the DB phase of VALOR study, there were 4 subjects with reported AF (see section 2.7.4.5), among which 3 subjects had a medical history of AF, and 2 subjects had medical history of coronary artery disease. 2 of the 4 subjects with AF had serious events of AF. One of these 2 subjects was reported with 2 events of AF and had a history of atrial perforation caused by atrial lead 6

months prior to screening. Additionally, in mavacamten-treated subjects, AF was not associated with a pattern of onset and not correlated with a pattern related to proximate mavacamten concentration.

Overall Pooled EXPLORER-HCM + VALOR-HCM

In the pooled analysis of the 2 Phase 3 studies AF was observed 8.4% for mavacamten and 5.5% in placebo. However, AF is not considered an ADR as it is the most common arrhythmia encountered in HCM patients. It is well recognized that the prevalence of AF in HCM patients is approximately 20%. See also section 3.3.7.3. “Serious adverse events, deaths, and other significant events”.

2.5.8.3. Serious adverse event/deaths/other significant events

Deaths

In the mavacamten integrated analyses, three deaths occurred in any subject while on study (3/314, 1.0%), which all were considered not related to study drug by the investigator.

One death occurred in a mavacamten-treated subject in Study MYK-461-007 (the subject had been treated with placebo in the parent study MYK-461-005). The death was reported as a fatal (Grade 5) SAE of endocarditis bacterial. Two additional subjects had a fatal AE (cardiac arrest, and acute myocardial infarction) in Study MYK-461-007.

One death occurred in a subject in the placebo arm of the randomized pivotal Study MYK-461-005. The death was reported as a fatal (Grade 5) SAE of sudden death and was considered causally related to study treatment by the treatment-blinded investigator.

In addition to deaths in the integrated analyses discussed above, there was also 1 death of a mavacamten-treated subject in the clinical pharmacology hepatic impairment Study MYK-461-015. The subject was in the moderate hepatic impairment group and had a medical history of headaches, hypertension, hepatic enzymes increased due to alcohol abuse, hepatosplenomegaly, and ascites. A fatal SAE of ischemic stroke occurred 40 days after a single dose of mavacamten. For this subject, mavacamten plasma concentration 35 days after dosing (5 days prior to the SAE) was 0.332 ng/mL.

VALOR study (MYK-461-017) – double-blind period

No subjects in the mavacamten group or placebo group had died in the double-blind period.

VALOR study (MYK-461-017) - long-term follow-up

One subject, who previously received placebo treatment until Week 16 and then received mavacamten treatment post Week 16, had a TEAE of sudden cardiac death at week 56.

Serious Adverse Events

A summary of serious adverse events (SAEs) is provided in the Table 62 below:

Table 62. Subject incidence of serious adverse events reported ≥2 subjects by preferred term.

Preferred Term	All-Mava combined N = 314 n (%)	oHCM		nHCM	
		RCT-Mava N = 123 n (%)	RCT– Placebo N = 128 n (%)	RCT-Mava N = 39 n (%)	RCT- Placebo N = 19 n (%)
At least 1 SAE	58 (18.5)	14 (11.4)	12 (9.4)	4 (10.3)	4 (21.1)
Atrial fibrillation	14 (4.5)	3 (2.4)	5 (3.9)	2 (5.1)	1 (5.3)
Cardiac failure	5 (1.6)	1 (0.8)	0	NR	NR
Syncope	3 (1.0)	3 (2.4)	1 (0.8)	NR	NR
Stress cardiomyopathy	2 (0.6)	2 (1.6)	0	NR	NR
Systolic dysfunction	2 (0.6)	1 (0.8)	0	1 (2.6)	0

Preferred Term	All-Mava combined N = 314 n (%)	oHCM		nHCM	
		RCT-Mava N = 123 n (%)	RCT– Placebo N = 128 n (%)	RCT-Mava N = 39 n (%)	RCT- Placebo N = 19 n (%)
Pneumonia	2 (0.6)	0	0	NR	NR
Ejection fraction decreased	2 (0.6)	0	0	NR	NR
Acute kidney injury	2 (0.6)	0	0	NR	NR
Urinary tract infection	0	0	2 (1.6)	NR	NR

In the RCT-Mava oHCM treatment group, SAEs were most frequently reported in the SOCs of cardiac disorders (4.1% [5 subjects] in RCT-Mava oHCM vs. 3.9% [5 subjects] in RCT-Placebo oHCM), nervous system disorders (3.3% [4 subjects] vs. 1.6% [2 subjects]), infections and infestations (2.4% [3 subjects] vs. 1.6% [2 subjects]), and injury, poisoning and procedural complications (1.6% [2 subjects] vs. 0). There were no other SOCs for which > 1 subject in the RCT-Mava oHCM group experienced an SAE.

The most frequently reported SAEs by individual PT in the RCT-Mava oHCM treatment group were atrial fibrillation (2.4% [3 subjects] in RCT-Mava oHCM vs. 3.9% [5 subjects] in RCT Placebo oHCM), syncope (2.4% [3 subjects] vs. 0.8% [1 subject]), and stress cardiomyopathy (1.6% [2 subjects] vs. 0). No other SAEs in the RCT-Mava oHCM group were experienced by > 1 subject.

The most frequently reported SAE by individual PT in the RCT-Mava nHCM treatment group was atrial fibrillation (5.1% [2 subjects] in RCT-Mava nHCM vs. 5.3% [1 subject] in RCT Placebo nHCM). No other SAEs in the RCT-Mava nHCM group were experienced by > 1 subject.

Atrial fibrillation was the most frequently reported SAE across all mavacamten-treated subjects in the integrated analyses, although as noted earlier in this section, it occurred more frequently in subjects who received placebo than in mavacamten-treated subjects in the pivotal study (RCT-Mava oHCM vs. RCT-Placebo oHCM, All-Mava combined SAEs: 2.4% vs. 3.9%, 4.5%). Atrial fibrillation is one of the most frequent events in subjects with oHCM; in the HCM population, the lifetime risk of atrial fibrillation is estimated to be 20%, with prevalence as high as 40% with age > 70 years. Other SAEs reported in > 1 subject in All-Mava combined were cardiac failure (1.6% [5 subjects]), syncope (1.0% [3 subjects]), stress cardiomyopathy (0.6% [2 subjects]), pneumonia (0.6% [2 subjects]), and systolic dysfunction (0.6% [2 subjects]).

VALOR study (MYK-461-017) – double-blind period

The overall proportions of subjects with on-Treatment SAEs were higher in the mavacamten group through week 16 than in placebo group (Table 63). Two subjects on mavacamten versus none of the subjects on placebo experienced cardiac disorders attributed to atrial fibrillation. One subject in the mavacamten group had acute COVID-19 infection. One subject in the placebo group had acute alcohol intoxication. No subjects experienced SAEs of congestive cardiac failure, syncope, or sudden cardiac death.

Study drug related serious on-treatment AEs, corresponding to cardiac disorders (atrial fibrillation), were observed only in one subject in the mavacamten treatment group.

Table 63. Serious On-Treatment Adverse Events by System Organ Class and Preferred Term by Severity - Safety Analysis Population (Double- Blind Period)

System Organ Class Preferred Term Severity	Mavacamten (N = 56) n (%)	Placebo (N = 55) n (%)
Total Number of Serious On-Treatment Adverse Events	4	1
Moderate	3 (75.0)	1 (100.0)
Severe	1 (25.0)	0
Number of Subjects with at Least One Serious On-Treatment Adverse Event	3 (5.4)	1 (1.8)
Moderate	2 (3.6)	1 (1.8)
Severe	1 (1.8)	0
Cardiac disorders	2 (3.6)	0
Moderate	2 (3.6)	0
Atrial fibrillation	2 (3.6)	0
Moderate	2 (3.6)	0
Infections and infestations	1 (1.8)	0
Severe	1 (1.8)	0
COVID-19	1 (1.8)	0
Severe	1 (1.8)	0
Injury, poisoning and procedural complications	0	1 (1.8)
Moderate	0	1 (1.8)
Alcohol poisoning	0	1 (1.8)
Moderate	0	1 (1.8)

VALOR study (MYK-461-017) - long-term follow-up

Nine (8.3%) subjects had SAEs in the LTFU. 1 subject in the previous mavacamten group experienced acute respiratory failure, it was a complication following SRT procedure and subject had stopped mavacamten 3 weeks prior to procedure (Table 64). Three (2.8%) subjects were reported with at least one study drug-related SAEs in the LTFU. Among these subjects, 1 (0.9%) subject was reported with AF, 1 (0.9%) subject was reported with congestive cardiac failure, and 1 (0.9%) subject had sudden cardiac death.

Table 64. Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term by Severity - Safety Analysis Population (Long-Term Follow-Up Period).

System Organ Class Preferred Term Severity	Previous Mavacamten (N = 56) n (%)	Previous Placebo (N = 52) n (%)	Total Mavacamten (N = 108) n (%)
Total Number of Serious Treatment-Emergent Adverse Events	10	6	16
Moderate	4 (40.0)	4 (66.7)	8 (50.0)
Severe	5 (50.0)	1 (16.7)	6 (37.5)
Life-threatening	1 (10.0)	0	1 (6.3)
Fatal	0	1 (16.7)	1 (6.3)
Number of Subjects with at Least One Serious Treatment-Emergent Adverse Event	5 (8.9)	4 (7.7)	9 (8.3)
Moderate	3 (5.4)	3 (5.8)	6 (5.6)
Severe	1 (1.8)	0	1 (0.9)
Life-threatening	1 (1.8)	0	1 (0.9)
Fatal	0	1 (1.9)	1 (0.9)
Cardiac disorders	3 (5.4)	1 (1.9)	4 (3.7)
Moderate	2 (3.6)	1 (1.9)	3 (2.8)
Severe	1 (1.8)	0	1 (0.9)
Atrial fibrillation	3 (5.4)	0	3 (2.8)
Moderate	2 (3.6)	0	2 (1.9)
Severe	1 (1.8)	0	1 (0.9)
Cardiac failure congestive	0	1 (1.9)	1 (0.9)
Moderate	0	1 (1.9)	1 (0.9)
Gastrointestinal disorders	1 (1.8)	1 (1.9)	2 (1.9)
[illegible]			
Severe	1 (1.8)	1 (1.9)	2 (1.9)
Large intestine perforation	1 (1.8)	0	1 (0.9)
Severe	1 (1.8)	0	1 (0.9)
Pneumatosis intestinalis	1 (1.8)	0	1 (0.9)
Severe	1 (1.8)	0	1 (0.9)
Gastroesophageal reflux disease	0	1 (1.9)	1 (0.9)
Severe	0	1 (1.9)	1 (0.9)
General disorders and administration site conditions	0	1 (1.9)	1 (0.9)
Fatal	0	1 (1.9)	1 (0.9)
Sudden cardiac death	0	1 (1.9)	1 (0.9)
Fatal	0	1 (1.9)	1 (0.9)
Infections and infestations	1 (1.8)	0	1 (0.9)
Severe	1 (1.8)	0	1 (0.9)
COVID-19	1 (1.8)	0	1 (0.9)
Severe	1 (1.8)	0	1 (0.9)
Clostridium difficile infection	1 (1.8)	0	1 (0.9)
Severe	1 (1.8)	0	1 (0.9)
Injury, poisoning and procedural complications	0	1 (1.9)	1 (0.9)
Moderate	0	1 (1.9)	1 (0.9)
Fall	0	1 (1.9)	1 (0.9)
Moderate	0	1 (1.9)	1 (0.9)
Renal and urinary disorders	0	1 (1.9)	1 (0.9)
Moderate	0	1 (1.9)	1 (0.9)
Nephrolithiasis	0	1 (1.9)	1 (0.9)
Moderate	0	1 (1.9)	1 (0.9)
Respiratory, thoracic and mediastinal disorders	2 (3.6)	0	2 (1.9)
Moderate	1 (1.8)	0	1 (0.9)
[illegible]			
Life-threatening	1 (1.8)	0	1 (0.9)
Acute respiratory failure	1 (1.8)	0	1 (0.9)
Life-threatening	1 (1.8)	0	1 (0.9)
Pulmonary embolism	1 (1.8)	0	1 (0.9)
Moderate	1 (1.8)	0	1 (0.9)
Vascular disorders	0	1 (1.9)	1 (0.9)
Moderate	0	1 (1.9)	1 (0.9)
Peripheral venous disease	0	1 (1.9)	1 (0.9)
Moderate	0	1 (1.9)	1 (0.9)

Adverse events of special interest

LVEF ≤30%

The AESI of LVEF ≤ 30% was defined based on site-read echocardiograms. No subjects in the RCT-Mava or RCT-Placebo populations for any indication (oHCM or nHCM) experienced an AESI of LVEF ≤30%.

No subject with oHCM across all mavacamten-treated subjects in the integrated analyses (All-Mava combined) experienced an AESI of LVEF ≤30%. There was one subject (0.3%) with nHCM in the integrated analyses (All-Mava combined) who experienced an AESI of LVEF ≤30% during the chronic treatment phase (extension SD330 of Study MYK-461-007). The LVEF reduction was reversible and the subject symptomatically improved after discontinuation of study treatment as described below.

VALOR study (MYK-461-017) – double blind period

No subjects experienced LVEF ≤ 30% based on echo measurements during scheduled site visits.

VALOR study (MYK-461-017) - long-term follow-up

Two (1.9%) subjects experienced LVEF ≤30% based on echo measurements during scheduled site visits.

Symptomatic Overdose

Symptomatic overdose was defined as any overdose reported on the specific AESI eCRF as associated with one or more AEs.

No subjects in the RCT-Mava or RCT-Placebo populations for any indication (oHCM or nHCM) experienced an AESI of symptomatic overdose.

There were 3 subjects (1.0%; 1 with oHCM and 2 with nHCM) across all mavacamten-treated subjects in the integrated analyses (All-Mava combined) who experienced an AESI of symptomatic overdose; all 3 occurred during participation in the long-term extension Study MYK-461-007.

Of the 3 subjects, the 1 subject with oHCM had an elevated mavacamten value that met protocol-specified criteria for mavacamten plasma trough concentration ≥1000 ng/mL after multiple data entry errors at the site that affected dose titration decisions; the reported associated symptom was a SAE of cardiac failure for which the subject interrupted and later permanently discontinued treatment (the SAE of cardiac failure occurred during a hospitalization for pneumonia complicated by anaphylactic shock after the second dose of azithromycin).

Of the 2 subjects with nHCM, 1 subject had mavacamten plasma trough concentration of 772 ng/mL and the reported associated symptom was a non-serious Grade 1 AE of lethargy; of note, this subject subsequently (>1 month later) had an elevated mavacamten value that met protocol-specified criteria for mavacamten plasma trough concentration ≥1000 ng/mL and interrupted and then permanently discontinued treatment due to AEs of atrial flutter and dyspnoea paroxysmal nocturnal (this subject also subsequently met protocol-specified criteria for LVEF <50% and had a Grade 1 AE of fall). The remaining 1 subject (with nHCM) had proximate mavacamten plasma trough concentration values <400 ng/mL and had two reported associated symptoms of anxiety and bradycardia (both non-serious Grade 1 AEs).

VALOR study (MYK-461-017) – double blind period

No subject had any on-treatment AEs of symptomatic overdose.

VALOR study (MYK-461-017) - long-term follow-up

No subject had any TEAEs of symptomatic overdose within the LTFU

Embryofoetal toxicity

Identification of embryofoetal toxicity as a mavacamten AESI was based on findings from the definitive nonclinical reproductive toxicology studies.

There are no clinical safety data for embryofoetal toxicity with mavacamten, as no pregnancies have been reported for female subjects or female partners of male subjects treated with mavacamten. As of this submission, 1 pregnancy has been reported in the mavacamten clinical program, occurring in a female partner of a male subject who received placebo.

VALOR study (MYK-461-017) – double blind period

No pregnancies were reported.

VALOR study (MYK-461-017) - long-term follow-up

No pregnancies were reported.

Events by Medical Concept

Analyses evaluated data for protocol-specified criteria, events adjudicated by the independent CEAC, and AE data in events of clinical interest (ECI) categories. Where relevant, analyses of other data (e.g. laboratory data, cardiac diagnostics data, vital signs data) are also presented.

A summary of the overall subject incidence of mavacamten ECIs by categories is provided in Table 65. Detailed discussions of mavacamten ECIs are provided under the relevant medical concepts in the sections below.

Table 65. Subject Incidence of Mavacamten Adverse Events of Clinical Interest (ECI).

Category	All-Mava combined N = 314 n (%)		oHCM				nHCM			
			RCT-Mava N = 123 n (%)		RCT-Placebo N = 128 n (%)		RCT-Mava N = 39 n (%)		RCT-Placebo N = 19 n (%)	
	All Grades	Grade **≥3**	All Grades	Grade **≥3**	All Grades	Grade **≥3**	All Grades	Grade **≥3**	All Grades	Grade **≥3**
Number of subjects with at least 1 ECI	196 (62.4)	24 (7.6)	66 (53.7)	7 (5.7)	61 (47.7)	8 (6.3)	22 (56.4)	2 (5.1)	6 (31.6)	1 (5.3)
Major Adverse Cardiovascular Event (MACE-SMQ) (multiple SMQs and CV death[a])	8 (2.5)	3 (1.0)	2 (1.6)	1 (0.8)	3 (2.3)	2 (1.6)	1 (2.6)	0	0	0
Atrial Fibrillation (grouped terms)	44 (14.0)	11 (3.5)	10 (8.1)	3 (2.4)	10 (7.8)	4 (3.1)	4 (10.3)	1 (2.6)	2 (10.5)	1 (5.3)
Ventricular arrhythmias (SMQ)	19 (6.1)	0	3 (2.4)	0	3 (2.3)	1 (0.8)	2 (5.1)	0	1 (5.3)	0
Syncope/Presyncope [narrow] (grouped terms)	16 (5.1)	3 (1.0)	8 (6.5)	3 (2.4)	7 (5.5)	1 (0.8)	0	0	1 (5.3)	0
Syncope/Presyncope [broad] (grouped terms)	68 (21.7)	4 (1.3)	30 (24.4)	4 (3.3)	25 (19.5)	1 (0.8)	7 (17.9)	0	3 (15.8)	0
Cardiac Failure (narrow SMQ)	32 (10.2)	6 (1.9)	3 (2.4)	1 (0.8)	5 (3.9)	1 (0.8)	3 (7.7)	1 (2.6)	0	0
Hypotension (grouped terms)	4 (1.3)	0	2 (1.6)	0	3 (2.3)	0	0	0	1 (5.3)	0
QTc Prolongation (PT)	2 (0.6)	0	0	0	1 (0.8)	0	0	0	0	0

Category	All-Mava combined N = 314 n (%)		oHCM				nHCM			
			RCT-Mava N = 123 n (%)		RCT-Placebo N = 128 n (%)		RCT-Mava N = 39 n (%)		RCT-Placebo N = 19 n (%)	
	All Grades	Grade **≥3**	All Grades	Grade **≥3**	All Grades	Grade **≥3**	All Grades	Grade **≥3**	All Grades	Grade **≥3**
Renal Events (narrow SMQ)	6 (1.9)	2 (0.6)	1 (0.8)	0	0	0	1 (2.6)	0	0	0
Hepatic Events (multiple SMQs)	11 (3.5)	1 (0.3)	4 (3.3)	0	4 (3.1)	0	1 (2.6)	0	0	0
Severe Cutaneous Adverse Reactions (SCAR) (narrow SMQ)	0	0	0	0	0	0	0	0	0	0
Fall-Related Adverse Events										
Dizziness (grouped terms)	69 (22.0)	1 (0.3)	29 (23.6)	1 (0.8)	18 (14.1)	0	7 (17.9)	0	1 (5.3)	0
Coordination and Balance Disturbances (HLT)	6 (1.9)	0	1 (0.8)	0	0	0	0	0	0	0
Fall (PT)	18 (5.7)	0	5 (4.1)	0	3 (2.3)	0	3 (7.7)	0	0	0
Accidents and Injuries (all) (narrow SMQ)	51 (16.2)	1 (0.3)	13 (10.6)	0	10 (7.8)	0	4 (10.3)	0	0	0
Accidents and Injuries (narrow SMQ, SAEs only)	4 (1.3)	1 (0.3)	2 (1.6)	0	0	0	0	0	0	0
Gastrointestinal Events (narrow SMQ)	67 (21.3)	1 (0.3)	12 (9.8)	0	19 (14.8)	0	12 (30.8)	0	2 (10.5)	0
Rhabdomyolysis/ Myopathy (narrow SMQ)	0	0	0	0	0	0	0	0	0	0
Autoimmune Disorders (HLGT)	2 (0.6)	1 (0.3)	1 (0.8)	1 (0.8)	1 (0.8)	1 (0.8)	0	0	0	0
Hypersensitivity (narrow SMQ)	36 (11.5)	1 (0.3)	9 (7.3)	0	15 (11.7)	0	1 (2.6)	0	0	0

No concerns have been found with hypotension, severe cutaneous adverse reactions (SCAR), fall-related events, gastro-intestinal events, rhabdomyolysis/myopathy, auto-immune disorders and hypersensitivity.

VALOR study (MYK-461-017) – double-blind period

The most common AECIs were:

- Mavacamten treatment group: atrial fibrillation (5 [8.9%] subjects), dizziness (4 [7.1%] subjects), nausea (4 [7.1%] subjects), and rash (4 [7.1%] subjects)
- Placebo group: ventricular tachycardia (5 [9.1%] subjects), and dizziness (3 [5.5%] subjects

VALOR study (MYK-461-017) - long-term follow-up

The most common AECIs were dizziness (9 [8.3%] subjects), atrial fibrillation (7 [6.5%] subjects), ejection fraction decreased (5 [4.6%] subjects), constipation (5 [4.6%] subjects), nausea (5 [4.6%] subjects), dermatitis contact (4 [3.7%] subjects), rash (4 [3.7%] subjects), dizziness postural (3 [2.8%] subjects) and falls (3 [2.8%] subjects).

LVEF reduction.

LVEF reduction in the RCTs

No subjects in either the RCT-Mava oHCM or RCT-Placebo oHCM treatment groups met protocol-specified permanent discontinuation criteria for site-read LVEF ≤30%, but 7 vs 2 subjects met protocol-specified criteria for temporary discontinuation of study treatment due to LVEF while on study treatment (median LVEF 48%, range 35-49%).

- For 4 of the 7 subjects in RCT-Mava oHCM, the LVEF value <50% was measured at the Week 30 end of treatment visit
- The remaining 3 of the 7 subjects in RCT-Mava oHCM and 2 subjects in RCT-Placebo oHCM underwent temporary discontinuation of blinded study treatment and subsequently resumed dosing (for 1 of the 3 mavacamten-treated subjects, the LVEF reduction occurred in the setting of stress cardiomyopathy).
- There was 1 additional subject in the RCT-Mava oHCM group, who also met protocol-specified criteria of LVEF <50% on SD146 during an episode of stress cardiomyopathy, but this subject had already temporarily discontinued blinded mavacamten dosing on SD137 due to meeting protocol-specified criteria for QTcF prolongation.

In the RCT-Mava oHCM treatment group, all LVEF reductions meeting protocol-specified criteria for temporary discontinuation were reversible based on subsequent LVEF values (including 1 subject with partial recovery to LVEF 50% and no subsequent study-related echocardiography available due to the COVID-19 pandemic.

LVEF reduction in all mavacamten exposed patients

In total, across the integrated analyses (All Mava oHCM and nHCM), there were 36 unique mavacamten-treated subjects (19 with oHCM and 17 with nHCM) who met protocol-specified criteria for LVEF reduction (Table 66). In addition, there were 2 subjects who received placebo who had LVEF reduction below protocol-specified safety thresholds; both were subjects with oHCM from the pivotal MYK-461-005 study.

Of the 19 subjects with oHCM and qualifying LVEF reductions, 2 oHCM subjects had qualifying LVEF reductions in both parent and extension studies. In addition, for 2 subjects, LVEF reduction occurred after study treatment had already been temporarily discontinued, in both cases due to meeting protocol-specified criteria for QTcF. Based on quantitative LVEF data for the lowest qualifying LVEF values for each unique individual subject, the median qualifying LVEF reduction for all 19 subjects with oHCM was LVEF 44.67% (range 34.8% to 49.3%), and the median qualifying LVEF reduction for 16 subjects with nHCM was LVEF 44.25% (range 20.0% to 49.3%); the qualifiying LVEF value for the remaining 1 subject (with nHCM) was based on qualitative assessment (no available quantitative value) and was not used for these summary statistics.

Based on review of concurrent AEs or SAEs, 9 of the 19 subjects with and 10 of the 17 subjects with nHCM had no symptoms associated with the LVEF reductions.

LVEF reduction and mavacamten plasma concentrations

Elevations in mavacamten plasma concentration did not consistently precede or coincide with changes in LVEF. Of the 19 subjects with oHCM and qualifying LVEF reductions, 2 subjects had mavacamten plasma trough concentration ≥1000 ng/mL, 7 subjects had mavacamten plasma trough concentrations between 700 and 1000 ng/mL, and the remaining 10 subjects had mavacamten plasma trough concentrations that were <700 ng/mL at the time of or most proximately prior to the LVEF measurement. Similar findings were seen for the nHCM group.

