CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214998Orig1s000

CLINICAL and STATISTICAL REVIEW(S)

Clinical and Statistical Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	214998
Priority or standard	Standard
Submit date(s)	1/28/2021
Received date(s)	1/28/2021
PDUFA goal date	4/28/2022
Division/office	Division of Cardiology and Nephrology (DCN)
Review completion date	4/26/2022
Established name	Mavacamten
(Proposed) trade name	Camzyos
Pharmacologic class	Cardiac myosin inhibitor
Code name	MYK-461
Applicant	Myokardia Inc.
Dose form/formulation(s)	Oral (b) (4)
Dosing regimen	The recommended starting dose is 5 mg QD. Assessment of Valsalva left ventricular outflow tract (VLVOT) gradient and left ventricular ejection fraction (LVEF) should be done at Week 4, Week 8, Week 12, and every 12 weeks thereafter. Early down-titration could occur if VLVOT < 20 mmHg at Week 4 and Week 8. Up-titration is not allowed until Week 12 if VLVOT ≥ 30 mmHg and LVEF ≥ 55%. Assess LVEF 4 weeks after any dose increase. Minimum 12 weeks between up-titrations. Available doses: 2.5 mg, 5 mg, 10 mg and 15 mg Interrupt therapy if LVEF < 50% at any visit or the patient experiences worsening clinical status; restart at the next lowest dose level after 4 weeks if LVEF ≥ 50%. Permanently discontinue if LVEF < 50% twice while receiving 2.5 mg QD.
Applicant proposed indication(s)/population(s)	For the treatment of symptomatic New York Heart Association (NYHA) class II-III obstructive hypertrophic cardiomyopathy (HCM) in adults to improve functional capacity, (b) (4) and symptoms.
Proposed SNOMED indication	45227007 Hypertrophic obstructive cardiomyopathy
Regulatory action	Approval
Approved indication(s)/population(s) (if applicable)	For the treatment of symptomatic New York Heart Association (NYHA) class II-III obstructive hypertrophic cardiomyopathy (HCM) in adults to improve functional capacity and symptoms.
Approved SNOMED indication	45227007 Hypertrophic obstructive cardiomyopathy

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Glossary

AE	adverse event
AF	atrial fibrillation
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BP	blood pressure
CDTL	Cross-Discipline Team Leader
CI	confidence interval
C_{max}	maximum plasma concentration
CMR	cardiac magnetic resonance imaging
CPET	cardiopulmonary exercise testing
CSR	clinical study report
CSS	clinical summary score
CT	computerized tomography
CYP	cytochrome P450
DBP	diastolic blood pressure
DDIs	drug-drug interactions
DILI	drug-induced liver injury
DPMH	Division of Pediatrics and Maternal Health
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCOA	electronic clinical outcome assessment
ECPR	extracorporeal cardiopulmonary resuscitation
EQ-5D-5L	EuroQoL 5 Dimensions 5 Levels
eCTD	electronic common technical document
EOP2	end-of-phase 2
EOT	end of treatment
FDA	Food and Drug Administration
FIH	First-in-human
FMQ	FDA MedDRA Query
FS	fractional shortening
GCP	good clinical practice
HCM	hypertrophic cardiomyopathy
HCMSQ	Hypertrophic Cardiomyopathy Symptom Questionnaire
HF	heart failure
HR	heart rate
ICD	implantable cardioverter-defibrillator
IND	investigational new drug
IRT	interdisciplinary review team
ISS	integrated summary of safety
ITT	intention-to-treat
IXRS	interactive response system
KCCQ-23	Kansas City Cardiomyopathy Questionnaire (23-item version)
LOCF	last observation carried forward

LV	left ventricular
LVEF	left ventricular ejection fraction
LVOT	left ventricular outflow tract
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NME	new molecular entity
NNH	number needed to harm
NNT	number needed to treat
NOAEL	no observed adverse effect level
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
OCP	Office of Clinical Pharmacology
OCS	Office of Computational Science
OCT	over the counter
nHCM	non-obstructive hypertrophic cardiomyopathy
oHCM	obstructive hypertrophic cardiomyopathy
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PGIC	Patient Global Impression of Change questionnaire
PGIS	Patient Global Impression of Severity questionnaire
PK	pharmacokinetics
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PRO	patient-reported outcome
PT	preferred term
PTSMA	percutaneous transluminal septal myocardial ablation
PVC	premature ventricular contractions
pVO_2	peak oxygen consumption
QD	once daily
QTcF	QT interval with Fridericia correction
REMS	risk evaluation and mitigation strategy
RVEF	right ventricular ejection fraction
RVR	rapid ventricular response
SAE	serious adverse event
SBP	systolic blood pressure
SCS	Summary of Clinical Safety
SD	standard deviation
SMQ	Standardized MedDRA Queries
SOC	system organ class
SU	safety update
TEAE	treatment-emergent adverse event