From the opposite perspective, there were a total of 9 subjects (5 with oHCM and 4 with nHCM) across the integrated analyses who met protocol-specified criteria for mavacamten plasma concentrations ≥1000 ng/mL. Of the 5 subjects with oHCM, 3 subjects had associated LVEF reduction <50% (including 2 subjects in long-term extension with LVEF values <50% on central-read or in-hospital echocardiograms that did not meet cohort definitions for protocol-specified criteria based on site-read LVEF values) and 2 subjects did not (both subjects had site-read LVEF 55% [corresponding to central-read LVEF 60.7% or central-read LVEF 58.3%] concurrent with mavacamten plasma trough concentration ≥1000 [1330 ng/mL or 1060 ng/mL, respectively]). For subjects with nHCM, dosing was designed to achieve pre-specified mavacamten plasma trough concentration targets, and there was stronger evidence of a causal association for LVEF reduction with mavacamten levels beyond the recommended therapeutic range. Of the 4 subjects with nHCM, 3 subjects had associated LVEF reductions meeting protocol-specified thresholds, and 1 subject did not (1 subject who had LVEF 59.8% measured concurrent with mavacamten plasma trough concentration 1030 ng/mL on SD120).

Table 66. Mavacamten-Treated Subjects with Protocol-Specified Criteria for LVEF Reduction Sorted by Lowest Qualifying LVEF Value

Qualifying LVEF	Study Day	Protocol-Specified Criterion	Mava Plasma Conc. (ng/mL)	Symptomatic Status Based on Concurrent AEs/SAEs (all concurrent AEs/SAEs are listed)	
All-Mava oHCM (mavacamten-treated subjects with oHCM)					
LVEF 34.8% central	RCT SD57	LVEF < 50%	<700	yes	stress cardiomyopathy (SAE)
LVEF 35% local (LVEF 30.7% central)	extension SD425	LVEF < 50%	826	yes	atrial flutter, ejection fraction decreased
LVEF 39% local (LVEF 39.7% central)	extension SD406	LVEF < 50%	1010	yes	ongoing asthenia
LVEF 41% local (LVEF 35.6% central)	extension SD378	LVEF < 50%	<700	no	none
LVEF 43% local (LVEF 46.9% central)	extension SD339	LVEF < 50%	878	yes	atrial fibrillation (SD304-SD378)
LVEF 48.7% local (LVEF 53.4% central)	extension SD367	LVEF < 50%	(142 on SD385 early termination)	yes	ejection fraction decreased (SD339-SD385)
LVEF 43.3%	RCT SD129	LVEF < 50%	807	no	none
LVEF 43.9% local (LVEF 54.2% central) [a]	extension SD218	LVEF < 50%	<700	no	none
LVEF 44% local (LVEF 48.3% central) [b]	extension SD118	LVEF < 50%	884	yes	atrial fibrillation
LVEF 48% local (LVEF 45.4 % central)	extension SD300	LVEF < 50%	907 SD258 and 149 SD 320	yes	asthenia, atrial flutter
LVEF 44.7%	RCT SD128	LVEF < 50%	560	no	photosensitivity reaction[c]
LVEF 48% local (LVEF 52.0% central)	extension SD121	LVEF < 50%	671		ejection fraction decreased

Qualifying LVEF	Study Day	Protocol-Specified Criterion	Mava Plasma Conc. (ng/mL)	Symptomatic Status Based on Concurrent AEs/SAEs (all concurrent AEs/SAEs are listed)	
LVEF 45% local (LVEF 39.6% central) [b]	extension SD122	LVEF < 50%	1150	no	ejection fraction decreased
LVEF 45% local (LVEF 40.9% central)	extension SD47	LVEF < 50%	<700	yes	atrial fibrillation, acute kidney injury, ejection fraction decreased, NT-proBNP increased (this AE was not ongoing at the time of LVEF reduction)
LVEF 45% local (LVEF 51.9% central)	extension SD253	LVEF < 50%	95.8	no	exacerbated hypertension
LVEF 47.7% local (LVEF 35.9% central)	extension SD260	LVEF < 50%	651	yes	atrial fibrillation (SD153 to ongoing), ejection Fraction Decreased (SD260 to SD288)
LVEF 48% local (LVEF 37.4% central)	extension SD166	LVEF < 50%	988	no	atrial fibrillation onset D124 to D127 and again on D134 and D135
LVEF 42% local (LVEF 52.4% central)	extension SD182	LVEF < 50%	960	no	
LVEF 48.5%	RCT SD211	LVEF < 50%	708	no	Nasopharyngitis[c], rash[c]
LVEF 48.9%	RCT SD214	LVEF < 50%	782	yes	atrial fibrillation, hypothyroidism, proteinuria[c]
LVEF 49.2%	RCT SD212	LVEF < 50%	658 (SD 213)	no	RCT: hepatic steatosis[c], inguinal hernia[c]
LVEF 45% local (LVEF 54.3% central)	extension SD246	LVEF < 50%	595	no	Ejection fraction decreased, ongoing Cough
LVEF 49.2%	RCT SD146	LVEF < 50%	99.1	yes	stress cardiomyopathy (SAE), GERD[c]
LVEF 49.3%	RCT SD218	LVEF < 50%	364	yes[e]	atrial fibrillation, peripheral edema, chest pain, GERD[c], oral candidiasis[c]
All-Mava nHCM (mavacamten-treated subjects with nHCM)					
LVEF 29.1%	extension SD330	LVEF £ 30%	1400	yes	cardiac flutter, dyspnea, fatigue (all 3 also concurrent with extension SD344 LVEF measurement)
LVEF 43.4%	extension SD344	LVEF < 50%	579		
LVEF 36.1%	extension SD253	LVEF < 50%	190	no	none
LVEF 55% local (LVEF 49.3% central)	extension SD925	LVEF < 50%	105	no	none
LVEF 55% local (LVEF 44.2% central)	extension SD959	LVEF < 50%	290	no	viral upper respiratory tract infection SD943 - continued
LVEF 37.9%	RCT SD79	LVEF £ 45%	<700	yes	ejection fraction decreased, cardiac failure, carotid artery stenosis[c], carotid artery dissection[c]
LVEF 39.9%	extension SD422	LVEF < 50%	591	no	none
LVEF 40.8%	extension SD120	LVEF < 50%	818	no	productive cough[c]
LVEF 41.2%	RCT SD85	LVEF £ 45%	554	yes[f]	dyspnea, fatigue, palpitations, insomnia[c], nasopharyngitis[c]

Qualifying LVEF	Study Day	Protocol-Specified Criterion	Mava Plasma Conc. (ng/mL)	Symptomatic Status Based on Concurrent AEs/SAEs (all concurrent AEs/SAEs are listed)	
LVEF 41.6%	RCT SD83	LVEF £ 45%	1090	no	ejection fraction decreased, upper respiratory tract infection[c]
LVEF 44.2%	RCT SD91	LVEF £ 45%	824	yes	atrial fibrillation (SAE), systolic dysfunction (SAE)
LVEF 44.8%	extension SD196	LVEF < 50%	227	yes	fatigue, muscle spasms[c]
LVEF 45% local (LVEF 44.3% central)	extension SD603	LVEF < 50%	<LLQ	yes	nausea, fatigue, muscle spasms, fatigue (symptom of LVEF reduction)
LVEF 45.0%	RCT SD86	LVEF £ 45%	334	no	tooth abscess[c]
LVEF 45.3% LVEF 48.6%	extension SD27 extension SD62	LVEF < 50% LVEF < 50%	152 18.3	yes	none concurrent with SD27 LVEF fatigue, palpitations, dyspnea exertional
LVEF 47.8%	extension SD429	LVEF < 50%	219	no	none
LVEF 60% local (LVEF 44.7% central)	extension SD593	LVEF < 50%	149	no	Oedema peripheral (SD76-Ongoing)
LVEF 48.3%	extension SD174	LVEF < 50%	872	no	asthenia[c,d], fatigue[c,d], paresthesia[c,d]
LVEF 48.7%	extension SD589	LVEF < 50%	328	no	none
LVEF 49.0%	extension SD106	LVEF < 50%	661	yes[g]	atrial flutter, dizziness postural, balance disorder, dyspnea paroxysmal nocturnal, skin laceration
LVEF 49.3%	extension SD113	LVEF < 50%	153	no	none
LVEF < 50% (qualitative only)	extension SD342	LVEF < 50%	740	no	none

VALOR-HCM study (MYK-461-017) – double- blind period

Two (3.6%) subjects the mavacamten treatment group and no subjects in the placebo treatment group met the protocol defined temporary discontinuation criterion of LVEF <50%. Both subjects were asymptomatic at the time of the reduced LVEF <50% and were able to resume mavacamten within a few weeks at one dose lower than the dose they were receiving at the time of their temporary discontinuations. Both subjects remain in the LTE period of the study.

VALOR-HCM study (MYK-461-017) - long-term follow-up

Two subjects in the mavacamten treatment group and no subjects in the previous placebo treatment group met the temporary discontinuation criterion of LVEF <50%. Both subjects were asymptomatic and able to resume mavacamten at the next lower dose. No subjects in the placebo to mavacamten treatment group met the criterion.

Major cardiovascular events (MACE)

In the pivotal Phase 3 study MYK-461-005 and the supporting LTE study MYK-461-007, a prespecified set of safety endpoints, including MACE, defined as the composite of adjudicated CV death, stroke, acute myocardial infarction, and hospitalization for heart failure; hereafter referred to as MACE-adjudicated, were prospectively adjudicated by the CEAC.

The adjudicated data from mavacamten studies MYK-461-005 and MYK-461-007 are summarized in the Table 67 below.

Table 67. Subject incidence of adjudicated CV events

	RCT Study MYK-461-005 (oHCM)		LTE Study MYK-461-007		All Mava MYK-461-005 + MYK-461-007	
Adjudication Outcome, n %	Mava (N = 123)	Placebo (N = 128)	nHCM (N = 44)	oHCM (N = 231)	oHCM (N = 239)	oHCM and nHCM (N = 283)
MACE-Adjudicated	5 (4.1)[a]	3 (2.3)	0	8 (3.5)	12 (5.0)	12 (4.2)
CV death	0	1 (0.8)	0	3 (1.3)	3 (1.3)	3 (1.1)
Stroke	1 (0.8)	0	0	1 (0.4)	2 (0.8)	2 (0.7)
Acute myocardial infarction	3 (2.4)	1 (0.8)	0	0	3 (1.3)	3 (1.1)
Heart failure hospitalization	3 (2.4)	1 (0.8)	0	5 (2.2)	7 (2.9)	7 (2.5)
Heart Failure	3 (2.4)	1 (0.8)	0	5 (2.2)	7 (2.9)	7 (2.5)
Heart failure hospitalization	3 (2.4)	1 (0.8)	0	5 (2.2)	7 (2.9)	7 (2.5)
Non-hospitalization urgent/emergent heart failure visit	0	0	0	0	0	0
Atrial fibrillation[b]	4 (3.3)	5 (3.9)	0	11 (4.8)	15 (6.3)	15 (5.3)
ICD therapy	1 (0.8)	0	0	0	1 (0.4)	1 (0.4)
CV hospitalization[c]	8 (6.5)	5 (3.9)	1 (2.3)	17 (7.4)	24 (10.0)	25 (8.8)
Exposure-Adjusted Event Incidence of Adjudicated CV Events						
MACE-adjudicated	5.75[d]	3.27	0	2.47	2.97	2.45

Abbreviations: CV = cardiovascular; ICD = implantable cardioverter-defibrillator; MACE-adjudicated = adjudicated major adverse cardiovascular events; Mava = mavacamten; nHCM = non-obstructive hypertrophic cardiomyopathy; oHCM = obstructive hypertrophic cardiomyopathy.

a All adjudicated events for Study MYK-461-005 are included in the summary table. During the treatment period (through Week 30), a similar rate of MACE-adjudicated events was observed in the treatment groups (3 subjects in each group; 2.4% vs 2.3%, mavacamten vs placebo).

b Per CEAC charter, adjudicated atrial fibrillation is defined as new onset atrial fibrillation or atrial flutter

c Includes adjudicated CV hospitalizations and adjudicated heart failure hospitalizations

d All adjudicated events for Study MYK-461-005 are included in the summary table, including the events with onset during the washout/follow-up period.

During the treatment period of the pivotal study MYK-461-005, a total of 3 subjects (3 of 123, 2.4%) in the mavacamten group and 3 subjects (3 of 128, 2.3%) in the placebo group experienced adjudicated MACE events. Of the 3 subjects in the mavacamten group, 1 subject experienced a Grade 3 SAE of syncope (adjudicated as Type II non-ST-elevation myocardial infarction [NSTEMI]), and for 2

subjects experienced a Grade 2 or Grade 3 SAEs of stress cardiomyopathy (adjudicated as Type II NSTEMI and heart failure hospitalization [1 subject] and as Type II NSTEMI [1 subject]). Of the 3 subjects in the placebo group 1 subject experienced a Grade 5 fatal event of sudden death that was adjudicated as CV death, and 2 subjects experienced Grade 3 SAEs of atrial fibrillation (adjudicated as Type II NSTEMI [1 subject] and heart failure hospitalization [1 subject]). In addition, 2 mavacamten-treated subjects (both with pre-existing atrial fibrillation) experienced adjudicated MACE events during clinical scenarios with multiple confounding factors in the washout/follow-up period. For 1 subject the clinical scenario involved cardiac tamponade and an iatrogenic atrial septal defect after an ablation procedure to treat atrial fibrillation with multiple reported SAEs (adjudicated MACE events were heart failure hospitalization and stroke), and for 1 subject the clinical scenario involved a diagnosis of SLE with pericarditis and pericardial effusion (adjudicated as heart failure hospitalization).

The incidence rate of total adjudicated MACE for oHCM patients in the pivotal study MYK 461 005 (including the washout/follow-up period) was 5.75 per 100 patient years for the mavacamten group and 3.27 per 100 patient years for the placebo group. When considering the longer exposure time of the LTE study MYK-461-007, the incidence rate of adjudicated MACE for the pivotal study together with the LTE study was 2.47 per 100 patient years for subjects with oHCM. Thus, the incidence rate of adjudicated MACE in oHCM patients did not increase with longer exposure time and is comparable to the incidence rate of subjects who received placebo in the Study MYK-461-005.

In the LTE study MYK-461-007, there were 8 (3.5%) subjects who had adjudicated MACE events (all were subjects with oHCM) at the time of the interim data cut-off date (31-Aug-2021): 5 (2.2%) subjects with hospitalization for heart failure; for 2 of these 5 subjects, the events occurred in the context of data entry errors at the site involving dose-blinded investigator clinicians that resulted in inappropriately high mavacamten doses (higher doses than the subjects would have received if dose-titration had been based on correct values). The remaining 3 subjects with a MACE adjudicated event in LTE had fatal outcomes (1 subject reported an SAE of bacterial endocarditis that was adjudicated as a CV death, 1 subject experienced the SAE of cardiac arrest, and 1 subject died unexpectedly at home due to myocardial infarction). As of the data cut-off, exposure adjusted incidence rates for adjudicated MACE in the LTE study MYK-461-007 were lower than for mavacamten-treated subjects in the parent pivotal study.

Analyses for MACE by Standardised MedDRA Query (MACE-SMQ) were also conducted with MedDRA-coded AE data, defined based on the narrow SMQ “myocardial infarction,” the SMQ “haemorrhagic central nervous system vascular conditions,” the SMQ “ischemic central nervous system vascular conditions,” PT “cardiac death,” PT “sudden cardiac death,” and PT “sudden death.” Analyses of MACE-SMQ were generally balanced between the treatment groups in the pivotal study (mavacamten vs. placebo: all grades, 1.6% vs. 2.3%; Grade 3, 0.8% vs. 0.8%), and review of data across the integrated analyses did not reveal additional findings of concern. The absence of additional significant events of MACE-SMQ in data from the LTE studies also supports CV safety of mavacamten administered over an extended period of time.

As described earlier in this section, a total of 2 subjects in the Study MYK-461-005 (and across the integrated analyses) had adjudicated MACE events of stress cardiomyopathy. Literature reviews of stress cardiomyopathy in patients with HCM suggest that unique predisposing factors in these patients include dynamic obstruction due to outflow tract septal thickening, abnormalities of the mitral valve apparatus (papillary muscle abnormalities, mitral leaflet elongation, systolic anterior motion), and genetically determined inefficient energy utilization that can predispose to apical ballooning in the absence of specific triggers of catecholamine excess (Sherrid et al. 2020). In addition, publications describing the presentation of stress cardiomyopathy in subjects with HCM estimate the incidence from a retrospective review of data to be approximately 0.9% (Sherrid et al. 2020; Sherrid et al. 2019; Medina de Chazal et al. 2018). Considering all mavacamten-treated subjects across the integrated

analyses (All-Mava combined), stress cardiomyopathy was observed in 0.6% of subjects (0.60 cases per 100 patient years). Additionally, in published data from an international consortium with data from 1750 patients with Takotsubo (stress) cardiomyopathy, 89.8% were women, mean age was 66.8years, 55.8% occurred in patients with neurologic or psychiatric disorders, and mean LVEF during the stress cardiomyopathy episode was 40.7mmHg which was markedly lower than the mean LVEF of age- and sex-matched patients with an acute coronary syndrome (Templin et al. 2015). Patient profiles for the 2 subjects with stress cardiomyopathy in the mavacamten integrated analyses were consistent with these published data for patients with stress cardiomyopathy; in the mavacamten clinical studies, both subjects who experienced stress cardiomyopathy were women, age > 65 years, with anxiety and emotional stress reported for 1 subject, and both subjects experienced marked reductions in LVEF during the acute episodes that subsequently recovered.

In summary, current data do not suggest an overall safety concern for MACE events (adjudicated or SMQ-based) with mavacamten, and these data also provide support for CV safety of mavacamten over an extended period of time.

VALOR study (MYK-461-017) – double blind period

No subject had any treatment-emergent MACE (MACE; comprised of acute MI, stroke, CV death, and heart failure hospitalization).

VALOR study (MYK-461-017) - long-term follow-up

MACEs were reported in 2 (1.9%) subjects during LTFU for total mavacamten treatment. Both MACE events occurred in the previous placebo group (Table 68). One (0.9%) subject was reported with MACE related to sudden cardiac death after permanently discontinued due to LVEF <30%. Additionally, 1 (0.9%) subject was reported with MACE related to heart failure hospitalization and LVEF <30% around Week 30.

Table 68. Incidence of Major Adverse Cardiac Events - Long Term Follow-up.

MACE Category	Previous Mavacamten (N = 56) n (%)	Previous Placebo (N = 52) n (%)	Total Mavacamten (N = 108) n (%)
Total Number of Treatment-Emergent Major Adverse Cardiac Events	0	2	2
Number of Subjects with at Least One Treatment-Emergent MACE	0	2 (3.8)	2 (1.9)
Cardiac death	0	1 (1.9)	1 (0.9)
Acute myocardial infarction (MI)	0	0	0
Heart failure hospitalization	0	1 (1.9)	1 (0.9)
Stroke	0	0	0

Heart failure and systolic dysfunction

Heart failure is a complication of HCM, and in a small percentage of subjects, the refractory nature of this complication of the underlying disease can lead to heart transplantation (Marstrand et al. 2020). The aetiology of heart failure for individual subjects in the mavacamten clinical program was often multifactorial, complex, and confounded by the underlying disease and atrial fibrillation or other factors. When heart failure occurred in the setting of normal or hyperdynamic LV systolic function after the end of treatment with mavacamten or in subjects who were not exposed to mavacamten, a drug-causal association with mavacamten was not supported by data (although a contributory role for mavacamten could not be ruled out in all cases).

Notably, in the randomized, placebo-blinded Study MYK-461-005, heart failure as adjudicated by the independent CEAC was balanced during the treatment period (up to Week 30) between subjects who received mavacamten or placebo (1 subject each). In addition, as assessed by summarized AE data in the narrow SMQ of cardiac failure, heart failure was balanced between the treatment groups in the pivotal study MYK-461-005 (mavacamten vs. placebo: any grade, 2.4% vs. 3.9%; Grade ≥3, 0.8% vs. 0.8%) (Table 69). The only serious heart failure events observed in mavacamten-treated subjects in the pivotal study occurred after the planned end of treatment according to study design; these events occurred in 2 mavacamten-treated subjects during the washout/follow-up/ period, at a time when mavacamten plasma concentrations were decreasing and LVOT gradients were returning (increasing) to baseline values. In addition, of the 4 mavacamten-treated subjects with serious events of heart failure (1.3% of All-Mava combined), events for 2 subjects occurred in the context of inappropriately high mavacamten doses that resulted from data entry errors at the site involving dose-blinded investigator clinicians. The limitations of dose blinding and the need to enter clinical data into a system to trigger dosing decisions are unique to the randomized double-blinded clinical trial setting; thus, similar data entry errors leading to inappropriately high mavacamten doses are not expected to occur with non-blinded physicians in the post-approval clinical setting. Overall, across the integrated studies, approximately half of subjects who met protocol-specified criteria for LVEF reduction had no symptoms associated with the LVEF reductions.

Exposure-response analysis demonstrates that on a population level, a relationship exists between mavacamten concentrations and LVEF; however, on a subject level, there is significant interindividual PK variability that does not allow concentrations to accurately predict LVEF. This variability can be overcome through direct measure by echocardiogram.

Table 69. Subject incidence of cardiac failure events of clinical interest by preferred term.

			oHCM				nHCM			
	All-Mava N = 314 n (%)		RCT-Mava N = 123 n (%)		RCT-Placebo N = 128		RCT-Mava N = 39		RCT-Placebo N = 19	
Category Preferred Term	All	Grade	All	Grade	All	Grade	All	Grade	All	Grade
Cardiac failure	32	6 (1.9)	3 (2.4)	1 (0.8)	5 (3.9)	1 (0.8)	3 (7.7)	1 (2.6)	0	0
Ejection fraction	15 (4.8)	2 (0.6)	0	0	0	0	2 (5.1)	1 (2.6)	0	0
Cardiac failure	14 (4.5)	4 (1.3)	3 (2.4)	1 (0.8)	3 (2.3)	0	2 (5.1)	1 (2.6)	0	0
Cardiac failure chronic	4 (1.3)	0	NR	NR	NR	NR	0	0	0	0
Cardiogenic shock	1 (0.3)	1 (0.3)	1 (0.8)	1 (0.8)	0	0	NR	NR	NR	NR
Cardiac failure acute	0	0	0	0	2 (1.6)	0	NR	NR	NR	NR
Cardiac failure	0	0	0	0	1 (0.8)	1 (0.8)	NR	NR	NR	NR

Abbreviations: Mava = mavacamten; nHCM = non-obstructive hypertrophic cardiomyopathy; NR = not reported in the analysis population; oHCM = obstructive hypertrophic cardiomyopathy; RCT = randomized controlled trial.

Therefore, considering the mechanism of action for mavacamten heart failure due to systolic dysfunction is proposed to be an important potential risk for mavacamten. This important potential risk can be mitigated through baseline and periodic monitoring of LVEF through echocardiograms, education of prescribers on the clinical context in which these events occurred in the mavacamten clinical program, and education of patients on signs and symptoms that may represent these events.

VALOR study (MYK-461-017) – double-blind period

In the VALOR-HCM DB period, no subjects experienced HF. Two (3.6%) subjects in the mavacamten group experienced an event of asymptomatic LVEF decrease and were able to resume study drug after

temporary discontinuation at one dose lower (Table 70). No subjects during DB period had LVEF ≤ 30%. (

Table 70. Incidence of Heart Failure and Decreased LVEF – VALOR-HCM study - Double-Blind Period.

System Organ Class Preferred Term	Mavacamten (N = 56) n (%)	Placebo (N = 55) n (%)
Total Number of On-Treatment Heart Failure and Decreased LVEF Events	2	0
Number of Subjects with at Least One On-Treatment Heart Failure and Decreased LVEF Event	2 (3.6)	0
Investigations	2 (3.6)	0
Ejection fraction decreased	2 (3.6)	0

VALOR study (MYK-461-017) – long-term follow-up

In the LTFU period, 6 (5.6%) subjects had at least one on-treatment HF and decreased LVEF events. One previous mavacamten subject (0.9%) was reported with cardiac failure after SRT procedure (3 week after stopping mavacamten treatment), and 1 previous placebo subject (0.9%) had congestive cardiac failure. Investigations with decreased EF were reported in 5 (4.6%) subjects (Table 71). Three subjects (previous mavacamten) had temporary treatment discontinuation due to LVEF <50% and subsequently resumed treatment at a lower dose. Two subjects (previous placebo) had permanent treatment discontinuation due to LVEF ≤ 30% while on mavacamten treatment. 1 of whom is the subject described above with event of congestive heart failure

One additional previous mavacamten subject had a temporary treatment discontinuation due to ejection fraction decreased but was not considered as an AE by the investigator.

Table 71. Incidence of Heart Failure and Decreased LVEF - Long-Term Follow-up.

System Organ Class Preferred Term	Previous Mavacamten (N = 56) n (%)	Previous Placebo (N = 52) n (%)	Total Mavacamten (N = 108) n (%)
Total Number of Treatment-Emergent Heart Failure and Decreased LVEF Events	4	3	7
Number of Subjects with at Least One Treatment-Emergent Heart Failure and Decreased LVEF Event	4 (7.1)	2 (3.8)	6 (5.6)
Cardiac disorders	1 (1.8)	1 (1.9)	2 (1.9)
Cardiac failure	1 (1.8)	0	1 (0.9)
Cardiac failure congestive	0	1 (1.9)	1 (0.9)
Investigations	3 (5.4)	2 (3.8)	5 (4.6)
Ejection fraction decreased	3 (5.4)	2 (3.8)	5 (4.6)

Arrhythmias.

In the HCM population, cumulative morbidity is dominated by atrial fibrillation and heart failure, with the prevalence of atrial fibrillation being ~1 in 5 patients in a large referral HCM population. In addition, ventricular arrhythmias significantly contribute to the morbidity and mortality burden in the HCM population, with risks of ventricular arrhythmia 23.5 times and cardiac arrest or sudden cardiac death 6.3 times higher in patients with HCM than in the non-HCM population.

Due to the clinical importance of these events for the population under study, mavacamten safety data were analysed for the medical concepts of atrial fibrillation and ventricular arrhythmias as ECI categories; analyses of cardiac rhythm monitoring data are also provided, followed by an overall discussion and summary.

A summary of events in the ECI category of atrial fibrillation and ventricular arrhythmias by preferred term is provided in Table 73.

Table 72. Subject incidence of atrial fibrillation and ventricular arrhythmias events of clinical interest by preferred term.

Category Preferred Term	All-Mava N = 314 n (%)		oHCM				nHCM			
			RCT-Mava N = 123 n (%)		RCT-Placebo N = 128 n (%)		RCT-Mava N = 39 n (%)		RCT-Placebo N = 19 n (%)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Atrial fibrillation	44 (14.0)	11 (3.5)	10 (8.1)	3 (2.4)	10 (7.8)	4 (3.1)	4 (10.3)	1 (2.6)	2 (10.5)	1 (5.3)
Atrial fibrillation	38 (12.1)	10 (3.2)	10 (8.1)	3 (2.4)	10 (7.8)	4 (3.1)	3 (7.7)	1 (2.6)	1 (5.3)	1 (5.3)
Atrial flutter	9 (2.9)	0	0	0	1 (0.8)	0	1 (2.6)	0	1 (5.3)	0
Ventricular arrhythmias	19 (6.1)	0	3 (2.4)	0	3 (2.3)	1 (0.8)	2 (5.1)	0	1 (5.3)	0
Ventricular tachycardia	16 (5.1)	0	2 (1.6)	0	2 (1.6)	1 (0.8)	1 (2.6)	0	1 (5.3)	0
Ventricular extrasystoles	4 (1.3)	0	1 (0.8)	0	1 (0.8)	0	1 (2.6)	0	1 (5.3)	0

In the randomized placebo-blinded studies, there was no imbalance of events to suggest an on-treatment effect of mavacamten for atrial fibrillation or ventricular arrhythmias. In addition, findings across the integrated analyses were consistent with the randomized data, including that all ventricular arrhythmia events in mavacamten-treated subjects were non-serious and low grade. In other analyses across the integrated dataset, no mavacamten-treated subject had significant other arrhythmias, including torsades de pointes or sudden death.

Overall, analyses of AE data and review of relevant cardiac rhythm monitoring data do not support arrhythmias (atrial fibrillation or ventricular arrhythmias) as an on-treatment effect of mavacamten. These data support the likelihood that there is no detrimental effect on CV outcomes (including arrhythmias) with prolonged exposure to mavacamten.

VALOR study (MYK-461-017) – double-blind period

Total number of on-treatment AEs of atrial fibrillation or atrial flutter reported were 6 in the mavacamten treatment group and none in the placebo group (Table 73). Atrial fibrillation or atrial flutter were observed in 4 (7.1%) subjects in the mavacamten group, out of which 3 (5.4%) subjects had recurrent Atrial fibrillation with known Atrial fibrillation medical history.

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Table 73. Incidence of Atrial Fibrillation / Flutter – VALOR-HCM study - Double-Blind Period

	Mavacamten (N = 56) n (%)	Placebo (N = 55) n (%)
Total Number of On-treatment AEs of Atrial Fibrillation or Atrial Flutter	6	0
Total Number of Recurrent On-treatment AEs of Atrial Fibrillation or Atrial Flutter	5	0
Total Number of New On-treatment AEs of Atrial Fibrillation or Atrial Flutter	1	0
Total Number of Subjects with On-treatment AEs of Atrial Fibrillation or Atrial Flutter	4 (7.1)	0
Total Number of Subjects with Recurrent On-treatment AEs of Atrial Fibrillation or Atrial Flutter	3 (5.4)	0
Total Number of Subjects with New On-treatment AEs of Atrial Fibrillation or Atrial Flutter	1 (1.8)	0

VALOR study (MYK-461-017) – long-term follow-up

In the LTFU, 7 (6.5%) subjects were reported with on-treatment AEs of atrial fibrillation or atrial flutter during LTFU (Table 74). Only 3 (2.8%) subjects were reported with new onset atrial fibrillation/flutter AEs.

Table 74. Incidence of Atrial Fibrillation / Flutter - Long-Term Follow-up.

	Previous Mavacamten (N = 56) n (%)	Previous Placebo (N = 52) n (%)	Total Mavacamten (N = 108) n (%)
Total Number of Treatment-Emergent AEs of Atrial Fibrillation or Atrial Flutter	7	4	11
Total Number of Recurrent Treatment-Emergent AEs of Atrial Fibrillation or Atrial Flutter	5	1	6
Total Number of New Treatment-Emergent AEs of Atrial Fibrillation or Atrial Flutter	2	3	5
Total Number of Subjects with Treatment-Emergent AEs of Atrial Fibrillation or Atrial Flutter	5 (8.9)	2 (3.8)	7 (6.5)
Total Number of Subjects with Recurrent Treatment-Emergent AEs of Atrial Fibrillation or Atrial Flutter	3 (5.4)	1 (1.9)	4 (3.7)
Total Number of Subjects with New Treatment-Emergent AEs of Atrial Fibrillation or Atrial Flutter	2 (3.6)	1 (1.9)	3 (2.8)

Syncope/presyncope.

A summary of events in the ECI category of syncope/presyncope by the preferred term is provided in the Table 75 below:

Table 75. Subject incidence of syncope/presyncope events of clinical interest by preferred term (narrow and broad definitions).

Category Preferred Term	All-Mava N = 314 n (%)		oHCM				nHCM			
			RCT-Mava N = 123 n (%)		RCT-Placebo N = 128 n (%)		RCT-Mava N = 39 n (%)		RCT-Placebo N = 19 n (%)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Syncope/Presyncope (narrow)	16 (5.1)	3 (1.0)	8 (6.5)	3 (2.4)	7 (5.5)	1 (0.8)	0	0	1 (5.3)	0
Syncope	9 (2.9)	3 (1.0)	7 (5.7)	3 (2.4)	2 (1.6)	1 (0.8)	NR	NR	NR	NR
Presyncope	9 (2.9)	0	2 (1.6)	0	5 (3.9)	0	0	0	1 (5.3)	0
Syncope/Presyncope (broad)	68 (21.7)	4 (1.3)	30 (24.4)	4 (3.3)	25 (19.5)	1 (0.8)	7 (17.9)	0	3 (15.8)	0
Dizziness	62 (19.7)	1 (0.3)	26 (21.1)	1 (0.8)	17 (13.3)	0	7 (17.9)	0	1 (5.3)	0
Syncope	9 (2.9)	3 (1.0)	7 (5.7)	3 (2.4.)	2 (1.6)	1 (0.8)	NR	NR	NR	NR
Presyncope	9 (2.9)	0	2 (1.6)	0	5 (3.9)	0	0	0	1 (5.3)	0
Hypotension	2 (0.6)	0	1 (0.8)	0	3 (2.3)	0	0	0	1 (5.3)	0
Orthostatic hypotension	2 (0.6)	0	1 (0.8)	0	0	0	NR	NR	NR	NR

When using a narrow definition for syncope/presyncope, incidence of any grade events in the randomized placebo-blinded studies were generally similar between treatment groups. Although incidence for Grade ≥3 events were numerically higher for mavacamten-treated subjects than in subjects who received placebo, these were due to Grade 3 SAEs of syncope (and not presyncope, for which there were no Grade ≥3 events).

When using a broad definition for syncope/presyncope, a numerical imbalance was observed between treatment groups in data from the randomized placebo-blinded studies. However, the majority of the increased incidence (from narrow to broad definitions) and the imbalance between treatment groups could be attributed to non-serious and low grade events of dizziness. Dizziness and syncope are considered ADRs for mavacamten.

QTc prolongation.

In the RCT studies, there were no mavacamten-treated subjects with AEs of electrocardiogram QT prolonged. There was 1 subject in the RCT-Placebo oHCM treatment group of the Study MYK-461-005 with 2 reported AEs of electrocardiogram QT prolonged; both events were considered by the investigator as related to study treatment. Both events were non-serious Grade 1 AEs that led to temporary interruption of blinded placebo.

Across the integrated analyses, there was 2 mavacamten-treated subjects in the MYK-461-007 study each with a Grade 1 AE of electrocardiogram QT prolonged; for one subject the AE led to temporary dose interruption and the subject resumed treatment. The second subject was permanently discontinued from treatment having met protocol-specific criteria for QT prolongation.

In the RCT-Mava oHCM compared with the RCT Placebo oHCM treatment group, 3 vs. 3 subjects met protocol-specified criteria for QTcF prolongation while on study treatment. All 6 subjects underwent temporary discontinuation of study treatment and subsequently resumed dosing, most at a lower dose according to protocol-specified guidance. Of the 3 subjects in the RCT-Mava oHCM treatment group, 1 subject met criteria based on an earlier protocol version and would not have qualified as meeting QTcF prolongation criteria under the protocol version that was in effect at the completion of the study, and 1 subject met criteria due to a baseline QTcF value that was subsequently re-adjudicated. For the remaining 1 mavacamten-treated subject, approximately 1 week into the temporary discontinuation period (while off treatment) the subject also met protocol-specified criteria for LVEF <50% in the clinical context of a Grade 3 SAE of stress cardiomyopathy.

In the RCT-Mava nHCM and RCT-Placebo treatment groups, no subjects met protocol-specified criteria due to QTcF prolongation while on study treatment. However, 1 subject in the mavacamten-treated group had QTcF of 500 ms that met the protocol-specified safety threshold (<500 ms) for the study after treatment had already been discontinued. One week prior to the QTcF value, this subject had permanently discontinued study treatment due to heart failure related to systolic dysfunction (also reported as a Grade 3 SAE of systolic dysfunction leading to permanent treatment discontinuation); the same subject also had an AE of atrial fibrillation reported as leading to permanent treatment discontinuation, and also (on the same day as the QTcF value) met the protocol-specified criterion of LVEF ≤45%.

Considering all mavacamten-exposed subjects across the integrated analyses (All-Mava combined), in addition to the randomized placebo-blinded studies discussed above there were 11 subjects (8 with oHCM and 3 with nHCM) who met protocol-specified temporary discontinuation thresholds for QTcF prolongation criteria during long-term extension. Ten of these subjects (8 with oHCM and 2 with nHCM) were on treatment at the time of the qualifying QTcF value(s) and were eligible for actions with study treatment (ie, for treatment interruption and dose reduction).

Of the 8 subjects with oHCM, 2 subjects subsequently permanently discontinued study treatment due to stopping criteria met; all mavacamten plasma trough concentrations for these 2 subjects were <55 ng/mL in the extension study. The 6 remaining subjects with oHCM all had a temporary treatment interruption of which 5 resumed mavacamten at a lower dose and 1 subject in long-term extension had not resumed treatment as of the data cutoff. Two of the 3 subjects with nHCM met protocol-specified criteria while on treatment. One of the subjects had no action taken based on investigator clinical

judgment and another subject permanently discontinued treatment due to prolonged QTcF and the study as the subject was on the lowest dose of the study drug.

Relatively few mavacamten-treated subjects in the integrated analyses met protocol-specified criteria for QTcF prolongation; in total there were 4 subjects identified, all of whom were subjects with oHCM, including 3 subjects from the pivotal study (balanced in the pivotal study with 3 subjects who received placebo also meeting protocol-specified criteria for QTcF prolongation; MYK-461-005 CSR Section 10.2.2). None of the 4 mavacamten-treated subjects who met protocol-specified criteria for QTcF prolongation had associated mavacamten plasma trough concentrations above 700 ng/mL, and 1 of the 4 subjects had associated.

Summarized ECG data from the mavacamten integrated studies for QTc interval values and changes from baseline are provided in Table 76.

Table 76. Electrocardiogram Data for QTcF intervals and changes from baseline in mavacamten integrated studies

Overall Population					
	All-Mava combined N = 314	oHCM		nHCM	
		RCT-Mava N = 123	RCT-Placebo N = 128	RCT-Mava N = 39	RCT- Placebo N = 19
Maximum Post-baseline					
n	314	123	128	39	19
Mean	461.14	453.68	459.10	460.87	466.79
Median	459.00	451.00	457.00	463.00	472.00
Min, Max	405.0, 547.0	404.0, 519.0	396.0, 528.0	405.0, 500.0	421.0, 499.0
Change					
Mean	19.54	13.89	15.76	14.85	17.74
Median	17.00	12.00	16.00	16.00	16.00
Min, Max	-27.0, 108.0	-34.0, 65.0	-121.0, 107.0	-29.0, 49.0	-15.0, 42.0
With ICD/Pacemaker					
	All-Mava combined N = 84	oHCM		nHCM	
		RCT-Mava N = 27	RCT- Placebo N = 29	RCT-Mava N = 24	RCT- Placebo N = 13
Maximum Post-baseline					
n	84	27	29	24	13
Mean	463.73	462.56	465.97	459.38	466.69
Median	462.00	460.00	460.00	461.50	462.00
Min, Max	405.0, 519.0	424.0, 519.0	418.0, 528.0	405.0, 500.0	432.0, 498.0
Change					
Mean	21.27	16.81	15.00	16.29	16.46
Median	18.50	12.00	15.00	17.50	16.00
Min, Max	-27.0, 104.0	-9.0, 60.0	-121.0, 107.0	-27.0, 49.0	-15.0, 42.0
Without ICD/Pacemaker					
	All-Mava combined N = 230	oHCM		nHCM	
		RCT-Mava N = 96	RCT- Placebo N = 99	RCT-Mava N = 15	RCT- Placebo N = 6
Maximum Post-baseline					
n	230	96	99	15	6
Mean	460.20	451.18	457.09	463.27	467.00
Median	456.50	450.50	455.00	465.00	475.00

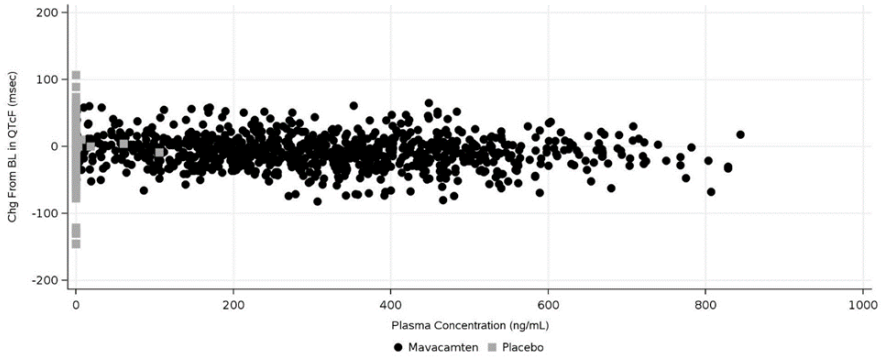
Min, Max	416.0, 547.0	404.0, 495.0	396.0, 526.0	433.0, 493.0	421.0, 499.0
Change					
Mean	18.91	13.06	15.98	12.53	20.50
Median	17.00	12.50	16.00	15.00	29.50
Min, Max	-27.0, 108.0	-34.0, 65.0	-24.0, 74.0	-29.0, 42.0	-3.0, 32.0

Categorical ECG data from the mavacamten integrated studies for QTc prolongation are provided in Table 77 below.

Table 77. Categorical Data for QTcF Prolongation in Mavacamten Integrated Studies.

Overall Population					
QTcF Category	All-Mava combined N = 314	oHCM		nHCM	
		RCT-Mava N = 123	RCT-Placebo N = 128	RCT-Mava N = 39	RCT- Placebo N = 19
Post-baseline					
> 450 ms	202 (64.3)	65 (52.8)	72 (56.3)	28 (71.8)	15 (78.9)
> 480 ms	77 (24.5)	20 (16.3)	32 (25.0)	7 (17.9)	5 (26.3)
> 500 ms	14 (4.5)	3 (2.4)	7 (5.5)	0	0
> 520 ms	3 (1.0)	0	2 (1.6)	0	0
> 550 ms	0	0	0	0	0
Change					
> 30 ms	81 (25.8)	22 (17.9)	20 (15.6)	11 (28.2)	4 (21.1)
> 60 ms	14 (4.5)	2 (1.6)	3 (2.3)	0	0
With ICD/Pacemaker					
QTcF Category	All-Mava combined N = 84	oHCM		nHCM	
		RCT-Mava N = 27	RCT- Placebo N = 29	RCT-Mava N = 24	RCT- Placebo N = 13
Post-baseline					
> 450 ms	58 (69.0)	17 (63.0)	19 (65.5)	16 (66.7)	10 (76.9)
> 480 ms	22 (26.2)	7 (25.9)	10 (34.5)	5 (20.8)	4 (30.8)
> 500 ms	4 (4.8)	3 (11.1)	4 (13.8)	0	0
> 520 ms	0	0	1 (3.4)	0	0
> 550 ms	0	0	0	0	0
Change					
> 30 ms	24 (28.6)	4 (14.8)	5 (17.2)	8 (33.3)	2 (15.4)
> 60 ms	3 (3.6)	0	2 (6.9)	0	0
Without ICD/Pacemaker					
QTcF Category	All-Mava combined N = 230	oHCM		nHCM	
		RCT-Mava N = 96	RCT- Placebo N = 99	RCT-Mava N = 15	RCT- Placebo N = 6
Post-baseline					
> 450 ms	144 (62.6)	48 (50.0)	53 (53.5)	12 (80.0)	5 (83.3)
> 480 ms	55 (23.9)	13 (13.5)	22 (22.2)	2 (13.3)	1 (16.7)
> 500 ms	10 (4.3)	0	3 (3.0)	0	0
> 520 ms	3 (1.3)	0	1 (1.0)	0	0
> 550 ms	0	0	0	0	0
Change					
> 30 ms	57 (24.8)	18 (18.8)	15 (15.2)	3 (20.0)	2 (33.3)
> 60 ms	11 (4.8)	0	1 (1.0)	0	0

Figure 44. MYK-461-005: Mavacamten Trough Concentration Versus Change from Baseline in QTcF (Safety Population).



Dose- and concentration-dependent modest QTc prolongation has been observed after prolonged administration of supratherapeutic doses in healthy (non-HCM) hearts (nonclinical healthy animal and clinical pharmacology healthy participants). In contrast, data do not support QTc prolongation in subjects with the underlying cardiac pathophysiology of HCM.

Clinical investigations of mavacamten in subjects with HCM, with regression analyses performed on centrally-read ECG data, revealed a very modest but consistent negative correlation between mavacamten plasma concentrations and change from baseline in QTcF (slope of the concentration-effect in the pivotal Phase 3 study: 0.0180).

Across the integrated analyses, there were no mavacamten-treated subjects with reported AEs coding to the MedDRA PT of electrocardiogram QT prolonged. Regarding potential clinical events relevant to QTc prolongation (including torsade de pointes, ventricular arrhythmias, syncope, seizures, or sudden death), or in analyses of mean and categorical QTcF intervals from ECGs, the data do not suggest a safety concern for mavacamten. Additionally, relatively few mavacamten-treated subjects in the integrated analyses met protocol-specified criteria for QTc prolongation (with numbers of subjects balanced in the pivotal study between the treatment arms); no clear relationship between these subjects and mavacamten plasma concentration was identified.

In summary, the QTc observations in healthy hearts exposed to mavacamten were not reproduced in analyses of subjects with HCM.

VALOR study (MYK-461-017) – double-blind period

In prior mavacamten studies subjects were required to have baseline QTcF <500 ms for enrollment. This was not an exclusion criterion in the VALOR-HCM study. Additionally, in prior mavacamten studies prolonged QTcF was used as a temporary discontinuation criterion. This was not a temporary discontinuation criterion in the VALOR-HCM study.

At baseline QTcF interval > 450 ms was similar between mavacamten and placebo groups, whereas QTcF interval > 500 ms was observed in 2 (3.6%) subjects of the mavacamten treatment group only (Table 78). One of the subjects was on disopyramide, which is known to prolong QTcF. During the study this subject's QTcF was <500 ms. The other subject had a baseline QTcF of 524 ms and maximum of 530 ms during the RCT period. Neither subject had left bundle branch block. Neither of the subjects had an ICD or a pacemaker.

For the overall safety population, a smaller proportion of subjects in the mavacamten group compared with the placebo group had a post baseline QTcF interval > 450 ms (51.8% vs 61.8%). Maximum

change from baseline > 60 ms was observed only in mavacamten treatment group in 3.6% of the subjects.

Twenty-two subjects were on disopyramide as part of their HCM SOC medication. 14 of the 22 subjects were in the mavacamten arm. The range of QTcF at baseline for mavacamten subjects on disopyramide was 426 ms – 514 ms. The maximum QTcF during the double-blind period for mavacamten subjects on disopyramide ranged from 439 ms to 509 ms. The range of QTcF at baseline for placebo subjects on disopyramide was 427 ms- 514 ms. The maximum QTcF during the double-blind period for placebo subjects on disopyramide ranged from 444 ms – 517ms. There is no safety concern of DDI of mavacamten and disopyramide regarding prolongation of QTcF.

Two subjects in the mavacamten arm with maximum post-baseline increase in QTcF >60 ms were the same 2 subjects having maximum increase >15% from baseline. One patient was paced and had baseline QTcF 423 ms; Week 4 QTcF 487 ms and Week 16 QTcF 477 ms. The other patient had history of atrial fibrillation with baseline QTcF 390 ms and Week 16 QTcF 452 ms following cardioversion for AF.

Table 78. Summary of QTcF Intervals – VALOR-HCM study Double Blind Period

QTcF Category	Mavacamten (N = 56) n (%)	Placebo (N = 55) n (%)
Baseline QTcF [1]		
> 450 msec	26 (46.4)	26 (47.3)
> 480 msec	8 (14.3)	7 (12.7)
> 500 msec	2 (3.6)	0
> 520 msec	1 (1.8)	0
> 550 msec	0	0
Maximum Post-baseline QTcF		
> 450 msec	29 (51.8)	34 (61.8)
> 480 msec	8 (14.3)	12 (21.8)
> 500 msec	4 (7.1)	4 (7.3)
> 520 msec	1 (1.8)	0
> 550 msec	0	0
Maximum Change from Baseline		
> 30 msec	5 (8.9)	7 (12.7)
> 60 msec	2 (3.6)	0
Maximum % Change from Baseline		
> 15%	2 (3.6)	0

Overall, a QTcF regression analysis was performed on all 56 subjects (53 were on SOC HCM medications) who were administered mavacamten, and showed a negative slope, thereby showing no concentration effect of mavacamten on QTcF (Table 79).

Table 79. Concentration-QTcF Regression Analysis Safety Analysis Population – VALOR-HCM study - Double Blind Period

	Mavacamten (N=56)				
	Estimate	DF	95% CI	SE	p-value
Effect					
Intercept	8.2433	113	-11.8640, 28.3506	10.1495	0.4184
Sex effect	5.8002	53	-4.8102, 16.4106	5.2893	0.2778
Pace effect	-18.1328	121	-36.4133, 0.1478	9.2337	0.0519
Concentration effect	-0.0066	209	-0.0219, 0.0087	0.0078	0.3952

Renal Events

A summary of renal events by the preferred term is provided in Table 80.

Table 80. Subject incidence of renal events of clinical interest by preferred term.

Category Preferred Term	All-Mava combined N = 314 n (%)	oHCM		nHCM	
		RCT-Mava N = 123 n (%)	RCT– Placebo N = 128 n (%)	RCT-Mava N = 39 n (%)	RCT- Placebo N = 19 n (%)
Renal Events (narrow SMQ)	6 (1.9)	1 (0.8)	0	1 (2.6)	0
Acute kidney injury	4 (1.3)	1 (0.8)	0	NR	NR
Renal failure	2 (0.6)	NR	NR	1 (2.6)	0

Considering all mavacamten-exposed subjects with any indication (All-Mava combined), 1.9% (6 subjects) were reported with renal events. In addition to the 1 subject reported in the RCT-Mava oHCM study, 3 subjects in the long-term extension study MYK-461-007 reported renal events of acute kidney injury; 1 was non-serious Grade 2 that was resolving as of the data cut for the study. The other 2 subjects with acute kidney injury and reported these events as Grade 3 and SAEs. One subject with an SAE of acute kidney injury was associated with a cytomegalovirus infection and the other subject with an SAE of acute kidney injury was associated with elevated creatinine levels (1.7 mg/dl). The 1 subject who reported an event of renal failure had a Grade 1 event that was nonserious and resolving as of the data-cut for this study.