TEE	transesophageal echocardiogram
TTE	transthoracic echocardiogram
ULN	upper limit of normal
USPI	US package insert
VLVOT	Valsalva left ventricular outflow tract
VO_2	oxygen consumption

I. Executive Summary

1. Summary of Regulatory Action

In the setting of a rare disease and significant unmet medical need, the agreed pre-submission plan for the NDA to approve mavacamten for the proposed indication to treat patients with symptomatic obstructive hypertrophic cardiomyopathy (oHCM) included a single Phase 3 pivotal trial that was expected to be highly persuasive with a convincing p-value, along with confirmatory evidence from a Phase 2 trial that provided hemodynamic data that aligned with and therefore substantiated the clinical evidence from the pivotal trial.

Based on the pivotal EXPLORER-HCM trial, it can be fairly concluded that the Applicant satisfied the statutory requirement for substantial evidence of effectiveness to support approval of mavacamten for the proposed indication. The treatment effect, measured at Week 30 compared to baseline, was defined as a ≥1.5 mL/kg/min increase in peak oxygen consumption (pVO_2) ***and*** at least one New York Heart Association (NYHA) class reduction, ***or*** a ≥ 3.0 mL/kg/min improvement in pVO_2 ***and*** no worsening of NYHA class. These results were clinically meaningful and highly statistically significant compared to placebo.

All secondary endpoint results showed superiority of mavacamten versus placebo in the intention-to-treat population: left ventricular outflow tract (LVOT) peak gradient; pVO_2; and patient reported outcomes (PRO), i.e., Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-23 CSS); and Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ).

Because mavacamten's mechanism of action is to reduce cardiac contractility, it has the potential to significantly reduce left ventricular ejection fraction (LVEF), especially in patients who are poor metabolizers of mavacamten or who take concomitant medications that interfere with its metabolism via the CYP2C19 or CYP3A4 metabolic pathways. This would clinically manifest as heart failure (HF) with reduced ejection fraction, thus adversely complicating the management of oHCM. Pharmacokinetic (PK) monitoring along with echocardiography were used in the Phase 3 trial to avoid excessive exposure and guide dose adjustments. There are limitations in monitoring the safety of mavacamten in the postmarketing setting where patients are not typically followed as closely as in clinical trials. Therefore, approval of mavacamten requires a risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) to ensure that the benefits outweigh the risks of heart failure due to systolic dysfunction.

Background
Hypertrophic cardiomyopathy (HCM) is a genetic myocardial disorder characterized by left ventricular (LV) hypertrophy, hyperdynamic contraction and impaired relaxation. The presence of obstruction in the left ventricular outflow tract (LVOT) is the major hallmark of the disease. Patients with oHCM have diverse clinical symptomatology and disease courses; and are at increased risk of developing other cardiac comorbidities and sudden cardiac death. Current guidelines for the pharmacologic management of HCM recommend the use of negative inotropic

agents, including beta-blockers, non-dihydropyridine calcium channel blockers, and disopyramide. Propranolol was approved in 1969 to improve NYHA functional class in symptomatic patients with hypertrophic subaortic stenosis (previous name for oHCM at the time of propranolol approval).

Septal myectomy, the gold standard treatment for oHCM, confers symptomatic relief but carries all the risks associated with open heart surgery. Percutaneous transluminal septal myocardial ablation with dehydrated alcohol is a cardiac catheterization procedure that induces an iatrogenic myocardial infarction at the thickened septal wall. This alternative procedure to septal myectomy has shown clinical benefit following reduction in LVOT obstruction. This percutaneous intervention, however, carries risks of iatrogenic induction of a wider myocardial infarction and post-procedure atrioventricular blocks that may require pacemaker placement.