Based on current review of AE data and relevant laboratory data, nephrotoxicity is not associated with mavacamten use. Evidence supports the safe use of mavacamten in patients with a range of renal functions ranging from normal to moderate (eGFRs ≥30 ml/min/1.73m2) renal insufficiency.

Hepatic Events.

Overall, hepatic ECIs were primarily non-serious and low-grade in the mavacamten clinical studies. Event incidences for mavacamten-treated oHCM subjects were comparable to incidence for subjects who received placebo in the randomized placebo-blinded studies with 3.3% vs. 3.1%, respectively (4 subjects each). In the RCT-Mava nHCM treatment group, there was 1 subject (2.6%) with events in the hepatic ECI category and none in the placebo group. The overall incidence rate was similar as in the all-Mava combined population, 3.5% (11 subjects) experienced any grade hepatic events. The infrequent events of transaminase elevations were either represented baseline disease (e.g. hepatic steatosis) or were clearly secondary to other alternative aetiologies, such as AST increased in the context of a diagnosis of a Klatskin's type cholangiocarcinoma or liver injury secondary to cardiogenic shock.

Across the integrated analyses, the subject incidence for abnormal elevations of liver laboratory tests was overall low. In the randomized placebo-blinded studies, no subjects had AST or ALT > 3x ULN or alkaline phosphatase (ALP) > 1.5x ULN elevations during the studies, and the proportions of subjects who had TBL > 1.5x ULN during the studies were balanced between mavacamten-treated subjects and subjects who received placebo (3 subjects each in RCT-Mava combined and RCT- Placebo combined). In the RCT-Mava oHCM treatment group, 1 subject with a medical history of hereditary spherocytosis and jaundice had a baseline TBL of 9.02 mg/dL on SD1 and post-baseline TBL values ranging up to 10.76 mg/dL during the study.

Considering all mavacamten-exposed subjects with any indication (All-Mava combined), <2% of subjects had TBL > 2x ULN, and <1% of subjects had AST or ALT > 3x ULN or ALP > 1.5x ULN. A detailed review of liver laboratory test data for these subjects revealed that most subjects meeting the indicated thresholds for abnormal elevations of post-baseline liver laboratory tests also had abnormal elevations at baseline (screening or SD1).

Based on the current review of hepatic AE data and relevant laboratory data, hepatotoxicity is not associated with mavacamten use.

2.5.8.4. Laboratory findings

Haematology

Summarized data are provided for the following core clinical haematology laboratory evaluations: absolute neutrophil count (ANC), haemoglobin, white blood cell (WBC) counts (leukocytes), and platelets. They are presented in Table 81 below:

Table 81. Haematology parameters

Laboratory Test (Unit) / Timepoint	Baseline	Post-Baseline: Low	Normal	High	Total
Hemoglobin (g/dL)					
RCT-Mava (n=120)	Low	2 (1.7)	1 (0.8)	0	3 (2.5)
	Normal	3 (2.5)	106 (88.3)	2 (1.7)	111 (92.5)
	High	0	4 (3.3)	2 (1.7)	6 (5.0)
	Total	5 (4.2)	111 (92.5)	4 (3.3)	120 (100)
RCT-Placebo (n=123)	Low	1 (0.8)	1 (0.8)	0	2 (1.6)
	Normal	4 (3.3)	115 (93.5)	0	119 (96.7)
	High	0	1 (0.8)	1 (0.8)	2 (1.6)
	Total	5 (4.1)	117 (95.1)	1 (0.8)	123 (100)
Leukocytes ((10^9)/L)					
RCT-Mava (n=120)	Low	1 (0.8)	0	0	1 (0.8)
	Normal	0	113 (94.2)	2 (1.7)	115 (95.8)
	High	0	1 (0.8)	3 (2.5)	4 (3.3)
	Total	1 (0.8)	114 (95.0)	5 (4.2)	120 (100)
RCT-Placebo (n=123)	Low	2 (1.6)	0	0	2 (1.6)
	Normal	0	116 (94.3)	3 (2.4)	119 (96.7)
	High	0	2 (1.6)	0	2 (1.6)
	Total	2 (1.6)	118 (95.9)	3 (2.4)	123 (100)
Neutrophils ((10^9)/L)					
RCT-Mava (n=120)	Low	1 (0.8)	1 (0.8)	0	2 (1.7)
	Normal	0	113 (94.2)	2 (1.7)	115 (95.8)
	High	0	3 (2.5)	0	3 (2.5)
	Total	1 (0.8)	117 (97.5)	2 (1.7)	120 (100)
RCT-Placebo (n=123)	Low	0	1 (0.8)	0	1 (0.8)
	Normal	3 (2.4)	113 (91.9)	5 (4.1)	121 (98.4)
	High	0	1 (0.8)	0	1 (0.8)
	Total	3 (2.4)	115 (93.5)	5 (4.1)	123 (100)
Platelets ((10^9)/L)					
RCT-Mava (n=120)	Low	13 (10.8)	9 (7.5)	0	22 (18.3)
	Normal	3 (2.5)	93 (77.5)	2 (1.7)	98 (81.7)
	High	0	0	0	0
	Total	16 (13.3)	102 (85.0)	2 (1.7)	120 (100)
RCT-Placebo (n=123)	Low	8 (6.5)	4 (3.3)	0	12 (9.8)
	Normal	4 (3.3)	105 (85.4)	1 (0.8)	110 (89.4)
	High	0	1 (0.8)	0	1 (0.8)
	Total	12 (9.8)	110 (89.4)	1 (0.8)	123 (100)

There were no clinically important mean changes in haematology parameters from baseline to the most extreme post-baseline values. The proportions of subjects with shifts of haematology parameters in the high or low directions from baseline to post-baseline values were generally similar between RCT-Mava combined, and RCT-Placebo combined treatment groups (representing mavacamten-treated subjects and subjects who received placebo in the randomized placebo-blinded studies).

Analyses of haematology parameters by indication (oHCM or nHCM) were consistent with analyses of haematology parameters in the integrated data summaries. Overall, there were no clinically important haematology safety findings for mavacamten.

VALOR study (MYK-461-017) – double-blind period

In both groups, all hematology laboratory mean values were within reference ranges at baseline, and were stable through Week 16. Individually, most subjects had normal hematology laboratory parameters at baseline and Week 16. Coagulation laboratory mean values were within normal ranges and were stable from baseline through Week 16.

VALOR study (MYK-461-017) – long-term follow-up

Overall, for each treatment group, hematology laboratory and coagulation laboratory values were within normal ranges and were stable from baseline through Week 80.

Clinical Chemistry

Summarized data are provided for the following core clinical chemistry laboratory evaluations: ALT, albumin, ALP, AST, total bilirubin (TBL), calcium, creatine kinase (CK), creatinine, creatinine clearance, glucose, magnesium, potassium, and sodium.

They are presented in Table 82 below:

Table 82. Chemistry parameters

Laboratory Test (Unit) Timepoint	Baseline	Post-Baseline Low	Normal	High	Total
ALT					
RCT-Mava (n=123)	Low	1 (0.8)	1 (0.8)	0	2 (1.6)
	Normal	0	87 (70.7)	22 (17.9)	109 (88.6)
	High	0	2 (1.6)	10 (8.1)	12 (9.8)
	Total	1 (0.8)	90 (73.2)	32 (26.0)	123 (100)
RCT-Placebo (n=128)	Low	2 (1.6)	2 (1.6)	0	4 (3.1)
	Normal	0	96 (75.0)	18 (14.1)	114 (89.1)
	High	0	1 (0.8)	9 (7.0)	10 (7.8)
	Total	2 (1.6)	99 (77.3)	27 (21.1)	128 (100)
Albumin					
RCT-Mava (n=123)	Low	0	0	0	0
	Normal	1 (0.8)	122 (99.2)	0	123 (100)
	High	0	0	0	0
	Total	1 (0.8)	122 (99.2)	0	123 (100)
RCT-Placebo (n=128)	Low	0	0	0	0
	Normal	0	128 (100)	0	128 (100)
	High	0	0	0	0
	Total	0	128 (100)	0	128 (100)
ALP					
RCT-Mava (n=123)	Low	2 (1.6)	0	0	2 (1.6)
	Normal	0	113 (91.9)	5 (4.1)	118 (95.9)
	High	0	1 (0.8)	2 (1.6)	3 (2.4)
	Total	2 (1.6)	114 (92.7)	7 (5.7)	123 (100)
RCT-Placebo (n=128)	Low	2 (1.6)	3 (2.3)	0	5 (3.9)
	Normal	0	118 (92.2)	2 (1.6)	120 (93.8)
	High	0	0	3 (2.3)	3 (2.3)
	Total	2 (1.6)	121 (94.5)	5 (3.9)	128 (100)
AST					
RCT-Mava (n=123)	Low	0	0	0	0
	Normal	0	106 (86.2)	13 (10.6)	119 (96.7)
	High	0	1 (0.8)	3 (2.4)	4 (3.3)
	Total	0	107 (87.0)	16 (13.0)	123 (100)
RCT-Placebo (n=128)	Low	0	0	0	0
	Normal	0	111 (86.7)	10 (7.8)	121 (94.5)
	High	0	2 (1.6)	5 (3.9)	7 (5.5)
	Total	0	113 (88.3)	15 (11.7)	128 (100)
total bilirubin (TBL)					

RCT-Mava (n=123)	Low	0	0	0	0
	Normal	0	110 (89.4)	4 (3.3)	114 (92.7)
	High	0	3 (2.4)	6 (4.9)	9 (7.3)
	Total	0	113 (91.9)	10 (8.1)	123 (100)
RCT-Placebo (n=128)	Low	0	0	0	0
	Normal	0	116 (90.6)	5 (3.9)	121 (94.5)
	High	0	1 (0.8)	6 (4.7)	7 (5.5)
	Total	0	117 (91.4)	11 (8.6)	128 (100)

Calcium

RCT-Mava (n=123)	Low	0	1 (0.8)	0	1 (0.8)
	Normal	0	117 (95.1)	4 (3.3)	121 (98.4)
	High	0	0	1 (0.8)	1 (0.8)
	Total	0	118 (95.9)	5 (4.1)	123 (100)
RCT-Placebo (n=128)	Low	0	0	0	0
	Normal	0	124 (96.9)	4 (3.1)	128 (100)
	High	0	0	0	0
	Total	0	124 (96.9)	4 (3.1)	128 (100)

Creatine kinase (CK)

RCT-Mava (n=123)	Low	0	0	0	0
	Normal	0	108 (87.8)	7 (5.7)	115 (93.5)
	High	0	1 (0.8)	7 (5.7)	8 (6.5)
	Total	0	109 (88.6)	14 (11.4)	123 (100)
RCT-Placebo (n=128)	Low	0	0	0	0
	Normal	0	99 (77.3)	14 (10.9)	113 (88.3)
	High	0	3 (2.3)	12 (9.4)	15 (11.7)
	Total	0	102 (79.7)	26 (20.3)	128 (100)

Creatinine

RCT-Mava (n=123)	Low	9 (7.3)	9 (7.3)	0	18 (14.6)
	Normal	0	100 (81.3)	4 (3.3)	104 (84.6)
	High	0	0	1 (0.8)	1 (0.8)
	Total	9 (7.3)	109 (88.6)	5 (4.1)	123 (100)
RCT-Placebo (n=128)	Low	10 (7.8)	5 (3.9)	0	15 (11.7)
	Normal	0	108 (84.4)	1 (0.8)	109 (85.2)
	High	0	1 (0.8)	3 (2.3)	4 (3.1)
	Total	10 (7.8)	114 (89.1)	4 (3.1)	128 (100)

glucose

RCT-Mava (n=123)	Low	0	0	0	0
	Normal	0	94 (76.4)	18 (14.6)	112 (91.1)
	High	0	5 (4.1)	6 (4.9)	11 (8.9)
	Total	0	99 (80.5)	24 (19.5)	123 (100)
RCT-Placebo (n=126)	Low	0	0	0	0
	Normal	0	101 (80.2)	9 (7.1)	110 (87.3)
	High	0	2 (1.6)	14 (11.1)	16 (12.7)
	Total	0	103 (81.7)	23 (18.3)	126 (100)

Magnesium

RCT-Mava (n=123)	Low	1 (0.8)	1 (0.8)	0	2 (1.6)
	Normal	0	121 (98.4)	0	121 (98.4)
	High	0	0	0	0
	Total	1 (0.8)	122 (99.2)	0	123 (100)
RCT-Placebo (n=128)	Low	0	0	0	0
	Normal	0	128 (100)	0	128 (100)
	High	0	0	0	0
	Total	0	128 (100)	0	128 (100)

potassium

RCT-Mava (n=123)	Low	0	0	0	0
	Normal	0	97 (78.9)	14 (11.4)	111 (90.2)
	High	0	7 (5.7)	5 (4.1)	12 (9.8)
	Total	0	104 (84.6)	19 (15.4)	123 (100)
RCT-Placebo (n=126)	Low	0	1 (0.8)	0	1 (0.8)
	Normal	0	96 (76.2)	19 (15.1)	115 (91.3)
	High	0	2 (1.6)	8 (6.3)	10 (7.9)
	Total	0	99 (78.6)	27 (21.4)	126 (100)

Sodium

RCT-Mava (n=123)	Low	0	0	0	0
	Normal	0	119 (96.7)	4 (3.3)	123 (100)
	High	0	0	0	0
	Total	0	119 (96.7)	4 (3.3)	123 (100)
RCT-Placebo (n=128)	Low	0	1 (0.8)	0	1 (0.8)
	Normal	0	122 (95.3)	3 (2.3)	125 (97.7)
	High	0	1 (0.8)	1 (0.8)	2 (1.6)
	Total	0	124 (96.9)	4 (3.1)	128 (100)

Overall, there were no clinically important mean changes in general chemistry laboratory tests from baseline to the most extreme post-baseline values. While some shift differences were observed, further interpretation was limited. For observed shifts in glucose values, pre-procedure fasting for cardiac assessments that were scheduled at the same visits may have resulted in application of fasting normal ranges to glucose values collected at those visits. For observed shifts in calcium and potassium,

interpretation was limited due to overall small numbers of subjects with abnormal values; in addition, differences in use of concomitant diuretics may have been a contributing factor. For observed shifts in magnesium as well as some observed shifts in potassium, data from subjects in the randomized placebo-blinded studies appeared to favour mavacamten-treated subjects over subjects who received placebo, suggesting that the observed shifts were spurious and not clinically meaningful.

In summary, after a detailed review of general chemistry parameters, no safety concerns for mavacamten were identified.

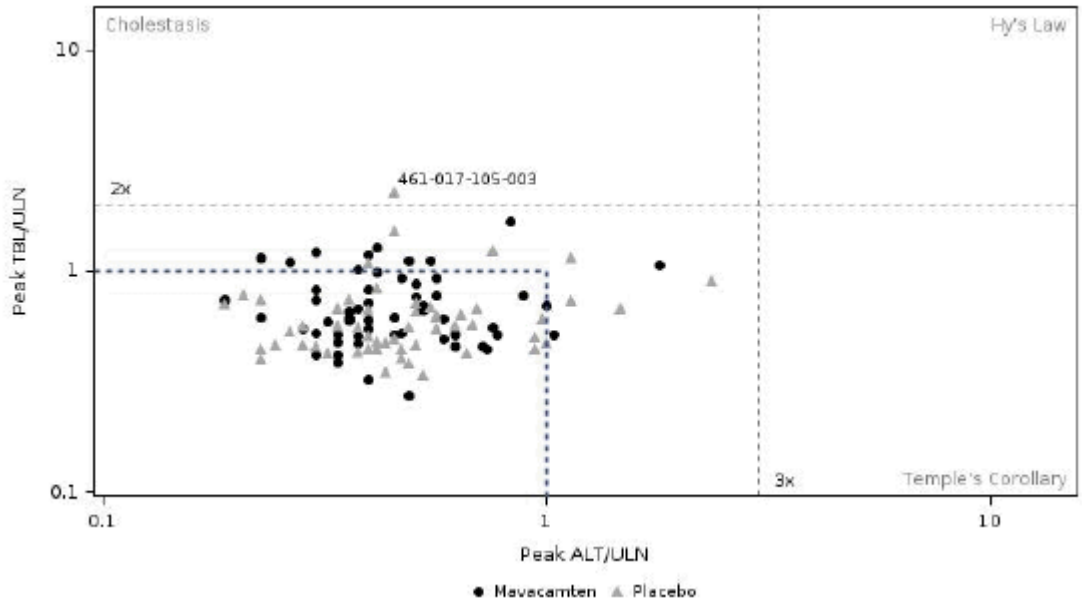
VALOR study (MYK-461-017) – double-blind period

In both groups, all chemistry laboratory mean values except indirect bilirubin (only measured in <5% of subjects) were within reference ranges or at a desirable (cholesterol, glucose, GFR) or expected (FSH for post-menopausal woman) level at baseline and were stable through Week 16. Individually, most subjects had normal chemistry laboratory parameters.

Liver toxicity was assessed by elevations in ALT, AST, ALP, and TBL. Across treatment groups, no subjects met any category of ALT > 3 × ULN, AST > 3 × ULN, or ALP > 1.5 × ULN. Review of liver enzyme tests indicated that no subjects met the criteria for DILI assessed by concurrent ALT or AST > 3 × ULN and bilirubin > 2 × ULN, where transaminase elevation coincided with or preceded TBL elevation (ie, possible Hy's Law cases).

Figure 45 is a graphic representation of peak ALT values versus peak TBL values during the treatment-emergent period (Day 1 to Week 16) by treatment group for the safety population. Subjects with TBL > 2 × ULN are identified on the graph.

Figure 45: Distribution of Peak Values of ALT versus Peak Values of TBL by Treatment Group – VALOR-HCM study - Double-Blind Period.



Urine pH and specific gravity mean values were within reference ranges at baseline and Week 16; other baseline urinalysis measurements were only available in few subjects.

VALOR study (MYK-461-017) – Long-term follow-up

Overall, chemistry laboratory values were within normal ranges and were stable from baseline through Week 80.

Across treatment groups, no subjects met any category of ALT > 3 × ULN, AST > 3 × ULN, or ALP > 1.5 × ULN. Review of liver enzyme tests indicated that no subjects met the criteria for DILI assessed by concurrent ALT or AST > 3 × ULN and bilirubin > 2× ULN, where transaminase elevation coincided with or preceded TBL elevation (ie, possible Hy's Law cases).

No notable or persistent urinalysis abnormalities were reported.

Cardiac Laboratory Tests

In the mavacamten clinical studies, NT-proBNP was a cardiac biomarker for myocardial wall stress and cTnI was a cardiac biomarker for myocardial injury.

In the randomized placebo-blinded studies (pivotal Study MYK-461-005 and supporting Study MYK-461-006), analyses were performed of changes from baseline in NT-proBNP and cTnI for subjects treated with blinded mavacamten compared with subjects who received blinded placebo. The results of these analyses supported a dose-dependent relationship between mavacamten treatment and reduction in NT-proBNP and decreases of cTnI. The pattern of changes in NT-proBNP observed in the extension Study MYK-461-007 with long-term use of mavacamten was consistent with those observed in the parent studies. Overall, these findings were consistent with a potential benefit and not a safety concern for mavacamten.

VALOR study (MYK-461-017) – double-blind period

Mean ECG measurements (heart rate, PR, QRS, and QTcF) were within normal ranges from baseline through Week 16, with no notable changes observed in either group.

In subjects with cardiac monitoring data at Week 16, AF was reported in 1 (1.8%) and 2 (3.6%) subjects in the mavacamten and placebo treatment groups, respectively. Maximum heart rate at Week 16 was 120.4 (± 21.95) vs 112.8 (± 19.36) beats / min in mavacamten vs placebo treatment groups, respectively. At least one NSVT episode at baseline was observed in 10 (17.9%) and 15 (27.3%) subjects vs at Week 16, 5 (8.9%) and 11 (20.0%) subjects in mavacamten and placebo treatment groups, respectively (Table 14.3.6). Ventricular tachycardia was reported only in 0 subjects in mavacamten group and 5 (9.1%) subjects in placebo group.

No notable changes from baseline in vital signs or physical findings were observed in either group.

VALOR study (MYK-461-017) – long-term follow-up

ECG parameters (heart rate, PR, QRS, and QTcF) were stable from baseline through Week 68, with no notable changes observed.

Holter monitoring was done after 16 weeks of mavacamten exposure in 44 previous mavacamten subjects and 28 previous placebo subjects. After 32 weeks of mavacamten exposure Holter monitoring was done in 30 subjects in the previous mavacamten arm and zero (0) subjects in the previous placebo arm.

In subjects with cardiac monitoring data, at 16 weeks of mavacamten exposure, AF was reported in 4 (3.7%) subjects, out of which 1 (1.8%) and.3 (5.8%) subjects were previously treated with mavacamten and placebo, respectively. No subjects were reported with AF at 32 Weeks of mavacamten exposure. Maximum heart rate after 16 weeks of mavacamten exposure was 120.5 (± 20.46) beats/min (120.1 +/- 21.8 in previous mavacamten arm and 121.2 +/- 18.5 in previous placebo arm). After 32 weeks of mavacamten exposure, maximum heart rate was 114.8 (± 16.03). At least one NSVT episode was observed in 9 (8.3%) subjects at 16 weeks of mavacamten exposure (5 in previous mavacamten arm and 4 in previous placebo arm), and in 8 (7.4%) subjects at 32 weeks of mavacamten exposure (all in previous mavacamten).

No notable changes from baseline in vital signs were observed

2.5.8.5. In vitro biomarker test for patient selection for safety

N/A

2.5.8.6. Safety in special populations

Intrinsic Factors

Effect of Sex

A summary of AEs occurring in ≥10% of subjects of either sex is provided in Table 83 below. By sex, 91.7% of male subjects and 94.0% of female subjects experienced any AE.

Overall, no safety concerns were identified in analyses of mavacamten-treated subjects across the integrated analyses stratified by sex subgroups, although more atrial fibrillation events were observed in male mavacamten-treated subjects and the converse was observed in subjects who received placebo.

Table 83. Subject Incidence of Adverse Events Occurring in ≥10% of Either Male or Female Subjects by Preferred Term

	All-Mava combined	
Preferred Term	Male N = 180 n (%)	Female N = 134 n (%)
At least 1 AE	165 (91.7)	126 (94.0)
Dizziness	34 (18.9)	28 (20.9)
Nasopharyngitis	27 (15.0)	20 (14.9)
Dyspnoea	27 (15.0)	15 (11.2)
Fatigue	30 (16.7)	19 (14.2)
Headache	25 (13.9)	21 (15.7)
Atrial fibrillation	28 (15.6)	10 (7.5)
Upper respiratory tract infection	19 (10.6)	13 (9.7)
Hypertension	16 (8.9)	19 (14.2)
Palpitations	14 (7.8)	14 (10.4)
Cough	9 (5.0)	15 (11.2)
Back pain	10 (5.6)	20 (14.9)
Nausea	6 (3.3)	15 (11.2)
Urinary tract infection	4 (2.2)	15 (11.2)

Effect of Age

Across the All-Mava combined population, 71/314 (22.6%) subjects of age <50 years, 131/314 (41.7%) subjects of age 50-64 years, and 112/314 (35.7%) subjects of age ≥65 years were dosed with mavacamten. By increasing age categories, 90.1%, 93.1%, and 93.8% of subjects experienced any AE (Table 84).

Integrated safety analyses of the effect of age for subjects treated with mavacamten did not reveal a safety concern for mavacamten use in older subjects with age >65 years. Although limited due to

small numbers, safety analyses for subjects >75 years of age also did not reveal safety concerns. A bimodal age distribution was noted for atrial fibrillation which may relate to the bimodal distribution of HCM where younger patients with the familial genetic-based disease are more likely to exhibit more severe disease with more adverse outcomes and marked cardiac hypertrophy, and older patients with sporadic disease are increasingly being recognized as incidental diagnoses of HCM.

Table 84. Subject Incidence of Adverse Events Occurring in ≥10% of Subjects in any Age Category by Preferred Term

	All-Mava combined		
Preferred Term	<50 years N = 71 n (%)	50-64 years N = 131 n (%)	**≥65** years N = 112 n (%)
At least 1 AE	64 (90.1)	122 (93.1)	105 (93.8)
Nasopharyngitis	12 (16.9)	22 (16.8)	13 (11.6)
Upper respiratory tract infection	11 (15.5)	12 (9.2)	9 (8.0)
Fatigue	11 (15.5)	15 (11.5)	23 (20.5)
Dizziness	10 (14.1)	24 (18.3)	28 (25.0)
Atrial fibrillation	10 (14.1)	12 (9.2)	16 (14.3)
Dyspnoea	9 (12.7)	17 (13.0)	16 (14.3)
Headache	8 (11.3)	19 (14.5)	19 (17.0)
Hypertension	4 (5.6)	10 (7.6)	21 (18.8)
Back Pain	8 (11.3)	9 (6.9)	13 (11.6)
Oedema peripheral	2 (2.8)	6 (4.6)	12 (10.7)

Effect of Race

Across the All-Mava combined population, 286/314 (91.0%) white subjects, 16/314 (5.1%) subjects of non-white (other) races, and 12/314 (3.8%) subjects of unknown race were dosed with mavacamten. By race categories, 92.3% of white subjects and 93.8% of non-white subjects experienced any AE.

Overall, no safety concerns were identified in analyses of mavacamten-treated subjects across the integrated analyses stratified by race subgroups. Analyses were generally limited by small numbers of non-white subjects.

Effect of renal function

A summary of AEs occurring in ≥10% of subjects in any renal function category (defined as normal or mildly impaired with CrCl ≥60 mL/min, or reduced with CrCl 30 to <60 mL/min), is provided in Table 85 below.

Across the All-Mava combined population, 289/310 (93.2%) subjects with normal or mildly impaired renal function and 21/310 (6.7%) subjects with reduced renal function were dosed with mavacamten.

By renal function category, 92.7% of subjects with normal or mildly impaired and 90.5% of subjects with reduced renal function experienced any AE.

In summary, integrated safety analyses of the effect of renal function for subjects treated with mavacamten did not reveal a safety concern for mavacamten use in subjects with reduced renal functions. The higher incidence of atrial fibrillation in mavacamten-treated subjects with reduced renal function than in subjects with normal or mildly impaired renal function is likely consistent with baseline demographics of the renal function subgroups, as the vast majority (90.5%) of subjects with reduced renal function were older subjects with age ≥65 years.

Table 85. Subject incidence of adverse events occurring in ≥10% of subjects in any renal function category by preferred term

Preferred Term	All-Mava combined	
	Normal or Mildly Impaired Renal Function N = 289 n (%)	Reduced Renal Function N = 21 n (%)
At least 1 AE	268 (92.7)	19 (90.5)
Dizziness	60 (20.8)	1 (4.8)
Nasopharyngitis	47 (16.3)	0
Dyspnoea	41 (14.2)	1 (4.8)
Fatigue	46 (15.9)	2 (9.5)
Upper respiratory tract infection	29 (10.0)	2 (9.5)
Headache	42 (14.5)	3 (14.3)
Atrial fibrillation	33 (11.4)	5 (23.8)
Urinary tract infection	16 (5.5)	3 (14.3)
Hypertension	29 (10.0)	5 (23.8)

Abbreviations: AE = adverse event; Mava = mavacamten. Data presented in this table are treatment emergent. Normal or mildly impaired renal function category is defined as estimated creatinine clearance (CrCl) ≥60 mL/min; reduced renal function is defined as estimated CrCl from 30 to <60 mL/min.

CYP2C19 Poor Metabolizers

Subjects with CYP2C19 PM genotype in the integrated analyses:

In the integrated populations, there were 6 subjects (all with oHCM) with PM genotype for CYP2C19, consisting of 5 subjects in the pivotal Study MYK-461-005 (2 subjects randomized to treatment with mavacamten, and 3 subjects randomized to treatment with placebo), and 1 subject in the supporting Study MYK-461-004. In total, 5 of these 6 subjects were dosed with mavacamten. Given the per-protocol individual dosing regimens by clinical response, mavacamten plasma trough concentrations over the treatment periods were not expected to be different for these subjects than for other subjects in the studies.

Of the 3 mavacamten-treated subjects with PM genotype for CYP2C19 who received mavacamten during participation in a parent study, all 3 subjects completed treatment in parent studies according to study design. There were 2 subjects who enrolled to supporting extension studies; for 1 subject no AEs have been reported (parent or extension study) and for 1 subject only non-serious low grade (Grade 1 or 2) AEs have been reported (parent or extension study) that have not led to actions taken with study treatment. Neither subject had on-study measurements of LVEF <50% or QTcF > 500 ms, and none of the 3 subjects had any mavacamten plasma trough concentration values of ≥1000 ng/mL. The remaining 1 subject with PM genotype for CYP2C19 did have LVEF <50% concurrent with treatment completion in the parent (pivotal) study, and subsequently (during the follow-up period) experienced a complex clinical scenario involving iatrogenic atrial septal defect and cardiogenic shock as complications of an ablation procedure for atrial fibrillation (all SAEs experienced by this subject recovered or resolved, and none were considered to be related to mavacamten); this subject did not participate in long-term extension.

Of the 2 subjects with PM genotype for CYP2C19 who received placebo during participation in a parent study but were dosed with mavacamten during participation in long-term extension, neither subject has had AEs reported or measurements of LVEF <50%, QTcF >500 msec, or mavacamten plasma

concentration ≥1000 ng/mL after exposure to mavacamten (1 subject had 4 non-serious Grade 1-2 AEs reported and a measured QTcF value > 500 msec during the parent study).

While limited, the experience in these PM subjects who completed treatment in Study MYK-461-005 and/or were dosed with mavacamten in Study MYK-461-007 supports that individualized dose titration (individualized dosing) and drug monitoring designed to balance the PD effects of LVOT reduction while maintaining LVEF, without genotypic testing or plasma concentration measurements, can optimize mavacamten use.

VALOR-HCM study

In VALOR-HCM study, 2 of the 56 subjects that received mavacamten treatment and none in the placebo treatment group were identified as poor CYP2C19 metabolizer genotype. None of these subjects had LVEF <50%. Since there was a small number of poor metabolizers, the interpretability of potential differences is limited.

Extrinsic Factors

Effect of Geographic Region

A summary of AEs occurring in ≥10% of subjects by region (US, ex-US) is provided in Table 86 below. Across the All-Mava combined population, 176/314 (56.0%) subjects in the US and 138/314 (43.9%) subjects in ex-US regions were dosed with mavacamten. By geographic region, 84.7% of US subjects and 78.4% of ex-US subjects experienced any AE.

Table 86. Subject incidence of adverse events occurring in ≥10% of subjects in any geographic region category by preferred term

	All-Mava combined	
Preferred Term	US N = 176 n (%)	ex-US N = 138 n (%)
At least 1 AE	164 (93.2)	127 (92.0)
Dizziness	42 (23.9)	20 (14.5)
Fatigue	37 (21.0)	12 (8.7)
Nasopharyngitis	31 (17.6)	16 (11.6)
Dyspnoea	30 (17.0)	12 (8.7)
Headache	28 (15.9)	18 (13.0)
Upper respiratory tract infection	24 (13.6)	8 (5.8)
Hypertension	21 (11.9)	14 (10.1)
Palpitations	20 (11.4)	8 (5.8)
Atrial Fibrilation	19 (10.8)	19 (13.8)
Cough	18 (10.2)	6 (4.3)
Back pain	15 (8.5)	15 (10.9)

Effect of Baseline Beta-Blocker Use in Subjects with oHCM

A summary of AEs occurring in >5% of subjects by baseline beta-blocker use (yes or no) is provided in Table 87 below. Across the All-Mava oHCM population, 192/260 (73.8%) subjects with (yes) baseline beta-blocker use and 68/260(26.2%) subjects without (no) baseline beta-blocker use were dosed with mavacamten. Overall, similar proportions of subject with (92.7%) and without (91.2%) baseline beta-blocker use experienced any AE.

By baseline beta-blocker use, there were no AEs of any grade reported by ≤5 percentage points more in subjects with baseline beta-blocker use than subjects without baseline beta-blocker use.

There were no Grade ≥3 AEs reported by ≥2 percentage points more than the other for either baseline beta-blocker use subgroup.

There were no SAEs reported by ≤2 percentage points more for subjects with baseline beta-blocker use than subjects without baseline beta-blocker use.

Overall, no safety concerns were identified for mavacamten-treated subjects with baseline beta-blocker use. Some analyses were limited due to small numbers of events. There were no meaningful differences in severe or serious events (Grade ≥3 AEs or SAEs, respectively) for subjects stratified by baseline beta-blocker use, and numerically lower proportions of subjects with (compared against subjects without) baseline beta-blocker use experienced AEs leading to actions with study treatment (permanent discontinuation or temporary interruption), events in the ECI category of cardiac failure, or had any post-baseline central-read LVEF <50%.

Table 87. Subject incidence of adverse events occurring in ≥5% of subjects with and without baseline beta-blocker use

	All-Mava (oHCM)	
Preferred Term	With Beta-Blocker Usage N = 192 n (%)	Without Beta-Blocker Usage N = 68 n (%)
At least 1 AE	178 (92.7)	62 (91.2)
Dizziness	36 (18.8)	16 (23.5)
Nasopharyngitis	28 (14.6)	8 (11.8)
Headache	28 (14.6)	12 (17.6)
Dyspnoea	22 (11.5)	11 (16.2)
Fatigue	26 (13.5)	11 (16.2)
Atrial fibrillation	26 (13.5)	9 (13.2)
Upper respiratory tract infection	15 (7.8)	8 (11.8)
Back pain	21 (10.9)	4 (5.9)
Arthralgia	13 (6.8)	5 (7.4)
Oedema peripheral	13 (6.8)	4 (5.9)
Hypertension	24 (12.5)	10 (14.7)
Diarrhoea	13 (6.8)	2 (2.9)
Cough	11 (5.7)	6 (8.8)
Pain in extremity	11 (5.7)	6 (8.8)
Corona virus infection	11 (5.7)	3 (4.4)
Fall	11 (5.7)	2 (2.9)
Palpitations	12 (6.3)	6 (8.8)
Urinary tract infection	10 (5.2)	5 (7.4)
Asthenia	10 (5.2)	1 (1.5)
Nausea	9 (4.7)	6 (8.8)
Cardiac failure	7 (3.6)	4 (5.9)
Gastrooesophageal reflux disease	5 (2.6)	7 (10.3)
Ejection fraction decreased	6 (3.1)	5 (7.4)
Rash	5 (2.6)	6 (8.8)
Dyspnoea exertional	4 (2.1)	5 (7.4)

Anxiety	2 (1.0)	4 (5.9)

Baseline disopyramide use in subjects with HCM (VALOR-HCM)

There were no major differences in the nature of TEAEs reported between subjects with and without disopyramide use at baseline. Due to a very small sample size of subjects with disopyramide use in the mavacamten treatment group and placebo to mavacamten treatment group, the interpretability of potential differences is limited.

Use in pregnancy and lactation

Pregnancy

Due to teratogenicity observed in 2 animal species (rats, rabbits), women of childbearing potential should be advised to use highly effective contraception (i.e. failure rate of <1% per year) during treatment with mavacamten and for 4 months (5 half-lives in CYP2C19 poor metabolizers) following discontinuation.

In non-clinical definitive reproductive toxicity studies, mavacamten maternal exposure was found to cause developmental abnormalities at exposure levels that were less than the maximum recommended human exposures. In rats, there were mavacamten-related increases in post-implantation loss, decreased mean fetal body weight, and fetal malformations (visceral and skeletal) in the highest (1.5 mg/kg/day) dose group. Malformations consisted of total situs inversus (thoracic and abdominal) in 1 fetus and absence of the right atrioventricular valve associated with a ventricular septum defect in a second fetus. Skeletal malformations consisted mainly of higher incidences of fused sternebrae. Maternal toxicity was not noted in pregnant rats at doses associated with developmental defects. In rabbits, maternal toxicity was noted at doses ≥1.2 mg/kg/day, in which developmental defects consisting of cleft palate, great vessels malformations (dilatation of pulmonary trunk and/or aortic arch), and fused sternebrae were noted. See Section 1.1.4 and refer to Module 2.6.6 Section 7 for additional detail.

The risk of embryofetal toxicity due to paternal exposure in the semen was assessed based on preclinical data, actual semen concentrations in healthy men volunteers (MYK-461-003 CSR synopsis), and the potential for these concentration levels to cause maternal systemic exposures that could be teratogenic. Based upon measurements of mavacamten in the semen of 4 male subjects who received 18.5 mg of mavacamten for 28 days, it was concluded that the risk of teratogenic effects was caused by mavacamten transferred by semen or other body fluids is negligible.

There are no clinical safety data for pregnancy with exposure to mavacamten. No pregnancies have occurred in female subjects treated with mavacamten. One pregnancy reported in a female partner of a male subject randomized to the placebo arm in the pivotal Study MYK-461-005 resulted in delivery by c-section of a normal male baby; as the male subject was not treated with mavacamten, safety data for this partner pregnancy are non-informative with regard to mavacamten.

Lactation

It is not known whether mavacamten or mavacamten metabolites are excreted in human breast milk. Because of the unknown adverse effects of mavacamten in breastfed newborns/infants, a decision must be made whether to discontinue breast-feeding during treatment and for 4 months after the last dose or to discontinue treatment, taking into account the benefit of breast-feeding for the child and the benefit of treatment for the woman.

Fertility

There are no clinical safety data on the effect of mavacamten on human fertility.

In nonclinical definitive reproductive toxicity studies, mavacamten was not shown to affect fertility in male or female rats, nor did it affect transgenerational reproductive capabilities of F1 offspring when F0 females were dosed while pregnant and lactating. See Section 1.1.4 for a summary of additional nonclinical findings and refer to Module 2.6.6 Section 7 for detailed information.

Overdose and medication errors

Overdose based on reported AEs

There was 1 subject (with oHCM) with a non-serious Grade 1 AE of an accidental overdose in the long-term extension Study MYK-461-007. The subject inadvertently took more than 1 dose of study medication within a 12 hour period and was also included in the subject counts of overdose based on pill counts; no additional AEs were reported in association with the accidental overdose.

Overdose based on returned pill counts reported on specific eCRFs

Collection of data for pill-count-based overdose events was based on retrospective recollection during study visits when a pill count was performed. In the randomized placebo-blinded studies (RCT-Mava combined and RCT-Placebo combined), there were 20 (12.3%) mavacamten-treated subjects and 29 (19.7%) subjects who received placebo with reported overdose based on returned pill counts. No AEs were reported in association with any of these returned pill counts that were categorized as overdose events.

Considering all mavacamten-exposed subjects with any indication (All-Mava combined), there were 45 subjects with reported overdose based on data for returned pill counts, of which 3 subjects (1 with oHCM and 2 with nHCM) were considered symptomatic based on association with 1 or more AEs. One subject with oHCM had an associated SAE of cardiac failure (during hospitalization for pneumonia complicated by anaphylactic shock after the second dose of azithromycin) and also met protocol-specified criteria for mavacamten plasma trough concentration ≥1000 ng/. The SAE led to permanent discontinuation of study treatment but resolved after 8 days, and LVEF reduction was reversible after mavacamten discontinuation. The 2 subjects with nHCM had associated non-serious Grade 1 AEs of lethargy.

Medication Errors

In mavacamten clinical studies across the integrated analyses, there was 1 AE reported that represented an event of medication errors. This was the non-serious Grade 1 AE of accidental overdose that occurred in Study MYK-461-007.

Drug Abuse

Mavacamten is not anticipated to have the potential for drug abuse or dependence based on the pharmacologic mechanism of action. There are no data in the mavacamten clinical program to support purposeful drug abuse as a safety concern for mavacamten.

Withdrawal and Rebound

Overall, approximately a third of subjects in mavacamten parent studies experienced AEs in the follow-up period after planned treatment completion. In the randomized placebo-blinded studies, dyspnea, dizziness, contusion, and syncope occurred more frequently after treatment completion of blinded mavacamten than completion of blinded placebo. Based on individual case review, 1 contusion AE that occurred during the follow-up period after treatment completion (in a subject with nHCM) was related to a fall.

Effects on ability to drive or operate machinery or impairment of mental ability

No specific studies on the effects of mavacamten on the ability to drive or operate machinery have been performed. Based on its pharmacological properties, mavacamten is expected to have no or negligible direct influence on the central nervous system.

In the review of AEs and SAEs, from the narrow MedDRA SMQ for accidents and injuries, 1 mavacamten-treated subject across the integrated studies had a Grade 1 SAE of contusion associated with a car accident; the event occurred during participation in the pivotal Study MYK-461-005.

Overall, mavacamten may have minor influence on the ability to drive and use machines. Dizziness may occur following administration of mavacamten. Patients should be advised not to drive or use machines, if they experience dizziness during treatment.

2.5.8.7. Immunological events

N/A

2.5.8.8. Safety related to drug-drug interactions and other interactions

Please be referred to the 'clinical pharmacology' section.

2.5.8.9. Discontinuation due to adverse events

Permanent discontinuations of study treatment due to AEs are provided in this section. These events are provided in Table 88.

Table 88. Subject incidence of adverse events leading to permanent discontinuation of study treatment by preferred term

Preferred Term	All-Mava N = 314 n (%)	oHCM		nHCM	
		RCT-Mava N = 123 n (%)	RCT-Placebo N = 128 n (%)	RCT-Mava N = 39 n (%)	RCT-Placebo N = 19 n (%)
Number of subjects with at least 1 AE leading to permanent treatment discontinuation	17 (5.4)	2 (1.6)	0	3 (7.7)	0
Ejection fraction decreased	4 (1.3)	NR	NR	2 (5.1)	0
Atrial fibrillation	2 (0.6)	1 (0.8)	0	1 (2.6)	0
Cardiac failure	2 (0.6)	0	0	NR	NR
Syncope	1 (0.3)	1 (0.8)	0	NR	NR
Systolic dysfunction	1 (0.3)	NR	NR	1 (2.6)	0
Acute myocardial infarction	1 (0.3)	0	0	NR	NR
Aspartate aminotransferase increased	1 (0.3)	0	0	NR	NR
Cardiac arrest	1 (0.3)	0	0	NR	NR
Dyspnoea	1 (0.3)	0	0	NR	NR
Dyspnoea paroxysmal nocturnal	1 (0.3)	NR	NR	0	0
Endocarditis bacterial	1 (0.3)	0	0	NR	NR
Fatigue	1 (0.3)	0	0	NR	NR
Muscular weakness	1 (0.3)	0	0	NR	NR
Oedema peripheral	1 (0.3)	0	0	NR	NR
Systemic lupus erythematosus	1 (0.3)	0	0	NR	NR

Abbreviations: AE = adverse event; Mava = mavacamten; oHCM = obstructive hypertrophic cardiomyopathy; nHCM = non-obstructive hypertrophic cardiomyopathy; NR = not reported; RCT = randomized control trial. Data presented in this table are treatment emergent.

In the RCT-Mava oHCM treatment group, 2 subjects (1.6%) permanently discontinued mavacamten due to a Grade 3 AE of atrial fibrillation (1 subject) and a Grade 3 SAE of syncope (1 subject). Permanent discontinuation of study treatment due to AE was not reported for any subject in the RCT-Placebo oHCM treatment group, but death was reported as the primary reason for treatment discontinuation for one subject.

Considering all mavacamten-exposed subjects with any indication (All-Mava combined), 17 subjects (5.4%) permanently discontinued study treatment due to AEs. For some subjects, multiple AEs were reported as leading to permanent discontinuation of study treatment (1 subject for whom SAEs leading to permanent discontinuation included atrial fibrillation and systolic dysfunction, and 1 subject for whom AEs leading to permanent discontinuation of study treatment included cardiac failure, dyspnea, and peripheral edema, all of which were considered by the investigator to be related to study drug). These 17 subjects were from the following studies: 2 subjects from the pivotal Study MYK-461-005, 1 subject from parent Study MYK-461-004, 3 subjects from parent Study MYK-461-006, 10 subjects from extension Study MYK-461-007, and 1 subject from extension Study MYK-461-008

Overall, in the proposed indication of oHCM, a low proportion of subjects in the pivotal Phase 3 study (1.6%, 2 subjects) permanently discontinued mavacamten due to AEs. As compared with the pivotal study in oHCM, permanent discontinuation of study treatment due to AEs occurred more frequently in the supporting parent study in nHCM, but this may have been due to differences in study design (dosing was not based on PD responses but rather to achieve protocol-defined mavacamten plasma concentration targets) and the AEs primarily represented decreases in LVEF or systolic dysfunction that upon follow-up were reversible. All 4 subjects with nHCM across the integrated analyses (including the 3 subjects in RCT-Mava nHCM) contemporaneously met protocol-specified criteria for LVEF reduction, and 2 of the 4 subjects with nHCM also met protocol-specified criteria for mavacamten plasma concentration <1000 ng/mL.

VALOR study (MYK-461-017) - double blind period

No subject had any on-treatment AEs resulting in permanent treatment discontinuation. There were no permanent treatment discontinuations due to LVEF ≤ 30%.

VALOR study (MYK-461-017) – long-term follow-up

Two (1.9%) subjects had at least one TEAEs resulting in permanent treatment discontinuation due to decreased LVEF ≤ 30%.

Treatment interruptions due to adverse events

Treatment interruptions due to AEs are provided in this section. These events are provided in Table 89.

Table 89. Subject incidence of adverse events leading to treatment interruptions of study treatment by preferred term

Preferred Term	All-Mava combined N = 314 n (%)	oHCM		nHCM	
		RCT-Mava N = 123 n (%)	RCT-Placebo N = 128 n (%)	RCT-Mava N = 39 n (%)	RCT- Placebo N = 19 n (%)
Number of subjects with at least 1 AE leading to dose interruption	28 (8.9)	3 (2.4)	6 (4.7)	2 (5.1)	0
Ejection fraction decreased	7 (2.2)	0	0	0	0
Electrocardiogram QT prolonged	2 (0.6)	0	1 (0.8)	NR	NR
Headache	2 (0.6)	0	1 (0.8)	0	0
Atrial fibrillation	2 (0.6)	0	0	NR	NR
Atrial flutter	2 (0.6)	NR	NR	0	0

Preferred Term	All-Mava combined N = 314 n (%)	oHCM		nHCM	
		RCT-Mava N = 123 n (%)	RCT-Placebo N = 128 n (%)	RCT-Mava N = 39 n (%)	RCT- Placebo N = 19 n (%)
Arthritis	1 (0.3)	NR	NR	1 (2.6)	0
Cardiac failure	1 (0.3)	NR	NR	1 (2.6)	0
Dizziness	1 (0.3)	1 (0.8)	0	NR	NR
Joint swelling	1 (0.3)	1 (0.8)	0	NR	NR
Renal failure	1 (0.3)	NR	NR	1 (2.6)	0
Syncope	1 (0.3)	1 (0.8)	0	NR	NR
Tinnitus	1 (0.3)	1 (0.8)	0	NR	NR
Acute kidney injury	1 (0.3)	0	0	NR	NR
Atrial thrombosis	1 (0.3)	0	0	NR	NR
Bundle branch block left	1 (0.3)	0	0	NR	NR
Cerebral hemorrhage	1 (0.3)	0	0	NR	NR
Discomfort	1 (0.3)	0	0	NR	NR
Fatigue	1 (0.3)	0	0	NR	NR
Food poisoning	1 (0.3)	0	0	NR	NR
Gastrointestinal hemorrhage	1 (0.3)	0	0	NR	NR
Muscular weakness	1 (0.3)	NR	NR	0	0
Musculoskeletal pain	1 (0.3)	0	0	NR	NR
Osteomyelitis	1 (0.3)	0	0	NR	NR
Ventricular extrasystoles	1 (0.3)	0	0	NR	NR
Enthesopathy	0	0	1 (0.8)	NR	NR
Facial paralysis	0	0	1 (0.8)	NR	NR
Gastritis viral	0	0	1 (0.8)	NR	NR
Vomiting	0	0	1 (0.8)	NR	NR

Abbreviation: AE = adverse event; Mava = mavacamten; nHCM = non-obstructive hypertrophic cardiomyopathy; NR = not reported in the analysis population; oHCM = obstructive hypertrophic cardiomyopathy; RCT = randomized controlled trial
Data presented in this table are treatment emergent.

In the RCT-Mava oHCM treatment group, 3 subjects (2.4%) experienced temporary interruptions of study treatment due to 4 AEs of dizziness, joint swelling, syncope, or tinnitus (1 subject each); for 1 subject, both dizziness and joint swelling (with the same AE onset date) were reported as AEs leading to temporary interruption of study treatment. In the RCT-Placebo oHCM group, 4.7% (6 subjects) experienced temporary interruptions of study treatment due to AEs of electrocardiogram QT prolonged, enthesopathy, facial paralysis, gastritis viral, headache, or vomiting. In the case of 1 subject who experienced 2 non-serious Grade 1 AEs of electrocardiogram QT, the subject also met protocol-specified criteria for QTcF prolongation.

In the RCT-Mava nHCM treatment group, 2 subjects (5.1%) experienced temporary interruptions of study treatment due to AEs of arthritis, cardiac failure, or renal failure; for 1 subject, both renal failure (onset SD1) and arthritis (onset SD55) were reported as AEs leading to temporary interruption of study treatment, and for 1 subject the non-serious Grade 3 AE of cardiac failure (onset SD73 with same day resolution) was concurrent with AEs of dyspnoea and fatigue and the subject subsequently (SD85) met protocol-specified LVEF reduction criteria for permanent discontinuation of study treatment. No subject in the RCT-Placebo nHCM group experienced a temporary interruption of study treatment due to AE.