Mavacamten is a new molecular entity (NME), a first-in-class, small molecule, and allosteric inhibitor of cardiac myosin, with a mechanism of action that results in diastolic relaxation and reduction of myocardial contractility, thereby reducing dynamic LVOT obstruction in patients with oHCM. Mavacamten serves as a complement to the current treatment paradigm and offers an alternative to patients who are not surgical candidates and those who prefer to not undergo an invasive surgical or percutaneous procedure.

Overview of EXPLORER-HCM

EXPLORER-HCM was a Phase 3, double-blind, randomized, placebo-controlled, multicenter, international, parallel group trial that enrolled 251 adults with oHCM and NYHA functional class II or III symptoms, LVEF ≥ 55%, and LVOT peak gradient ≥ 50 mmHg at rest or with provocation.

Eligible patients were randomized (1:1 ratio) to receive either placebo or a starting dose of 5 mg of mavacamten once daily for 30 weeks. Randomization was stratified by NYHA class II or III, treatment with beta-blocker (yes or no), type of exercise used for the primary efficacy endpoint assessment (treadmill or bicycle) and consent for cardiac magnetic resonance (yes or no).

Guided mavacamten dosing (2.5 mg, 5 mg, 10 mg and 15 mg) was based on regular monitoring of mavacamten plasma concentrations and on the LVEF and Valsalva LVOT gradient assessed by echocardiography. Several pre-specified criteria for dosing discontinuation were used to maintain safety and avoid excessive pharmacologic effects.

The primary efficacy endpoint was a composite clinical response at Week 30, compared to baseline, defined as a ≥1.5 mL/kg/min increase in pVO_2 ***and*** at least one NYHA class reduction, ***or*** a ≥ 3.0 mL/kg/min increase in pVO_2 ***and*** no worsening of NYHA class.

Secondary endpoints that were evaluated within the confines of an alpha-sparing hierarchy included the change from baseline to Week 30 in post-exercise LVOT peak gradient, change from baseline to Week 30 in pVO_2, proportion of subjects with at least one class improvement in NYHA class, change in reported health-related quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire-23 (KCCQ-23)-Clinical Summary Score (CSS), and the change in patient-reported severity of HCM symptoms as assessed by the Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ)-Shortness of Breath (SoB) domain.

The planned sample size of 220 subjects was estimated to provide 96% power to detect a 25% difference between treatment groups for the primary efficacy endpoint (2-sided α 0.05).

The trial enrolled 123 subjects in the mavacamten arm and 128 subjects in the placebo arm. All randomized subjects received at least one dose of study drug. In the mavacamten arm, 88 of 123 subjects completed the trial (71.5%). In the placebo arm, 90 of 128 subjects completed the trial (70.3%).

Demographics and baseline characteristics: age (mean 59 years), gender (59% male), region (43% USA), race (91% white), blood pressure, body mass index (BMI), and heart rate, were similar between the two study arms. The distribution of CYP2C19 metabolizer phenotype was similar between the two arms (37% normal, 24% rapid, 26% intermediate, 3% ultra-rapid, 2% poor). Thus, there are limited data in CYP2C19 ultra-rapid and poor metabolizers in this study.

EXPLORER-HCM Efficacy Findings

A total of 45 of 123 (37%) subjects in the mavacamten arm met the composite primary efficacy endpoint compared to 22 of 128 (17%) subjects in the placebo arm (between-group difference of 19.4%; 95% CI 8.7, 30.1; p = 0.0005). Mavacamten was also superior to placebo on each component of the primary efficacy endpoint. Thirty-three percent (33%) of mavacamten-treated subjects compared to 14% of placebo-treated subjects met the component endpoint of *≥ 1.5 mL/kg/min improvement in pVO_2 and at least one NYHA class reduction* (between group difference 19.3%, 95% CI 9.0%, 29.5%; p = 0.0006). Similarly, 24% of mavacamten-treated subjects compared to 11% of placebo-treated subjects met the component endpoint of *≥ 3.0 mL/kg/min improvement in pVO_2 and no worsening in NYHA class* (between group difference 12.6%, 95% CI 2.4%, 22.3%; p = 0.013).