Considering all mavacamten-exposed subjects with any indication (All-Mava combined), 28 subjects (8.9%; includes the 5 mavacamten-treated subjects from the randomized placebo-blinded studies described earlier in this section) experienced temporary interruptions of study treatment due to AEs. The AEs leading to temporary interruption of study treatment in the All-Mava combined group in ≥2 subjects was ejection fraction decreased, QT prolongation, headache, atrial fibrillation and atrial flutter.

VALOR study (MYK-461-017) - double blind period

Temporary treatment discontinuations / drug interruption due to AEs were reported in 4 (7.1%) subjects in the mavacamten treatment group and 1 (1.8%) subject in the placebo group (Table 90).

2 subjects in the mavacamten group met the criteria for temporary discontinuation for LVEF<50%. 1 subject in the mavacamten group had 2 temporary interruptions of study drug for worsening atrial fibrillation (interruption of 1 day and 5 days; each time mavacamten was resumed at the same dose). 1 subject in the mavacamten group had temporary interruption of study drug for worsening palpitations, fatigue, and shortness of breath (subject proceeded to SRT without resuming mavacamten). 1 subject in the placebo group had temporary dose interruption for worsening dizziness and dyspnea (subject proceeded to SRT without resuming IP).No subjects discontinued study due to COVID-19 .

Table 90. VALOR - On-Treatment Adverse Events Resulting in Treatment Interruption by System Organ Class and Preferred Term - Double-Blind Period

System Organ Class Preferred Term	Mavacamten (N = 56) n (%)	Placebo (N = 55) n (%)
Total Number of On-Treatment Adverse Events Leading to Treatment Interruption	7	2
Number of Subjects with at Least One On-Treatment Adverse Event Leading to Treatment Interruption	4 (7.1)	1 (1.8)
Cardiac disorders	2 (3.6)	0
Atrial fibrillation	1 (1.8)	0
Palpitations	1 (1.8)	0
General disorders and administration site conditions	1 (1.8)	0
Fatigue	1 (1.8)	0
Investigations	2 (3.6)	0
Ejection fraction decreased	2 (3.6)	0
Nervous system disorders	0	1 (1.8)
Dizziness	0	1 (1.8)
Respiratory, thoracic and mediastinal disorders	1 (1.8)	1 (1.8)
Dyspnoea	1 (1.8)	1 (1.8)

VALOR study (MYK-461-017) – long-term follow-up

During the LTFU, 6 subjects in the previous mavacamten treatment group and no subjects in the previous placebo treatment group had interruption of study therapy. There were no dose interruptions or delays due to COVID-19.

Five (4.6%) subjects had any on-treatment AEs resulting in temporary treatment discontinuation. The reported AEs leading to temporary treatment discontinuation were atrial fibrillation (1 subject), palpitations (1 subject), fatigue (1 subject), ejection fraction decreased (3 subjects), and dyspnoea (1 subject).

2.5.8.10. Late breaking information

After the data cut-off for the SCS (30-Oct-2020), the Sponsor was notified of an accidental exposure of mavacamten to an infant. The exposure involved a 10-month-old child of a male subject receiving

mavacamten in the long-term extension Study MYK-461-007, and the exposure was reported as 45 mg mavacamten (3 capsules of 15 mg each) resulting in cardiac arrest and subsequently to death.

2.5.9. Discussion on clinical safety

Clinical safety database. The safety evaluation is based on the pivotal phase 3 EXPLORER-HCM study (MYK-461-005), and supplemented by safety data from the phase 2 studies (MYK-461-004 and MYK-461-006) and data from the two ongoing long-term extension studies (MYK-461-007 and MYK-461-008) with a cut-off date of 31 August 2021. This pooled analysis approach can be considered appropriate for an evaluation of, amongst others, the cardiovascular safety profile, as mentioned in the 'Reflection paper on the assessment of the cardiovascular safety profile of medicinal products (EMA/CHMP/50549/2015).

Three integrated populations, categorized by indication (i.e. oHCM and nHCM), were used for further analyses: All patients in the 5 studies who received at least one dose of mavacamten (all-mava), patients in the RCTs who received at least one dose of mavacamten (RCT-mava), and patients in the RCTs who received placebo (RCT-placebo), which can be considered acceptable.

Further, all safety data for the pivotal VALOR-HCM study (MYK-461-017) up to a cut-off date of 7 February 2022 are presented, in addition to the integrated analyses of pooled safety data from five earlier mentioned clinical studies.

Exposure. Of the 314 mavacamten-treated subjects in the integrated safety analyses, 123 subjects were in the RCT-mava oHCM population. The average daily dose of these subjects was 6.69 mg (range: 2.2 - 11.6 mg). This is generally in line with the doses as recommended in the SmPC of mavacamten (2.5 – 15 mg). Doses in the nHCM patients and all-mava were in the same range. The median exposure duration was 7.0 months (range: 0.3 - 9.3 months), as the study had a duration of 30 weeks. Total exposure of RCT-mava was 70.87 patient-years. Comparable with the MYK-461-005 study, the most frequent dose received in the VALOR-HCM double-blind (DB) period was 5 and 10 mg. The mean (SD) duration of exposure was 17.0 (2.13) weeks for subjects who received mavacamten. Overall, the mean (SD) duration of exposure was 32.59 (20.012) weeks for all the subjects (n=108) who received mavacamten during the DB period plus long-term follow-up (LTFU).

Patients who completed treatment in the parent studies had a washout/follow-up period prior to enrolling and prior to being exposed again to study treatment in the extension studies, which was 15.7 weeks for 115 subjects who had their last dose in study MYK-461-005 and their first dose in study MYK-461-007. A similar time interval was seen in the patients from study MYK-461-006 to study MYK-461-007. For 13 subjects from study MYK-461-004 to study MYK-461-008 the time interval between studies was even more with 53.3 weeks. Since these patients had a large non-treatment time interval between the parent and extension studies, mavacamten exposure cannot be considered continuous.

A total of 245 subjects qualified as having >1 year duration of exposure in a single study, and 59% and 25% of these 245 subjects completed at least 18, and 24 months of mavacamten treatment, respectively. The median duration of exposure was 19 months (range: 12.0 - 39.8 months). Total exposure of oHCM patients treated >1 year was 325 patient-years. It should be noted that a substantial part of the exposure time was during the titration phase, while patients were still on a suboptimal dose. The VALOR-HCM study is still ongoing and since only 14 patients are exposed to mavacamten for > 1 year, such data have not been presented.

According to the guideline ICH-E1 'Population Exposure: The Extent of Population Exposure to Assess Clinical Safety' 100 patients exposed for a minimum of one-year is considered to be acceptable to

include as part of the safety database at dosage levels intended for clinical use. Currently, since the documented safety exposure consists of a total of 245 subjects (207 subjects with oHCM and 38 subjects with nHCM) qualified as having >1 year duration of exposure in a single study, the current data fulfil the requirements of the guideline ICH-E1.

Generally, the applicant followed the Scientific Advices of the EMA and MEB. However, concerns were raised regarding exclusion of a detrimental effect on cardiovascular safety, and it was questioned whether a PASS could provide sufficient reassurance. On the other hand, it was acknowledged that after EXPLORER-HCM, there could be doubts on the ethical acceptability of a cardiovascular outcomes trial in oHCM. As discussed further below, cardiovascular safety remains of important concern, since mavacamten is a first-in-class selective myosine inhibitor, that directly targets the pathophysiology of the disease, i.e. oHCM, by specifically targeting the cardiac mechanisms, which might have deleterious effects on contractility, resulting in reduced ejection fraction and heart failure in the long term. The applicant provided an extensive discussion on how the concerns on the safety profile, including the detrimental effect of cardiovascular safety, of mavacamten should be further addressed. Based on the reasoning of the applicant, a cardiovascular trial is considered unfeasible and unethical to be performed and, according to the guideline, the applicant's suggestion to conduct a meta-analysis, with continuous monitoring of the cardiovascular safety of mavacamten by routine pharmacovigilance, the ongoing LTE studies and the two non-interventional observational studies, is agreed and currently included as a category 3 study in the RMP.

Impact of COVID-19. The impact of COVID-19 pandemic on the collection of data was significant since site visits were not possible, and many of the protocol-specified assessments were not performed for 67 subjects in the pivotal study MYK-461-005 at Week 38 (26%; 31/123 in the mavacamten and 37/128 subjects in the placebo group). These subjects completed their Week 38/end of study visit via telephone. Further, in total, 24 subjects in the MYK-461-007 study (all with oHCM) were discontinued, since the required safety monitoring assessments could not be performed in the clinic. All of these subjects subsequently re-enrolled into the same study. Within the pooled safety database, three COVID-19 infections were reported during the study periods. No action was taken with study treatment, and it can be considered that this had no significant consequences for the available study results on safety. The same findings were presented for the VALOR-HCM study, where COVID-19 did not impact the overall quality or outcome of the study.

Adverse events (AEs). In study MYK-461-005 (EXPLORER-HCM), TEAEs were frequently reported, and the percentage of subjects with ≥1 AEs was higher in the mavacamten (87.8%) than in the placebo (81.3%) group in the oHCM patients. Generally findings were similarly seen in the nHCM patients (89.7% vs 68.4%, respectively) and appeared to be in line with the all-mava population of the pooled safety database (92.7%) and with the study populations of VALOR-HCM (73.2% vs 61.8% for mavacamten and placebo respectively).

The most frequently reported AEs (≥5% in mavacamten group and at least 2 % higher than the placebo group) in the pivotal Study MYK-461-005 were dizziness (21.1% in RCT-Mava oHCM vs. 13.3% in RCT-Placebo oHCM), dyspnoea (14.6% vs. 10.2%), headache (12.2% vs. 7.8%), atrial fibrillation (8.1% vs 2.4%), upper respiratory tract infection (8.1% vs 4.7%), back pain (8.3% vs 6.3%), cough (8.1% vs 3.1%), and arthralgia (5.7% vs 1.6%). Data were generally in line with the nHCM group and VALOR-HCM study population. In the VALOR-HCM DB period the most frequently reported AEs (≥5% in the mavacamten group and at least 2% higher than the placebo group) were fatigue (8.9% vs 3.6% for mavacamten and placebo, respectively), atrial fibrillation (7.1% vs 0), nausea (7.1% vs 1.8%), dizziness (7.1% vs 5.5%), dyspnea (7.1% vs 5.5%), rash (7.1% vs 0%), urinary tract infection (5.4% vs 1.8%), and hypertension (5.4% vs 3.6%).

For the adverse drug selection process, data from the 2 Phase 3 placebo-controlled studies (EXPLORER-HCM through Week 38 and VALOR-HCM through Week 16 double-blind period) were pooled. Selection criteria for ADR consideration were based on the AE occurrence ⩾5% (all causality) in mavacamten-treated subjects and ⩾2% higher than subjects who received placebo. The AEs, more frequently observed in mavacamten-treated subjects than in subjects who received placebo included dizziness, dyspnea, atrial fibrillation, arthralgia, cough, upper respiratory tract infection. Further assessment of analyses of the events of upper respiratory tract infection, cough, and arthralgia showed no reasonable possibility of a causal relationship of the use of mavacamten and the event, based on non-related cases and low numbers. They were not included as an ADR in the SmPC of mavacamten. However, regarding dizziness, based on the comparative incidence (n= 30, 16.8% vs n=20, 10.9% in the RCT-MAVA and RCT-placebo group, respectively), which can be considered relatively high, dizziness should be considered an ADR. Inclusion of this ADR in section 4.8 of the SmPC of mavacamten, as proposed by the applicant, is agreed. Also, there was observed an imbalance in dyspnoea events in the oHCM population in the RCT-mava with the RCT-placebo treatment groups (n=22, 12.3% vs. n=16, 8.7%). During the on-treatment period of MYK-461-005, dyspnoea events were balanced between groups (7.4% vs 8.2%, resp.), while dyspnoea events were more frequently reported during the follow-up/washout period in mavacamten-treated subjects than subjects who received placebo (14 subjects vs 4 subjects). This may be a consequence of a decreasing effect of mavacamten, since plasma levels are decreasing during washout, and LVOT gradients returning (increasing) back to baseline. The applicant has accepted the CHMP recommendation to add dyspnea as an ADR in section 4.8 of the SmPC, although there are confounding factors. Further, regarding headache, the applicant presented an imbalance with the oHCM population (n=15, 12.2% in mavacamten vs. n=10, 7.8% in placebo) in the pivotal study MYK-461-005. Although the imbalance was not seen in subjects without beta-blocker use (RCT-Mava combined vs. RCT-Placebo combined: headache in subjects with beta-blocker use, 9.3% vs. 4.1%; headache in subjects without beta-blocker use, 1.9% vs. 3.4%). Furthermore, during the DB period of the VALOR-HCM study, headache was reported in a lower frequency in the mavacamten group compared with the placebo group (n= 2 (3.6%) vs n=5 (9.1%) respectively). Therefore, based on the evaluation of the recently available pooled analysis of Week 38 and Week 16 safety data of EXPLORER-HCM and VALOR-HCM, the event “headache” is not included as an ADR, which is agreed. Further, there was a disbalance in the incidence in atrial fibrillation (AF) (8.4% vs 5.5%) in the pooled analyses. However, AF is not considered an ADR as it is the most common arrhythmia encountered in HCM patients, since it is well recognized that the prevalence of AF in HCM patients is approximately 20%, which is also indicated by the high percentage of recurrent AF events (see below “events by medicinal concept” for further discussion). Although syncope was not an ADR based on the used criteria, syncope is included as an ADR in section 4.8 of the SmPC based on a numerical imbalance in the EXPLORER-HCM study; however, the applicant considers that events of syncope are heavily confounded by other factors.

Serious adverse events (SAEs). Three deaths have been reported in the safety database. One occurred in the placebo arm, the other two cases in the mavacamten-treated population, for which a possible relationship with the use of mavacamten and death is considered unlikely. In the VALOR-HCM study (in the long-term follow-up period) one subject died. The patient, who previously received placebo treatment until Week 16 and then received mavacamten treatment post Week 16, had a sudden cardiac death at week 56. Since the event was confounded to underlying HCM, ventricular fibrillation, pulmonary fibrosis and new-onset pneumonia, a clear relationship with the use of mavacamten cannot be concluded.

In the pivotal study, the incidence of SAEs was relatively low with no large differences in percentages in subjects in the RCT-mava compared to the RCT-placebo group (n=14, 11.4% vs n=12, 9.4%), which is reassuring. Generally similar findings were seen in the nHCM patients and figures appeared to be in line with the all-mava population. The most frequent reported SAEs were atrial fibrillation (n=3,

2.4% in RCT-Mava oHCM vs. n=5, 3.9% in RCT Placebo oHCM), syncope (n=3, 2.4% vs. n=1, 0.8%, respectively), and stress cardiomyopathy (n=2, 1.6% vs. 0%, respectively). No patterns for a new unexpected safety signal could be identified from the current available SAE safety data, but the number of events were too low in order to make firm conclusions. Also, in the VALOR-HCM study the incidence of SAEs was relatively low, although with a higher proportion (n=3, 5.4%) in the mavacamten group through week 16 than in placebo group (n=1, 1.8%). Two subjects on mavacamten versus none of the subjects on placebo experienced cardiac disorders attributed to atrial fibrillation. One subject in the mavacamten group had acute COVID-19 infection. One subject in the placebo group had acute alcohol intoxication. Atrial fibrillation events are further discussed below. No subjects experienced SAEs of congestive cardiac failure, syncope, or sudden cardiac death.

Adverse events of special interest. In the RCT population, no event of LVEF ≤30% was reported. In the all-mava population, only one nHCM patient in the extension study MYK-461-007 experienced an LVEF reduction to <30%, related to the study drug. Mavacamten is currently not indicated for patients with nHCM. In the VALOR-HCM LTFU period, 2 (1.9%) subjects experienced LVEF ≤ 30%, which were both considered related to study therapy by the investigator, although there were confounding factors.

None of the patients in the RCTs, including the VALOR-HCM study, suffered from a symptomatic overdose (none reported), but there were 3 identified in the extension studies (1 oHCM, 2 nHCM). Overall, overdose cases were low, and this concern is currently well reflected in section 4.9 of the SmPC based on data from the phase 1 PK studies in HCM patients and healthy subjects. No further information is needed, based on the currently available overdose data from the integrated safety database and the VALOR-HCM study data.

Regarding embryofoetal toxicity, currently no clinical data exist on the safety of mavacamten during pregnancy in humans, while significant foetal toxicity and teratogenicity potential have been demonstrated for mavacamten in two animal species and should be regarded as a potential human developmental toxicant. This safety concern is included as an important potential risk in the RMP, which is appropriate.

Events by medical concept. No concerns have been found with hypotension, severe cutaneous adverse reactions (SCAR), gastro-intestinal events, rhabdomyolysis/myopathy, renal and hepatic events, fall-related events and hypersensitivity.

In the pivotal oHCM study, the percentages of subjects with a syncope AE were higher in the mavacamten group compared with placebo (n=7, 5.7% vs. n=2, 1.6%, respectively). However, the percentages of AEs in presyncope showed a converse effect on AEs (n=2, 1.6% on mavacamten vs n=5, 3.9% on placebo). Further, the total number of AEs of syncope and pre-syncope events between the groups were generally similar (n=8, 6.5% vs n=7, 5.5%, respectively), which is reassuring, but might be the effect of the converse findings of the two events. Similar results are found in the nHCM population and when the broader definition of syncope events has been used. Overall, although some cases have alternate aetiologies that could better explain the occurrence of the event, the imbalance points to a possible relationship of the use of mavacamten and the occurrence of syncope in the cases. Syncope is therefore added as an ADR to section 4.8 of the SmPC.

Data analysis for the major pre-defined cardiovascular events have been evaluated and adjudicated by an independent committee (CEAC). These are discussed below:

In the pivotal Study MYK-461-005, the percentage of subjects who met protocol-specified criteria for LVEF reduction <50% was higher in the mavacamten group compared to the placebo group (relative risk 3.64 (95%CI 0.77, 17.19); n=7, 5.7% and n=2, 1.6%, respectively). In total, across the integrated analyses, there were 36 unique mavacamten-treated subjects (19 with oHCM and 17 with nHCM) who met protocol-specified criteria for LVEF reduction. Based on quantitative LVEF data for the

lowest qualifying LVEF values for each unique individual subject, the median qualifying LVEF reduction for all 19 subjects with oHCM was LVEF 44.67% (range 34.8% to 49.3%), and the median qualifying LVEF reduction for 16 subjects with nHCM was LVEF 44.25% (range 20.0% to 49.3%). Most (28/36) of the LVEF reductions <50% were not reported as AEs, since this parameter was part of the dose adjustment strategy. Four subjects with oHCM and 2 subjects with nHCM permanently discontinued study treatment. The LVEF values were all reversible, which is not unexpected based on the mechanism of action of mavacamten. The data in the all-mava population were consistent with the data from the pivotal studies, with similar reversibility. Seventeen out of the 36 (47%) mavacamten-treated patients with LVEF reductions experienced symptomatic AEs. Also, of the 19 subjects with oHCM and qualifying LVEF reductions, 2 subjects had mavacamten plasma trough concentration ≥1000 ng/mL, 7 subjects had mavacamten plasma trough concentrations between 700 and 1000 ng/mL, and the remaining 10 subjects had mavacamten plasma trough concentrations that were <700 ng/mL at the time of or most proximately prior to the LVEF measurement. Similar findings were seen for the nHCM group. Regarding the DB period of the VALOR-HCM study, no subjects experienced heart failure (HF). Two (3.6%) subjects in the mavacamten treatment group were reported with decreased LVEF event of <50% during the DB, which were asymptomatic and had no associated signs of HF. Also in the LTFU period, two subjects in the mavacamten treatment group and no subjects in the previous placebo treatment group met the temporary discontinuation criterion of LVEF <50%. Another 6 (5.6%) patients were reported with at least one on-treatment HF and decreased LVEF event, were considered as AEs. These data show that LVEF reduction <50% can be considered as a conservative approach regarding cardiovascular safety. Since there is an imbalance identified in the pivotal study and since an association seems reasonable based on the mechanism of action, it is agreed that LVEF reduction <50% is included as an ADR in section 4.8 of the SmPC. Further, the safety concern is also included as an important identified risk in the RMP.

MACE was defined as acute myocardial infarction, stroke, CV death and heart failure hospitalization, and is in line with the definition for MACE as reflected in the 'Reflection paper on assessment of cardiovascular safety profile of medicinal products' (EMA/CHMP/50549/2015), and can thus be considered acceptable. Overall, the risk for MACE was considered higher (relative risk 1.73; 95% CI: 0.42-7.10) in the mavacamten group (n=5, 4.1%) vs the placebo group (n=3, 2.3%) in the pivotal study, with a higher incidence rate of 5.75/100 patient-years (PY) for the mavacamten group and 3.27/100 PY for the placebo group. Of note, 2 of the patients in the mavacamten group experienced MACE events in the washout period. No MACE was reported in the double-blind period of the VALOR-HCM study, but 2 (1.9%) subjects during LTFU period for total mavacamten treatment. Both MACE events occurred in the previous placebo group. One (0.9%) subject was reported with MACE related to sudden cardiac death after permanently discontinued due to LVEF <30%. Additionally, 1 (0.9%) subject was reported with MACE related to heart failure hospitalization and LVEF <30% around Week 30. However, the number of oHCM patients who experienced MACE was low, and should therefore be interpreted with caution.

Based on the AEs reported in the pivotal study MYK-461-005, although the event rate was very low, heart failure (HF) was balanced between the treatment groups (mavacamten vs. placebo: any grade n=3, 2.4% vs. n=5, 3.9%; Grade ≥3 n=1, 0.8% vs. n=1, 0.8%), also when adjudicated by the CEAC. The incidence of events (n=22, 7.1%) was more substantial in the all-mava population. The occurrence of the events is not unexpected, since HF is importantly confounded by the underlying disease and can be considered a consequence of the LVEF reduction due to the use of mavacamten. In the DB period of the pivotal VALOR-HCM study, there were no events of HF.

In the RCTs, the percentage of oHCM patients with AEs of atrial fibrillation was similar on both the mavacamten vs the placebo group (n=10, 8.1% vs n=10, 7.8%, respectively). Similar figures were shown for the nHCM groups and in the all-mava population. There was also no imbalance observed on

the events of ventricular arrhythmias with even lower numbers (2.4% vs 2.3%, respectively). It is noted that there was an imbalance of atrial fibrillation at baseline (9.8% vs 18.0% in mavacamten and placebo, respectively), but cases of both incident AF and recurrent AF were generally similar in number and frequency on treatment during the study. Further, the AF event rate per 100-patient-year on mavacamten was not observed to increase over time. In the VALOR-HCM study, atrial fibrillation or atrial flutter were observed in a higher frequency in the mavacamten group compared with the placebo group (7.1% (n=4) vs 0). However, 3 of the 4 subjects had recurrent atrial fibrillation with known atrial fibrillation in the medical history, which is reassuring. One additional AF SAE was reported during the long-term follow-up period. Post hoc analyses in subjects with AF at different (more than one) dose level and by plasma concentration do not show a clear concentration dependence for AF, which is reassuring. Moreover, AF is the most common arrhythmia encountered in HCM patients and can arise under various circumstances; the prevalence of AF in HCM patients is approximately 20%.

Across the integrated safety analyses, in first instance no imbalances in QT-interval and arrhythmia AEs and ECG data have been observed in the placebo and treatment and all-mava groups. Of note, while the QT-effect of mavacamten on healthy volunteers and animals resulted in prolongation of cardiac ventricular repolarization, a slight QTcF shortening was observed in oHCM subjects in the clinical studies, going towards normalization of the QT interval in these patients, since their QT interval was prolonged at baseline. There is no signal of torsade de pointes in subjects with oHCM caused by mavacamten. The findings in the integrated clinical safety database are in line with the findings in the PD analyses. Regarding the VALOR-HCM study, maximum change from baseline > 60 ms was observed only in mavacamten treatment group in 3.6% of the subjects in the double-blind period. Overall, a QTcF regression analysis was performed on all 56 subjects (53 were on SOC HCM medications) who were administered mavacamten, and showed a negative slope, thereby showing no concentration effect of mavacamten on QTcF. No new significant safety concerns have been identified by these data.

Overall, apart from the expected effect on LVEF reduction, no other significant safety concerns regarding cardiovascular effects have been observed from the currently available safety data, although these data are limited and current numbers were too low to draw firm conclusions. Therefore, in addition to continuous monitoring of the cardiovascular safety of mavacamten by routine pharmacovigilance, the ongoing LTE studies and the two non-internventional observational studies, a meta-analysis to evaluate the cardiovascular safety profile of mavacamten will be conducted, which is considered acceptable. This meta-analysis includes data from existing and planned well-controlled, double-blind, randomized phase 3 studies of mavacamten versus placebo (from EXPLORER-HCM, VALOR-HCM, nHCM Phase 3 and China oHCM Phase 3) and is currently included as a category 3 study in the RMP.

Laboratory findings. No clinically meaningful differences with respect to most of the haematology parameters and clinical chemistry lab values were observed. However, a larger increase in glucose levels was seen in the oHCM mavacamten group combined vs the placebo group combined (mean glucose value change, 17.9 mg/dL vs. 10.3 mg/dL, respectively). However, the clinical importance of this difference can be considered small, since maximum post-baseline glucose values were overall balanced between the groups (mean, 113.7 mg/dL vs. 113.9 mg/dL; median, 106.0 mg/dL vs. 105.0 mg/dL; Q3, 121.0 mg/dL vs. 115 mg/dL; maximum, 351.0 mg/dL vs. 316 mg/dL). Findings in the VALOR-HCM study were similar.

Further, regarding the cardiac biomarker for myocardial wall stress NT-proBNP and the cardiac biomarker for myocardial injury cTnI a reduction was seen in both parameters. The effect was consistent in the extension studies. This effect is probably not adverse. It is also not unexpected and is in line with the effect of the mechanism of action of mavacamten.

Vital signs. By evaluation of the incidence of ICD therapy and resuscitated cardiac arrest in the pivotal study, the study-scheduled ICD downloads did not reveal any shocks, with the exception that one subject in the mavacamten group had an SAE of device inappropriate shock delivery. The patient had a high BMI and it was noted that the subject had a tendency to go into sinus tachycardia during physical exercise and stopped study therapy 25 days before the event occurred. The event was dissolved on the same day. A causal association of the high energy inappropriate shocks delivered by ICD and the use of mavacamten is not likely. Also in the VALOR-HCM study no notable changes have been observed.

Special population and situations. Currently, the comparisons of the safety in special populations in the RCT-mava and RCT-placebo populations and in the all-mava population did not identify new relevant safety concerns.

No relevant effects from gender, race, beta-blocker use and renal function could have been identified due to low numbers. Atrial fibrillation events were observed more in male mavacamten-treated subjects compared to females and the converse was seen in the placebo groups. However, numbers remained low. No new relevant safety concerns, based on age categories could be identified from the safety data. No relevant large imbalances were revealed, although an increase in the incidence of events is observed for dizziness, dyspnoea and headache, which is not unexpected with age increase.

Regarding CYP2C19 metabolizers, only 5 subjects with PM genotype for CYP2C19 received mavacamten in the randomised studies and 2 continued in the extension study (one subject had no AEs, one subject had some mild AEs), which is considered very limited to further evaluate this population based on clinical data. Uncertainties remain in the clinical pharmacology studies on PM of CYP2C19 (see clinical pharmacology section). CYP2C19 PM is included in the summary of safety concerns of the RMP.

Regarding use in pregnancy and lactation, in the non-clinical studies, mavacamten was detected in extra-embryonic tissues, such as the placenta. Placenta transfer could be indicative of transfer in the mother milk. Clinical data are however not available, but it is a critical gap in knowledge for the use with mavacamten. Therefore, ‘pregnancy’ is included as a contra-indication in section 4.3 of the SmPC and ‘use during lactation’ is included in the RMP as missing information.

No relevant safety signals have been observed in the overdose, medication errors or drug abuse cases.

No specific studies on the effects of mavacamten on the ability to drive or operate machinery have been performed. Dizziness is currently included as ADR in the SmPC of mavacamten. Patients are advised in section 4.7 of the SmPC not to drive or use machines if they experience dizziness during treatment.

AEs leading to discontinuation. The incidence of AEs leading to discontinuation was higher in the mavacamten group, as compared to the placebo group (n=2, 1.6% vs 0%) in RCT oHCM patients. Similar findings were observed with the nHCM patients (n=3, 7.7% vs 0%) and in all-mava (n=17, 5.4%). The most frequent AEs leading to discontinuations were atrial fibrillation and ejection fraction decreased and cardiac failure, which is in line with the mechanism of action or underlying disease. Furthermore, no other pattern with respect to type of AE leading to discontinuation of study drug has been observed. Also no trend with respect to type of AE leading to drug interruptions has been identified. Regarding the VALOR-HCM study, none in the double-blind period, but 2 (1.9%) subjects had at least one TEAEs resulting in permanent treatment discontinuation in the long-term follow-up period. The reported investigations were due to decreased EF ≤ 30% in 2 (1.9%) of the subjects, which are discussed earlier in this section.

Late-breaking information. There was reported an accidental exposure of mavacamten to a 10-month-old infant. The seemingly healthy child took 3 capsules of 15 mg and suffered from cardiac

arrest and subsequently to death. The mavacamten study medication supply was provided by the sponsor in bottles with child-resistant caps and with warning labels "Keep out of reach and sight of children". No further measures are considered currently needed.

Additional expert consultation

N/A.

Assessment of paediatric data on clinical safety

N/A.

2.5.10. Conclusions on the clinical safety

Mavacamtenis indicated for the treatment of symptomatic (NYHA class II-III) oHCM in adult patients. and reflects its mechanism of action as a (first-in-class) selective myosine inhibitor, since LVEF reduction was (more) frequently reported in the test population. Mavacamten appeared to be generally well tolerated with dizziness and dyspnoea as most common reported AEs. Although the current safety profile of mavacamten does not suggest any safety concerns, a detrimental effect on cardiovascular safety could not be excluded. Therefore, a meta-analysis, with continuous monitoring of the cardiovascular safety of mavacamten by routine pharmacovigilance, LTE studies and two non-interventional observational studies, will be conducted to follow-up this uncertainty. The proposed posology in the SmPC for mavacamten in patients with an unknown CYP2C19 genotype was questioned from a safety perspective (i.e. potential systolic dysfunction). CYP2C19 poor metabolisers have a 3-fold higher plasma exposure compared to CYP2C19 non-poor metabolisers.

The effect of a high plasma concentration can be expected to translate to clinical efficacy and safety due to the clear relationship between plasma exposure and LVEF and VLVOT. Limited safety data on CYP2C19 poor metabolizers are currently available in the target population. Therefore, an adjusted posology for CYP2C19 poor metabolizers is recommended in the SmPC. If treatment initiation occurs prior to determination of CYP2C19 phenotype, patients should follow dosing instructions for poor metabolisers until CYP2C19 phenotype is determined.

2.6. Risk Management Plan

2.6.1. Safety concerns

Summary of safety concerns

The applicant provided an RMP version 2.0, with the following agreed Summary of safety concerns.

Table Error! No text of specified style in document.-91: 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

2.6.2. Pharmacovigilance plan

Table Error! No text of specified style in document.-92: 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 authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Mavacamten Real-World Safety - A Post-Authorization Long-term Observational Study in Europe (CV027013) (PASS) Planned	The primary objectives of this study are to: • Estimate the incidence rate of heart failure with systolic dysfunction (defined as worsening symptomatic status with LVEF <50%) among adult patients with oHCM who received mavacamten or non-mavacamten treatment during the study period. • Estimate the incidence rate of heart failure with systolic dysfunction among adult patients with oHCM who received mavacamten or non-mavacamten treatment during the study period - AND - who received a concomitant CYP2C19 inhibitor and/or moderate or strong CYP3A4 inhibitors.	• 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)	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 Error! No text of specified style in document.-92: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
	• Estimate the incidence rate of MACE (a composite endpoint consisting of acute myocardial infarction, stroke, hospitalization due to heart failure, and cardiovascular mortality), of the individual components of MACE and of all-cause mortality among adult patients with oHCM who received mavacamten or non-mavacamten treatment during the study period. • Estimate the incidence rate of arrhythmia (defined as atrial fibrillation, atrial flutter, sustained ventricular tachycardia, and/or ventricular arrhythmia) among adult patients with oHCM who received mavacamten or non-mavacamten treatment during the study period. • Compare the risk of heart failure with systolic dysfunction, of MACE (as composite endpoint and individual component endpoints), of allcause mortality, and of arrhythmia among adult patients with oHCM who received mavacamten to those patients who received non-mavacamten treatment. The secondary objectives of this study are to: • Estimate the incidence rate of heart failure with systolic dysfunction, of MACE (as composite endpoint and individual endpoints), of all-cause mortality, and of arrhythmia among adult patients with oHCM who received mavacamten during the study period - AND - who had	• Long-term safety, including detrimental CV effects		

Table Error! No text of specified style in document.-92: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
	concomitant use of single or combination use of the following medications: disopyramide and/or β-blockers and/or non-dihydropyridine calcium-channel blockers (verapamil/diltiazem) • Assess changes in clinical responses from baseline (as measured by changes in NYHA class, LVOT gradient, LVEF, and N-terminal-pro BNP at select time points for adult patients with oHCM who received mavacamten or non-mavacamten treatment during the study period. The exploratory objective of this study is to: • Assess the primary and secondary objectives in a subset of adult patients with oHCM - AND - NYHA Class IV functional classification and preserved LVEF (>55%) at baseline who received mavacamten or non-mavacamten treatment during the study period			

Table Error! No text of specified style in document.-92: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Meta-analysis to assess CV outcome safety Planned	A meta-analysis of Phase 3, placebo-controlled, double-blind, randomized studies of mavacamten in patients with symptomatic HCM, to evaluate the cardiovascular safety profile. The MACE meta-analysis will assess CV safety based on a composite endpoint of time to first occurrence of MACE meta-analysis event. It will include three clinical trials in symptomatic oHCM population (EXPLORER-HCM, VALOR-HCM, China oHCM Phase 3 trial) and one clinical trial in 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
MYK-461-017/CV027006 (VALOR-HCM [LTFU]): A Randomized, Double-blind, Placebo-controlled Study to Evaluate	This is a randomized, double-blind, placebo-controlled, multi-center study in the US that will evaluate the effect of mavacamten treatment on reducing the number of SRT procedures performed in subjects with symptomatic obstructive hypertrophic cardiomyopathy (oHCM [also known as	• Heart failure due to systolic dysfunction • Patients with Class IV NYHA • Patients being treated with disopyramide	1. Final CSR	Jun-2025

Table Error! No text of specified style in document.-92: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Mavacamten in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy Who Are Eligible for Septal Reduction Therapy Primary endpoint analysis completed LTFU ongoing	HOCM]) who are eligible for SRT based on ACCF/AHA 2011 and/or ESC 2014 guidelines. Although, the VALOR-HCM placebo-controlled, double-blind period (Day1 to Week 16) was completed and reported in the submitted primary CSR, the study is ongoing. Cumulative LTFU data from this ongoing study will continue to inform the mavacamten safety profile. LTFU is used to describe any event that occurs from first day of mavacamten treatment. Safety and efficacy results for the LTFU are reported in terms of cumulative number of weeks of mavacamten exposure where mavacamten treatment begins on Day 1 for those in the original mavacamten arm and Week 16 for those in the original placebo arm; therefore, LTFU data are inclusive of data in the double-blind period for subjects previously in the mavacamten arm that continue treatment during the ongoing LTFU. The LTFU data will be the principal source of data contributing to additional pharmacovigilance activities.	• Patients being treated with a combination of β-blockers and nondihydropyridine calcium-channel blockers (verapamil/diltiazem) • Long-term safety, including detrimental CV effects		
CV027012 (DISCOVER-HCM): Deliver Insights on Safety in Hypertrophic Cardiomyopathy and Observe Endpoints in Real-world	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 50 sites in the US and Puerto Rico to enroll approximately 1,500 patients with oHCM including at least 700 patients initiating treatment with mavacamten	• Heart failure due to systolic dysfunction • Patients with Class IV NYHA • Patients being treated with disopyramide • Patients being treated with a combination of β-	1. Interim CSR 2. Study progress report	Within 1 year of the end of the 2-year patient selection period Annually for the first 6 years

Table Error! No text of specified style in document.-92: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Ongoing	at enrollment, once it is available. Enrollment is estimated to require two years.	blockers and non-dihydropyridine calcium-channel blockers (verapamil/diltiazem) • Long-term safety, including detrimental CV effects	3. Final CSR	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 Planned	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 52-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	Jul-2025
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	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

Table Error! No text of specified style in document.-92: On-going and Planned Additional Pharmacovigilance Activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestone(s)	Due Date(s)
Hypertrophic Cardiomyopathy Ongoing				

2.6.3. Risk minimisation measures

A summary of risk minimisation measures and pharmacovigilance activities by safety concern is provided in Table 5.3-93.

Table Error! No text of specified style in document.-93: 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. **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:** • MAVA-LTE (MYK-461-007/CV027003) • VALOR-HCM (LTFU) (MYK-461-017/CV027006) • DISCOVER-HCM (CV027012) Planned post-authorization safety studies: • Mavacamten Real-World Safety - A Post-Authorization Long-term Observational Study in Europe (CV027013)
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)

Table Error! No text of specified style in document.-93: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		Planned post-authorization safety studies: • Mavacamten Real-World Safety - A Post-Authorization Long-term Observational Study in Europe (CV027013)
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:** • VALOR-HCM (LTFU) (MYK-461-017/CV027006) • DISCOVER-HCM (CV027012) Planned post-authorization safety studies: • Mavacamten Real-World Safety - A Post-Authorization Long-term Observational Study in Europe (CV027013)
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:** • VALOR-HCM (LTFU) (MYK-461-017/CV027006) • DISCOVER-HCM (CV027012) Planned post-authorization safety studies: • Mavacamten Real-World Safety - A Post-Authorization Long-term Observational Study in Europe (CV027013)
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) • VALOR-HCM (LTFU) (MYK-461-017/CV027006) • DISCOVER-HCM (CV027012)

Table Error! No text of specified style in document.-93: Summary of Risk Minimisation Measures and Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		• Planned meta-analysis to assess CV outcome safety Planned post-authorization safety studies: • Mavacamten Real-World Safety - A Post-Authorization Long-term Observational Study in Europe (CV027013)
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)

2.6.4. Conclusion

The PRAC and the CHMP and consider that the risk management plan version 2.0 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the IBD to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request an alignment of the PSUR cycle with the international birth date (IBD). The IBD is 28 April 2022.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Camzyos (mavacamten) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The target indication applied for by the applicant is:

“Camzyos is indicated for the treatment of symptomatic (New York Heart Association, NYHA, class II-III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients (see section 5.1).”

Hypertrophic cardiomyopathy is a primary myocardial disorder defined by left ventricular (LV) hypertrophy that cannot be explained by another cardiac or systemic disease (Marian and Braunwald 2017). HCM is a chronic, progressive disease of the cardiomyocyte and largely of the cardiac sarcomere, with a diverse clinical presentation and course. HCM can be familial and is the most common genetic disease affecting the heart muscle. Mutations in cardiac myosin and other sarcomere proteins increase calcium sensitivity of myofilaments and can dysregulate sarcomere structure, favouring the formation of excess cross-bridges during systole and diastole, altering sarcomere kinetics, and increasing sarcomere energy utilization, resulting in ventricular hypercontractility accompanied by reduced LV compliance, which is reflected clinically as reduced ventricular chamber size, often supranormal ejection fraction, and diastolic dysfunction. Over time, HCM leads to tissue remodelling characterized histologically by myocyte hypertrophy and disarray, microvascular remodelling, and fibrosis.

Obstructive HCM and nonobstructive HCM (nHCM) are 2 subclassifications of HCM. Both subtypes of HCM are characterized by LV hypercontractility, hypertrophy, and reduced compliance. However, oHCM

also has reduced LV outflow, defined as peak LV outflow gradient ≥30 mmHg at rest or with provocation, due to structural changes in the LVOT.

Subjects with oHCM experience progressive diminishing cardiac function and are at greater risk of developing heart failure and symptoms from systolic dysfunction and atrial fibrillation, which increases the risk of thromboembolic stroke. Additionally, patients with HCM have an increased risk of sudden cardiac death (SCD) ranging from 0.5%-2% per year, which is directly related to changes in cardiac structure and function, including LVOT gradient, maximal wall thickness, and left atrial volume index (LAVI).

Subjects with oHCM often experience symptoms which include shortness of breath at rest or with exertion, fatigue, chest pain, and limited exercise capacity that worsen over time in the absence of effective treatment. The presence and degree of symptoms vary across patients. Variability in symptom presentation may lead to delays in diagnosis, misdiagnosis, and receiving treatment that targets diseases other than HCM.

3.1.2. Available therapies and unmet medical need

Currently, there are no approved disease-specific or sarcomere-targeted therapies for oHCM in EU. The European Society of Cardiology (ESC) guideline states that in the absence of large randomized clinical studies, pharmacological therapy is administered on an empirical basis to improve functional capacity, reduce symptoms, and prevent disease progression. The current guideline relies on the use of established negative inotropic agents, including beta-blockers, non-dihydropyridine calcium channel blockers, and disopyramide, resulting in a reduction of SAM/septal contact and LVOT obstruction (Elliott et al. 2014) (Ommen et al. 2020). Non-vasodilating beta-blockers (propranolol or nadolol) are recommended as first-line therapy in patients with symptomatic LVOT obstruction. Calcium channel blockers (verapamil or diltiazem) are recommended in patients who are intolerant or have contra-indications to beta-blockers. Disopyramide is recommended in addition to a beta-blocker (or, if this is not possible, with verapamil) if beta-blockers alone are ineffective. A combination of a beta-blocker and a calcium channel blocker is not recommended. However, none of the recommendations is supported by Level A Evidence, as the available clinical data are not supported by adequate, well-controlled, randomized, double-blind trials.

Nonpharmacological, invasive therapies, including septal myectomy and septal alcohol ablation, are available for patients with LVOT gradient ≥50 mmHg, NYHA Class III or IV, and/or recurrent exertional syncope despite maximal pharmacological therapy (Elliott et al. 2014). These procedures can be effective in reducing obstruction and improving LV outflow, but they do not address the underlying myocardial disease and are not a permanent treatment, as residual or recurrent obstruction may occur and/or underlying diastolic dysfunction with symptoms may remain. An implantable cardioverter defibrillator (ICD) may be considered in HCM to prevent sudden cardiac death (SCD).

The main goals of treatment in HCM are diminishing disease progression, and control of symptoms and improvement of exercise limitation, abolition or reduction of dynamic intraventricular gradients, treatment of LV dysfunction and heart failure, control of atrial fibrillation and ventricular arrhythmias, and prevention of cardio-embolism (Ammirati et al. 2016), thereby decreasing mortality and morbidity. Despite maximally tolerated treatment with current therapeutic options, many patients continue to show pathophysiological evidence of disease (e.g., LVOT gradient > 50 mmHg, systolic anterior motion (SAM) of the mitral valve, enlarged atria, elevated cardiac biomarkers) and/or impaired function (NYHA Class II-III and reduced patient-reported health status).

Therefore, the limited pharmacological and surgical options to treat the chronic and progressive symptomology of oHCM leave a treatment gap for oHCM patients and an unmet medical need for a targeted therapy that addresses the underlying disease pathophysiology of oHCM.

3.1.3. Main clinical studies

The main evidence of efficacy and safety to support this MAA comes from the two pivotal studies EXPLORER-HCM (MYK-461-005) and VALOR-HCM (MYK-461-017).

EXPLORER-HCM is a pivotal phase III, double-blind, randomized, placebo-controlled, multicenter, international, parallel-group study evaluating the efficacy and safety of mavacamten, when added to HCM-background therapy, in subjects with symptomatic oHCM defined by 1) unexplained LV hypertrophy with nondilated ventricular chambers in the absence of other cardiac or systemic disease and with maximal LV wall thickness ≥15 mm (or ≥13 mm with positive family history of HCM) and 2) LVOT peak gradient ≥50 mmHg during screening as assessed by echocardiography at rest, after Valsalva manoeuvre, or post exercise. Further, at screening, subjects were required to have documented LVEF > 55% at rest, Valsalva LVOT peak gradient ≥30 mmHg, and NYHA Class II or III. A total of 251 subjects were randomized 1:1 to receive 2.5, 5, 10, or 15 mg mavacamten (n = 123) or placebo (n = 128) once daily for 30 weeks, followed by 8 weeks of posttreatment follow-up. Subjects initiated treatment with mavacamten 5 mg. At Week 6, Week 8, and Week 14, the mavacamten dose was up-titrated or down-titrated for individual subjects based on pre-specified criteria, including mavacamten plasma concentration and echocardiography responses at week 4, 6 and 12, respectively. The primary endpoint was a composite functional response at Week 30, defined as achieving 1) An improvement of ≥1.5 mL/kg/min in pVO_2max as determined by CPET and a reduction of ≥1 NYHA class or 2) an improvement of ≥3.0 mL/kg/min in pVO_2max with no worsening in NYHA class. Key secondary endpoints included the individual components of the primary endpoint, pVO_2max and NYHA class, post-exercise LVOT peak gradient and patient-reported outcomes.

VALOR-HCM is a confirmatory phase 3, randomized, double-blind, placebo-controlled study of mavacamten vs placebo in subjects ≥18 years old with symptomatic oHCM who met the 2011 American College of Cardiology Foundation (ACCF)/AHA guideline criteria for SRT, were referred for an SRT procedure within the past 12 months and were actively considering scheduling the procedure. Eligible subjects were randomized in a 1:1 ratio to the mavacamten (n=56) or placebo (n=56) treatment groups and stratified by the type of SRT procedure recommended (myectomy or ASA) and NYHA functional class. Subjects were treated in 3 dosing periods, including a placebo-controlled or double-blind period (Day 1 to Week 16), an active-controlled dosing period (Week 16 to Week 32), and an LTE dosing period (Week 32 to Week 128). The starting dose was 5 mg. At Week 4, the mavacamten dose could be down-titrated based on echocardiography response, e.g. VLVOT <30 mmHg and up-titrated at Week 8 and 12 to a maximum dose of 15 mg based on LVEF ≥50% and VLVOT ≥30 mmHg dose. Of note, in Study MYK-461-017, dose adjustments were clinically guided based on ECHO assessments during scheduled evaluations of LVOT gradients, whereas Study MYK-461-005 required scheduled PK/PD assessments of serum mavacamten concentrations (PK) and LVOT gradient and LVEF (PD) for the dose adjustment algorithm. The primary endpoint was the composite of a patient's decision to proceed with SRT or eligibility for SRT according to the ACCF/AHA 2011 guidelines after 16 weeks of treatment.

Supportive data are obtained from the ongoing long-term extension studies MAVA-LTE (Study MYK-461-007) and PIONEER-OLE (Study MYK-461-008) and the phase II dose-ranging study PIONEER-HCM.

3.2. Favourable effects

EXPLORER-HCM

Primary endpoint. In the pivotal study EXPLORER-HCM, treatment with mavacamten resulted in a higher response rate (definition see above) than placebo, 36.6% vs 17.2%, respectively; treatment difference: 19.4%, 95% CI: 8.67, 30.13; p=0.0005).

Subgroups. Subgroup analysis concerning age, gender, BMI, LVEF at baseline, NYHA class, type of exercise testing, NT-proBNP at baseline, and HCM genotype generally showed consistent results on the primary endpoint.

pVO_2max. The second sequentially tested secondary endpoint in this study was pVO_2max, which is considered the most important efficacy endpoint in this application. Mavacamten demonstrated a significant increase compared with placebo (1.4 ml/kg/min vs -0.05 ml/kg/min, respectively; treatment difference: 1.4 ml/kg/min, 95% CI: 0.59, 2.12; p=0.0006). This corresponds to an absolute mean change for mavacamten from 18.9 ml/kg/min at baseline to 20.4 ml/kg/min at week 30.

Other secondary endpoints. Mavacamten demonstrated a significant treatment effect on post-exercise LVOT gradient of -35 mmHg compared to placebo (-47 mmHg vs -10 mmHg; 95% CI: -43.2, -28.1; p<0.0001). This corresponds to an absolute mean change in post-exercise LVOT gradient of 86 mmHg at baseline to 38 mmHg at week 30. This latter value is below the level of consideration for SRT (≥50 mmHg) but still above the ≥30 mmHg criterion that defines obstruction in HCM patients. Additionally, treatment with mavacamten resulted in a higher percentage of subjects who had an ≥1 class improvement from baseline in NYHA class (65.0% mavacamten vs 31.3% placebo; treatment difference 33.8, 95% CI: 22.15, 45.43; p <0.0001). Only one subject worsened in NYHA class (from NYHA class II to class III). Mavacamten treatment compared with placebo was associated with greater improvements in health status measured by KCCQ-23 CSS (mean (SD) of 13.6 (14.42) vs 4.2 (13.68), 95% CI: 5.46, 12.66; p<0.0001) and by HCMSQ SoB score (mean (SD) of -2.8 (2.68) vs -0.9 (2.41), 95% CI: -2.40, -1.20; p<0.0001).