Subgroup analyses of the primary efficacy endpoint by baseline characteristics and stratification factors showed a consistent effect with the notable exception of subjects receiving beta-blocker therapy at baseline, whereby the treatment effect for the primary efficacy endpoint lost statistical significance in that subgroup. There was an attenuated improvement in mean pVO_2 in the subgroup of subjects receiving beta-blockers at baseline (mean difference between mavacamten and placebo 1.1 mL/kg/min) compared to those who did not receive beta-blockers at baseline (mean difference between mavacamten and placebo 2.2 mL/kg/min). However, the results for other secondary endpoints including post-exercise LVOT peak gradient and PROs, demonstrated consistent treatment effects of mavacamten irrespective of beta-blocker use. Early in the review, there was serious consideration given to a limitation-of-use to patients not on beta-blocker therapy. However, analysis of the datasets showing no interaction between beta-blocker use at baseline and secondary efficacy endpoints attenuated this consideration in deference to a label description. The observed blunted treatment effect in subjects receiving beta-blockade at baseline for the primary efficacy endpoint and for pVO_2 may be a chance finding, but a true interaction cannot be ruled out.

All secondary endpoint results showed superiority of mavacamten versus placebo in the intention-to-treat population: LVOT peak gradient; pVO_2; KCCQ-23 CSS; and HCMSQ.

Sensitivity analyses performed to evaluate the effect of approximately 30% missing data for KCCQ-23 CSS and HCMSQ scores showed no impact on the PRO efficacy conclusions.

Although it is unclear whether the magnitude of improvement in pVO_2 in this trial (mean treatment effect for pVO_2 of 1.4 mL/kg/min) will lead to improved mortality, the consistency of effect between variables (i.e., improvement of pVO_2, reduction or no worsening of NYHA class,

improvements in PROs and reduction of the LVOT gradient), provided compelling evidence of the utility of mavacamten for improving how patients with oHCM feel and function.

EXPLORER-HCM Safety Findings

The overall safety profile of mavacamten was similar to placebo in the setting of careful safety monitoring based on plasma mavacamten concentrations and echocardiographic assessments. However, from the integrated safety dataset, the risk of serious adverse events (SAEs) of HF and/or systolic dysfunction was 1.70 and 0.99 per 100 patient-years on mavacamten and placebo, respectively. The main concern is mavacamten-mediated reversible induction of systolic dysfunction in the real-world setting where rigorous safety monitoring may not occur, thus potentially magnifying the differential risk of HF and/or systolic dysfunction observed in the Phase 3 trial.

Mavacamten is predominantly metabolized by CYP2C19 and, to a lesser extent, CYP3A4. Therefore, a CYP2C19 poor metabolizer and drug-drug interactions (DDI) involving CYP2C19 and CYP3A4 inhibitors could lead to higher mavacamten exposures and systolic dysfunction. Polypharmacy, potential sub-optimal health records on concomitant medications, and unreported use of over the counter drugs, could significantly impact patient safety when prescribed mavacamten. Hence, to ensure that the benefit of mavacamten outweighs the risk, an ETASU-REMS is required for approval. The objectives of the ETASU-REMS include: 1) requirements for periodic echocardiograms to monitor LVEF and make dose adjustments when indicated in the REMS; and 2) screening for concomitant interacting drugs by a pharmacist prior to each dispense. Prescribers, pharmacists and patients will be educated on the risk of HF due to systolic function and the potential for DDIs to ensure achieving the objectives of the ETASU-REMS.

Proposed Posology

The Office of Clinical Pharmacology (OCP) recommended a universal posology and monitoring schedule that will allow mavacamten to be used both efficaciously and safely in all patients irrespective of CYP2C19 genotype. All patients will start mavacamten at a dose of 5 mg once daily followed by clinical visits (including echocardiograms) scheduled at Week 4, Week 8, Week 12 and every 12 weeks thereafter. The current posology allows for early opportunities to down-titrate at Week 4 and Week 8 based on Valsalva LVOT gradient and LVEF to minimize the risk for patients with altered pharmacokinetics predisposing to slow rate of mavacamten accumulation after exposure. Up-titration is allowed for eligible patients at Week 12 (and then no sooner than every 12 weeks) based on Valsalva LVOT and LVEF. In order to ensure safety at the new dose level, an additional clinical visit with echocardiogram assessment of Valsalva LVOT and LVEF is required 4 weeks following any dose increase. Safety criteria for temporary or permanent discontinuation have also been developed.