Exploratory endpoints. Improvement in exercise performance and cardiac output was further supported by improvement in peak VE/VCO_2, VE/VCO_2 slope, peak circulatory power, ventilatory power, peak MET, percent predicted VO_2 and ventilatory threshold as measured by cardiopulmonary testing. Furthermore, consistent with the MoA of mavacamten, which causes reduced contractility, treatment with mavacamten resulted in a slight increase in left ventricular end-systolic volume index (LVESVI). Further favourable effects of mavacamten were reductions in the percentage of subjects with systolic anterior motion (SAM) of the mitral valve and mitral regurgitation, E/e', and LAVI, suggesting improvements in LV filling during diastole, i.e. improved diastolic function. No differences were observed with respect to LV stroke volume (LVSV), heart rate, and cardiac output, which are indicators of cardiac function. Moreover, treatment with mavacamten resulted in a reduction in NT-proBNP and cardiac troponin, indicating a reduction in LV wall stress and myocardial injury.

Cardiac magnetic resonance substudy. Treatment with mavacamten resulted in a reduction in the LV mass index (mean difference -15.8 g/m2; 95% CI:-22.6, -9.0; p<0.0001), and a reduction in the exploratory endpoints of LV maximal wall thickness (mean difference -2.4 mm; 95% CI: -3.9, -0.9; p<0.0079), and in left atrial volume index over the 30-week treatment period. At the same time, myocardial contraction fraction and contractile fraction (stroke volume/LV mass ratio), which are load-independent measures of LV pump reserve, were maintained.

Long-term efficacy data. Results of the EXPLORER-LTE cohort of the long-term extension (MYK-461-007) demonstrated that subjects receiving mavacamten continue to experience therapeutic benefit generally consistent with that achieved in the parent study with respect to LVOT gradient, NYHA class,

and other transthoracic echocardiographic parameters. However, maintenance of the effect on pVO_2max has not been demonstrated as this has not been assessed in this LTE.

VALOR-HCM

Primary endpoint. In the pivotal study VALOR-HCM, treatment with mavacamten resulted in a lower proportion of subjects that decided to proceed with SRT or remained guideline eligible at Week 16 compared with placebo (17.9% vs 76.8%, respectively; treatment difference (95% CI), 58.93 (43.989,73.868); p <0.0001).

Subgroups. Subgroup analyses with respect to age, baseline resting LVOT gradient, duration since oHCM diagnosis, beta-blocker use at baseline, number of background HCM medication, baseline NT-proBNP showed consistent results on the primary endpoint.

Secondary endpoints. Mavacamten treatment resulted in significant improvements compared to placebo on secondary endpoints of post-exercise LVOT gradient (treatment difference (95% CI): -37.2 (-48.08, -26.24) mmHg; p<0.0001), ≥1 NYHA class improvement (treatment difference (95% CI): 41.07 (24.48, 57.66); p<0.001), improvement in KCCQ- 23 CSS (treatment difference (95% CI) 9.45 (4.868, 14.041) points; p<0.0001) and NT-proBNP and cardiac troponin I between groups geometric mean ratio, 0.33 (0.266, 0.421) and 0.53 (0.406, 0.700); both p<0.0001).

Long-term efficacy data. As of the 07-February-2022 data cut, 71 subjects were randomized at least 32 weeks (38 subjects in the mavacamten group and 33 in the placebo group). In the previous placebo group, 2 out of 33 (6.1%) subjects with Week 32 data proceeded to SRT, and 3 out of 33 (9.1%) subjects remained SRT eligible. These data is similar as those observed in the mavacamten group in the double-blind period. In the previous mavacamten group, 2 out of 38 (5.3%) subjects have proceeded to SRT and 2 out of 38 (5.3%) are SRT guideline eligible, which suggest maintenance of treatment effect or even increased magnitude of effect at Week 32. Maintenance of effect after 32 weeks of treatment has also been demonstrated for these secondary endpoints.

3.3. *Uncertainties and limitations about favourable effects*

EXPLORER-HCM

Primary endpoint. Exercise capacity in terms of pVO_2max is acceptable as a primary efficacy endpoint; however, the primary endpoint, which is a composite of pVO_2max and NYHA class is difficult to interpret and not adequately justified. As such, the focus in order to assess the B/R in this application was mainly be on the data of the individual component pVO_2max, which was the second sequentially tested secondary endpoint in this study.

Subgroups. A heterogeneity of effect on pVO_2max was observed with respect to beta-blocker usage at baseline. Subjects who were not using beta-blocker showed a greater magnitude of the treatment effect on pVO_2max compared with subjects who were using beta-blockers (between-group difference: 2.7 ml/kg/min vs 1.0 ml/kg/min, respectively. The observed difference could be explained by the blunting effect of beta-blockers on cardiopulmonary exercise testing (CPET).

Maintenance of effect. pVO_2max has only been assessed in the pivotal study EXPLORER-HCM and not in its LTE study EXPLORER-LTE (MYK-461-007). Therefore, maintenance of effect on pVO_2max has not been demonstrated.

Both pivotal studies

Health status. The improvements in health status measured by KCCQ-23 (between-group treatment difference: 9.1; p<0.0001 in EXPLORER-HCM and 9.45; p<0.0001 in VALOR-HCM) and HCMSQ SoB

(between-group treatment difference: -1.8 ; p<0.0001 in EXPLORER-HCM) were both just below the clinically meaningful within-patient change thresholds (an increase of ≥10 and decrease ≥ 2.5 points respectively).

3.4. Unfavourable effects

Exposure. The updated pooled safety database consists of n=207 oHCM subjects exposed for a minimum of 1 year, which fulfils the requirements of the guideline ICH-E1 'Population Exposure' (i.e. 100 patients exposed for a minimum of 1 year at clinically recommended doses).

Adverse events (AEs). The most frequently reported AEs (≥5% in mavacamten group and at least 2 % higher than in the placebo group) in the pivotal Study MYK-461-005 were dizziness (21.1% in RCT-Mava oHCM vs. 13.3% in RCT-Placebo oHCM), dyspnoea (14.6% vs. 10.2%), headache (12.2% vs. 7.8%), atrial fibrillation (8.1% vs 2.4%), upper respiratory tract infection (8.1% vs 4.7%), back pain (8.3% vs 6.3%), cough (8.1% vs 3.1%), and arthralgia (5.7% vs 1.6%). Data were generally in line with the nHCM patients and pooled data of mavacamten-treated patients.

Serious adverse events (SAEs). The incidence of SAEs was relatively low with generally no large differences in the mavacamten group compared to the placebo group (11.4% vs 9.4%). Generally, similar findings were seen in the nHCM patients, and findings appeared to be in line with the pooled data of mavacamten-treated patients. No patterns for a new unexpected safety signal could be identified from the current available SAE safety data.

Deaths. Three deaths have been reported in the safety database; one in the placebo arm and two in the mavacamten arm, for which a possible relationship to the study drug is considered unlikely.

Cardiovascular safety. Data analyses for the major pre-defined cardiovascular events have been evaluated and adjudicated by an independent committee (CEAC). In the pivotal study, reported AEs of *LVEF reduction* were higher in the mavacamten group compared to the placebo group (7 subjects and 2 subjects, respectively), but numbers were low. The data in the pooled mavacamten-treated population were consistent with the data from the pivotal studies, with similar reversibility. More than half (56%) of the patients experience no symptoms from the LVEF reduction of mavacamten. These data show that LVEF reduction <50% in the posology can be considered as a conservative approach regarding cardiovascular safety. Further, although again the event rate was very low, *heart failure* was generally balanced between the treatment groups (mavacamten vs. placebo: 2.4% vs. 3.9%). The incidence of heart failure events (n=22, 7.1%) was more substantial in the pooled mavacamten population. The occurrence of the events is not unexpected since heart failure is importantly confounded by the underlying disease and can also be considered a consequence of the LVEF reduction due to the use of mavacamten. Also, no important imbalances in *QT-interval and arrhythmia* AEs and ECG data have been observed in the pivotal study (0 events in the mavacamten oHCM group and 2 events in one subject in the placebo oHCM group). The ECG data for QTcF intervals and changes from baseline and the categorical data for QTcF intervals demonstrated a generally similar mean change in the mavacamten group (13.89 ms) vs the placebo group (15.76 ms), with similar findings in the nHCM patients and the pooled mavacamten population. Of note, while the QT effect of mavacamten on healthy volunteers and animals resulted in prolongation of cardiac ventricular repolarization, a slight QTcF shortening was observed in oHCM subjects in the clinical PD studies, which have been ascribed to a degree of normalization of the QT interval in the patients, since their QT interval was prolonged at baseline. The findings in the integrated clinical safety database are generally in line with the earlier findings of the PD analyses. No new significant safety concerns have been identified by these data. Also, although numbers were low, no relevant imbalance on *atrial fibrillation* was found (n=10 8.1% in mavacamten vs n=10 7.8% in placebo, respectively).

Further, there are no new safety signals on hypotension, severe cutaneous adverse reactions (SCAR), gastro-intestinal events, rhabdomyolysis/myopathy, renal and hepatic events in the provided data.

Tolerability. The incidence of AEs leading to discontinuations was higher in the mavacamten group, as compared to the placebo group (1.6% (2 subjects) vs 0%). Similar findings were observed with the nHCM patients (7.7% (3 subjects) vs 0%) and in the pooled data of mavacamten-treated patients (3.2% (10 subjects)). The most frequent AEs leading to discontinuation were atrial fibrillation and ejection fraction decreased and cardiac failure, which is in line with the mechanism of action of the drug or the underlying disease. Furthermore, no other pattern with respect to the type of AE leading to discontinuation or interruptions of the study drug has been observed.

VALOR-HCM study. The safety findings of the pivotal VALOR-HCM study were comparable to those observed in the pivotal EXPLORER-HCM study. In the VALOR-HCM DB period, the most frequently reported AEs (≥5% in the mavacamten group and at least 2% higher than the placebo group) were fatigue (8.9% vs 3.6% for mavacamten and placebo, respectively), atrial fibrillation (7.1% vs 0), nausea (7.1% vs 1.8%), dizziness (7.1% vs 5.5%), dyspnoea (7.1% vs 5.5%), rash (7.1% vs 0%), urinary tract infection (5.4% vs 1.8%), and hypertension (5.4% vs 3.6%). The incidence of SAEs was relatively low, although with a higher proportion (n=3, 5.4%) in the mavacamten group through week 16 than in placebo group (n=1, 1.8%). In the DB period, two (3.6%) subjects in the mavacamten treatment group were reported with a decreased LVEF event of <50%, however, no subjects experienced HF. In the DB period, no subject had any on-treatment AEs resulting in permanent treatment discontinuation, whereas in the LTFU period, two (1.9%) subjects had at least one TEAE resulting in permanent treatment discontinuation due to decreased LVEF ≤ 30%, which were both considered related to study therapy by the investigator, although there were confounding factors.

3.5. Uncertainties and limitations about unfavourable effects

Cardiovascular safety. The number of oHCM patients who experienced *MACE* was low but was higher (relative risk 1.73; 95% CI: 0.42-7.10) in the mavacamten group (5 of 123, 4.1%, all SAE) vs the placebo group (3 of 128, 2.3%, all SAE) in the pivotal study MYK-461-005. In the pivotal study VALOR-HCM, no MACE was reported in the double-blind period. Overall, these figures are considered too low to draw firm conclusions.

Cardiovascular safety - meta analysis. Mavacamten is a first-in-class selective inhibitor of cardiac myosin ATPase, that directly targets the pathophysiology of the disease, i.e. oHCM, by specifically targeting the cardiac mechanisms, which might have deleterious effects on contractility, resulting in reduced ejection fraction and heart failure in the long term. Also, in Scientific Advices, important concerns were raised regarding the exclusion of a detrimental effect on cardiovascular safety. Since a CV outcome study is unfeasible and unethical to be performed, a meta-analysis will be conducted with continuous monitoring of the cardiovascular safety of mavacamten by routine pharmacovigilance, LTE studies and two non-interventional observational studies.

Subgroups. The impact of CYP2C19 phenotype on the pharmacokinetics of mavacamten is substantial. Clinical pharmacology studies have shown that mavacamten exposures increase dramatically (up to ~3 fold) in poor CYP 2C19 healthy volunteer metabolizers. The effect of a high plasma concentration can be expected to translate to clinical efficacy and safety due to the clear relationship between plasma exposure and LVEF and VLVOT. Limited safety data on CYP 2C19 poor metabolizers are currently available in the target population. Therefore, an adjusted posology for CYP2C19 poor metabolizers is recommended in the SmPC.

3.6. Effects Table

Table 94. Effects table for mavacamten for the treatment of symptomatic oHCM (EXPLORER-HCM; 20 October 2020).

Effect	Short Description	Unit	Mava	Pbo	Uncertainties/ Strength of evidence
Favourable Effects					
Primary endpoint	Achieved Composite Functional Endpoint at Week 30 Either: improvement of ≥1.5 mL/kg/min in pVO_2max AND improvement of ≥1 NYHA class OR improvement of ≥3.0 mL/kg/min in pVO_2max AND no worsening in NYHA class	N (%)	45 (36.6)	22 (17.2)	SoE: Difference (95% CI): 19.3 (8.67, 30.13); p=0.0005 Consistent effect across subgroups, except for beta-blocker usage Unc: Interpretation difficult No demonstration of maintenance of effect
Secondary endpoint	pVO_2max , change from baseline to Week 30	mean (SD) mL/kg/min	1.4 (3.12)	-0.05 (3.02)	SoE: Difference (95% CI): 1.4 (0.59, 2.12); p=0.0006 Responders pVO_2max inc⩾1.5 : 42% mava vs 25% pbo Responders pVO_2max inc ⩾3.0: 24% mava vs 13% pbo Unc: Consistent effect across subgroups, except for beta-blocker usage No demonstration of maintenance of effect
	Post-exercise LVOT gradient , change from baseline to Week 30	mean (SD) mmHg	-47 (40.3)	-10 (29.6)	SoE: Difference (95% CI): -35 (-43.2, -28.1); p<0.0001
	Improved by ≥1 NYHA Class change from baseline to Week 30	N (%)	80 (65.0)	40 (31.3)	SoE: Difference (95% CI): 33.8 (22.15, 45.43); p<0.0001
	KCCQ-23 CSS, change from baseline to Week 30	mean (SD)	13.6 (14.42)	4.2 (13.68)	SoE: Between-group difference (95% CI): 9.1 (5.46, 12.66); p<0.0001 Responders score inc ⩾10: 53.9% mava vs 33.8% pbo Unc: clinically meaningful within-patient change threshold ≥10 points.
	HCMSQ SoB Domain Score, change from baseline to Week 30	mean (SD)	-2.8 (2.68)	-0.9 (2.41)	SoE: Between-group difference (95% CI): -1.8 (-2.4, -1.2); p<0.0001 Responders score decrease ⩾2.5: 50.0% mava vs 21.3% pbo Unc: clinically meaningful within-patient change threshold of 2.5-point decrease
Unfavourable Effects					
LVEF <50%	Left ventricle ejection fraction reduction to below <50%	n/N (%)	7/123 (5.7)	2/128 (1.6)	SoE: Relative risk 3.64 (95% CI: 0.77; 17.19) Unc: Low numbers. No long-term data

Effect	Short Description	Unit	Mava	Pbo	Uncertainties / Strength of evidence
MACE	Major adverse cardiovascular events defined as acute myocardial infarction, stroke, CV death or heart failure hospitalization	n/N (%)	5/123 (4.1)	3/128 (2.3)	SoE: Relative risk 1.73 (95% CI: 0.42-7.10) Unc: Low numbers. No long-term data

Abbreviations: mava: mavacamten; pbo placebo; inc increase; LVEF Left ventricle ejection fraction; MACE Major adverse cardiovascular events;
Notes: All data based on EXPLORER-HCM

Table 95. Effects table for mavacamten for the treatment of symptomatic oHCM (VALOR-HCM)

Effect	Short Description	Unit	Mava	Pbo	Uncertainties / Strength of evidence
Favourable Effects					
Primary endpoint	Composite of: - Decision to proceed with SRT prior to or at Week 16 - SRT guideline eligible at Week 16 based on the 2011 ACCF/AHA HCM Guidelines	N (%)	10 (17.9)	43 (76.8)	SoE: Difference (95% CI): 58.93 (43.99, 73.87); p<0.0001 Maintenance of effect up to Week 32
Secondary endpoint	Post-exercise LVOT gradient (mmHg) , change from baseline to Week 16	mean (SD)	-39.1 (36.51)	-1.8 (28.82)	SoE: Difference (95% CI): -37.2 (-48.08, -26.24); p<0.0001
	Improved by ≥1 NYHA Class change from baseline to Week 16	N (%)	35 (62.5)	12 (21.4)	SoE: Difference (95% CI): 41.07 (24.48, 57.66); p<0.0001
	KCCQ-23 CSS, change from baseline to Week 16	mean (SD)	10.4 (16.06)	1.8 (12.01)	SoE: Between-group difference (95% CI): 9.45 (4.87, 14.04); p<0.0001 Unc: clinically meaningful within-patient change threshold ≥10 points
	NT-proBNP (ng/L), from baseline to Week 16	Geometric mean ratio (95% CI)	0.35 (83.68)	1.13 (57.81)	SoE: Difference (95% CI): 0.33 (0.266, 0.421); p<0.0001
	hs-Cardiac Troponin-I (ng/L), from baseline to Week 16	Geometric mean ratio (95% CI)	0.50 (100.99)	1.03 (85.72)	SoE: Difference (95% CI): 0.53 (0.41, 0.70); p<0.0001
Unfavourable Effects					
LVEF <50%		n/N (%)	2/56 (3.6)	0/55 (0)	SoE: Unc: Low numbers, No long-term data
MACE		n/N (%)	0	0	SoE: Unc: Low numbers, No long-term data

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Patients with oHCM experience considerable symptoms, functional impairment, and poor quality of life. Additionally, patients with HCM have an increased risk of sudden cardiac death (0.5% to 2% per year in adults with HCM). Currently, there are no disease-specific or sarcomere-targeted pharmacological therapies for oHCM available, only symptomatic treatment. Nonpharmacological invasive therapies include septal reduction therapies; however, they also do not address the underlying myocardial disease and are not a permanent treatment. Therefore, the limited pharmacological and surgical options to treat the chronic and progressive symptomology of oHCM leave a significant treatment gap for oHCM patients and an unmet medical need for a targeted therapy that addresses the underlying disease pathophysiology of oHCM.

The current application is based on the results of two pivotal studies, EXPLORER-HCM and VALOR-HCM. In the EXPLORER-HCM study, the primary endpoint (a composite of pVO_2max and NYHA) is difficult to interpret and not considered appropriate for this application. Consequently, the individual component pVO_2max, which was the second sequentially tested secondary endpoint, is considered the most relevant efficacy endpoint. In the VALOR-HCM study, the primary endpoint of the composite of a patient's decision to proceed with SRT or eligibility for SRT according to the ACCF/AHA 2011 guidelines after 16 weeks of treatment is considered a more robust ("hard") clinical endpoint compared with pVO_2max in the EXPLORER-HCM, since SRT is clinically relevant to patients and clinicians as it is a highly invasive surgery associated with significant consequential risk.

In EXPLORER-HCM, results show a significant but modest improvement in exercise capacity measured by pVO_2max in oHCM patients administered mavacamten compared with placebo (1.4 ml/kg/min vs -0.05 ml/kg/min, respectively; treatment difference (95% CI): 1.4 ml/kg/min (0.59, 2.12); p=0.0006), particularly in the subgroup of subjects using a beta-blocker (treatment difference: 1.0 ml/kg/min) which was the majority of the study population (75.3%). In support of the clinical relevance of the effect on pVO_2max, reference was made to the HF-ACTION study (Swank AM, 2012), which showed that every 6% increase in pVO_2max (0.9 ml/kg/min) was associated with a 5% lower risk of the primary endpoint of time to all-cause mortality or all-cause hospitalization (hazard ratio=0.95; CI=0.93-0.98; P<0.001). However, the study had several limitations, i.e. exercise intervention was not blinded to the patient and investigator due to the nature of the intervention, and a large amount of patients (30%) were excluded from the primary analyses because they either did not have a baseline or 3-month CPX test or experienced a primary outcome before the 3-month test, which could have biased the outcome. Additionally, it remains uncertain whether the results of the HF-ACTION study can be directly extrapolated to the EXPLORER-HCM study since the population is different; The HF-ACTION trial enrolled a broader HF population, however, with reduced LVEF (≤ 35%), whereas the EXPLORER study included patients with obstructive HCM with normal LVEF (> 55%). Further, the subjects enrolled in the HF-ACTION study received exercise as an intervention vs. mavacamten in EXPLORER-HCM. Exercise positively affects the body in many different ways, which may have contributed to the improved clinical outcome observed in the HF-ACTION trial. After all, the improvement in pVO2max after exercise training was relatively modest (0.6 ml/kg/min vs 0.2 ml/kg/min for usual care alone).

The most important support for the clinical relevance of the effect on pVO_2max observed in the EXPLORER-HCM study can be derived from the *ongoing* VALOR-HCM study, a phase 3 randomized, double-blind, placebo-controlled study in US patients with oHCM eligible for septal reduction therapy

(SRT) according to the ACCF/AHA 2011 guideline. As of 07 February 2022 (the clinical cut-off data of the primary CSR), all subjects participating in the study completed the study through Week 16 and, as such, the primary analysis was conducted. These results showed that, after 16 weeks of treatment, a lower percentage of subjects in the mavacamten group continued to meet guideline criteria for SRT or elected to undergo the procedure compared with the placebo group (10/56 (17.9%) vs 43/56 (76.8%), respectively; $p<0.001$). Moreover, a beta-blocker subgroup analysis of VALOR-HCM data showed similar improvements in SRT eligibility, regardless of beta-blocker use (treatment difference: 52.41% beta-blocker no vs 61.71% beta-blocker yes), indicating internal consistency. During the procedure, the applicant has adequately justified that the overall positive beneficial results of the VALOR-HCM study can be extrapolated to the entire target population of the EXPLORER-HCM study, including the less compromised NYHA class II subpopulation based on the following 4 aspects: 1) overlapping study populations; 2) Consistent results for endpoints assessed in both studies; 3) consistent results on septal reduction therapy eligibility; 4) comparable safety profile.

Furthermore, the beneficial effect on exercise capacity (pVO_2max) and preventing patients from (progressing to) septal reduction therapy eligibility is supported by significant improvements in other relevant secondary/exploratory endpoints, including post-exercise LVOT, NYHA functional class, NT-proBNP, and health status (KCCQ-23 CSS and HCMSQ SoB).

The uncertainty regarding the maintenance of effect on PVO_2max still remains, since only a benefit over a short period of 30 weeks has been demonstrated in the EXPLORER-HCM study, and the effect on exercise capacity has not been assessed in the LTE study. However, preliminary data up to at least 32 weeks of the VALOR-HCM showed maintenance of treatment effect. Additionally, maintenance of effect up to at least 96 weeks has been demonstrated in terms of the secondary endpoints Valsalva LVOT, NYHA class, and NT-proBNP in the LTE studies.

Based on the above, it can be concluded that the pivotal studies EXPLORER-HCM and VALOR-HCM demonstrate that mavacamten treatment results in clinically relevant improvements across the entire population of symptomatic NYHA Class II-III oHCM patients.

The impact of CYP2C19 phenotype on the pharmacokinetics of mavacamten is significant. Therefore, an adjusted posology for CYP2C19 poor metabolizers is recommended in the SmPC.

Safety data are primarily based on the pivotal phase 3 study EXPLORER-HCM supplemented with 2 phase II studies and 2 ongoing LTE studies, providing 207 patients with an exposure of >1 year and on the ongoing pivotal phase 3 VALOR-HCM study (MYK-461-017) up to a cut-off date of 7 February 2022. Mavacamten appeared to be generally well tolerated with dizziness and dyspnoea as the most common reported AEs. Apart from the expected effect on LVEF reduction due to the MoA, no other significant safety concerns regarding cardiovascular effects have been identified from the currently available safety data, although these data are limited and current numbers were too low to draw firm conclusions. Therefore, in addition to continuous monitoring of the cardiovascular safety of mavacamten by routine pharmacovigilance, the ongoing LTE studies and the two non-interventional observational studies, a meta-analysis to evaluate the cardiovascular safety profile of mavacamten will be conducted, which is considered acceptable. This meta-analysis includes data from existing and planned well-controlled, double-blind, randomized phase 3 studies of mavacamten versus placebo (from EXPLORER-HCM, VALOR-HCM, nHCM Phase 3 and China oHCM Phase 3) and is currently included as a category 3 study in the RMP.

3.7.2. Balance of benefits and risks

The benefits of mavacamten in terms of significant improvement in exercise capacity (pVO_2max) and preventing patients from (progressing to) septal reduction therapy eligibility are accompanied by limited risks. Nevertheless, the safety database remains too limited in order to exclude a detrimental effect on cardiovascular safety, for which a meta-analysis (with continuous monitoring of the cardiovascular safety of mavacamten by routine pharmacovigilance, LTE studies and two non-interventional observational studies) will be conducted.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall benefit/risk balance of Camzyos is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Camzyos is favourable in the following indication(s):

Camzyos is indicated for the treatment of symptomatic (New York Heart Association, NYHA, class II III) obstructive hypertrophic cardiomyopathy (oHCM) in adult patients (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

- Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- Risk Management Plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- Additional risk minimisation measures

Prior to the launch of Camzyos in each Member State, the 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that mavacamten is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.