Proposed Management for Drug-Drug Interactions

Inducers and inhibitors of CYP2C19, and moderate to strong inhibitors or inducers of CYP3A4, may affect the exposure of mavacamten. Concomitant administration of mavacamten with moderate or strong CYP2C19 inhibitors/inducers, strong CYP3A4 inhibitors/inducers, or moderate CYP3A4 inducers, are contraindicated. As noted above, concomitant use of these inhibitors could lead to higher mavacamten exposures, increasing the risk for heart failure/systolic dysfunction. Concomitant use of these inducers could considerably reduce efficacy due to decreased mavacamten exposures. Also, stopping these inducers could inadvertently increase the risk for HF/systolic dysfunction if the same mavacamten dose is continued. Patients that intend to initiate a weak CYP2C19 or moderate CYP3A4 inhibitor while on mavacamten should reduce their dose of mavacamten by one level.

Summary and Conclusions

The mavacamten trials were not designed to show a survival benefit and such an effect has not been demonstrated. However, mavacamten has met the pre-specified efficacy criteria for success, leading to highly statistically significant and clinically meaningful improvements compared to placebo in how patients with symptomatic oHCM function and feel, including a compelling effect on the primary composite endpoint plus a reduction in NYHA class, reduction in the LVOT pressure gradient, and improvement on fit-for-purpose PROs. The main serious risk with mavacamten is iatrogenic HF caused by too high a dose in patients who are poor CYP2C19 metabolizers or those with interacting prescription or over-the-counter medications. This risk cannot adequately be mitigated by labeling alone, thus requiring an ETASU REMS to ensure that the benefits outweigh the risk. Prescribing mavacamten under REMS requirements will be complex, which may limit real-world use by patients with symptoms not controlled with other negative inotropes. However, we expect that mavacamten will be predominantly prescribed by cardiologists, a specialty skilled with interpreting echocardiograms, and who are expected with adequate training through certifying for the REMS to be able to appropriately dose mavacamten for their patients.

Postmarketing Requirements and Commitments

Given mavacamten's potential risk of embryo-fetal toxicity, a postmarketing requirement (PMR) will be issued to conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to mavacamten during pregnancy and/or lactation to assess the risk of pregnancy and maternal complications, and adverse effects on the developing fetus, neonate and infant. Infant outcomes will be assessed through at least the first year of life.

In addition, there is an ongoing 2-year carcinogenicity study that is being allowed to complete postmarketing given the rarity of the disease and unmet need. This carcinogenicity study will be a PMR to ensure that we receive timely results.

2. Benefit-Risk Assessment

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hypertrophic cardiomyopathy (HCM) is a rare genetic myocardial disorder characterized by left ventricular (LV) hypertrophy, hyperdynamic contraction and impaired relaxation. • The prevalence of asymptomatic HCM among young adults in the United States has been estimated at 1/200 to 1/500, with symptomatic HCM being less common based on medical claims data (estimated at < 1:3000). • About 70% of individuals diagnosed with HCM have obstructive HCM (oHCM). The presence of left ventricular outflow tract (LVOT) obstruction is an important prognostic factor in HCM. The prevalence of symptomatic oHCM is estimated to be between 2 and 5 per 10,000 people. • Complications of oHCM include arrhythmias, dilated cardiomyopathy, mitral regurgitation, heart failure (HF), stroke, and sudden death from ventricular tachycardia / ventricular fibrillation. The incidence of sudden death is approximately 1%/year, often in people < 30 years of age. The cause of death from oHCM is age-dependent (sudden death in the younger population, HF in middle age, and stroke in the elderly). • Patients with oHCM have a wide range of symptom presentations and disease courses. The typical symptoms of oHCM include dyspnea, reduced exercise tolerance, angina, palpitations, and syncope. Some patients suffer significant debilitating consequences and high symptom burden, with profound effects on their quality of life.	oHCM is a rare, chronic, progressive disease of cardiomyocyte disarray, hypercontractile myocardium, and impaired LV relaxation with variable clinical presentations and clinical course. oHCM is associated with significant cardiovascular (CV)-related morbidity, including a risk of sudden cardiac death and could have a profound impact on patients' quality of life.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Propranolol is the only therapy approved for improving NYHA functional class in patients with oHCM. The approval was based on an uncontrolled series of 13 subjects. • Current guidelines for the pharmacologic management of HCM recommend the use of negative inotropic agents, including beta-blockers, non-dihydropyridine calcium channel blockers, and disopyramide. These treatments offer limited and variable relief in symptoms and functional status. • The gold standard treatment for oHCM is septal myectomy. As an alternative to this open-heart surgical procedure, patients may opt for percutaneous transluminal septal myocardial ablation (PTSMA), which is a cardiac catheterization procedure whereby concentrated alcohol is infused into a target septal artery that feeds the thickened septal wall. The resulting iatrogenic myocardial infarction results in reducing the septal thickness and thus decreasing the LVOT gradient. Although this procedure is effective, complications can include spill-over (alcohol infusion into other arteries thus causing an expanded myocardial infarction) and disruption of electrical conduction causing blocks and potential pacemaker requirements. Resurgence of LVOT obstruction can also occur, requiring a repeat procedure.	There are currently no FDA-approved sarcomere-targeted therapies for oHCM. There is limited evidence for the efficacy and safety of propranolol and off-label use of other pharmacologic therapies. The two procedures (septal myectomy and PTSMA) have important risks, such that patients may not be candidates nor elect to undergo such procedures. Therefore, there remains an unmet need for additional effective and safe treatments for oHCM.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The effectiveness of mavacamten in the treatment of patients with oHCM was primarily evaluated in the EXPLORER-HCM trial, a double-blind, randomized, placebo-controlled, multicenter, international, parallel group study in 251 patients with symptomatic oHCM. • The primary efficacy endpoint was a composite clinical response at Week 30, compared to baseline, defined as a ≥1.5 mL/kg/min increase in pVO_2 *and* at least one NYHA class reduction, ***or*** a ≥ 3.0 mL/kg/min improvement in pVO_2 *and* no worsening of NYHA class. • The study met its primary endpoint. The proportion of subjects with a positive response on the composite primary endpoint was statistically significantly greater in the mavacamten arm as compared to placebo (36.6% vs. 17.2%, between-group difference of 19.4%; 95% CI: [8.7, 30.1], p=0.0005). Mavacamten was superior to placebo on both components of the primary endpoint: o Thirty-three percent of mavacamten-treated subjects (41/123) compared to 14% of placebo-treated subjects (18/128) met the component endpoint of ≥ *1.5 mL/kg/min improvement in pVO_2 and at least one NYHA class reduction* (between group difference 19.3%, 95% CI 9.0%, 29.5%; p = 0.0006). o Twenty-four percent of mavacamten-treated subjects (29/123) compared to 11% of placebo-treated subjects (14/128) met the component endpoint of ≥ *3.0 mL/kg/min improvement in pVO_2 and no worsening in NYHA class* (between group difference 12.6%, 95% CI 2.4%, 22.3%; p = 0.013). • Subgroup analyses of the primary efficacy endpoint by baseline characteristics and stratification factors showed a consistent effect with the notable exception of beta-blocker use at baseline. The efficacy was lower in subjects on beta-blocker therapy at baseline. The difference in the proportion of responders in the mavacamten group compared to placebo was 8.7% among beta-blocker users versus 52.6% among non-beta-blocker users. Also, there was an attenuated improvement in pVO_2 in the subgroup of subjects receiving beta-blockers at baseline compared to those who did not receive beta-blockers (the between group differences were 1.1 vs. 2.2 mL/kg/min, respectively; interaction p = 0.016). However, the results for post-exercise LVOT peak gradient and the PROs, demonstrated consistent	The results of EXPLORER-HCM met the pe-specified criteria for success with a highly statistically significant difference between mavacamten and placebo for the primary efficacy endpoint, as well as for all secondary efficacy endpoints within the alpha-conserving strategy. It is unclear whether the magnitude of improvement in pVO_2 in this trial with mavacamten vs. placebo (mean treatment effect of 1.4 mL/kg/min) will lead to improved mortality. However, mavacamten's clinically meaningful effects compared to placebo on a variety of endpoints, including the proportion of patients with a reduction of NYHA class, improvements in the PROs and reduction of the LVOT gradient, clearly establish that mavacamten improves how patients with oHCM function and feel. The primary efficacy results were consistent across all subgroups with the only exception of patients using beta-blocker therapy at baseline. In the presence of baseline beta blocker therapy, there was no statistically significant difference between mavacamten and placebo. However, other parameters (LVOT peak gradient, and PROs) were unaffected by baseline beta-blocker treatment. Therefore, whether there is a true interaction effect or a play of chance is unclear. This finding will be reflected in labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

treatment effects of mavacamten irrespective of beta-blocker use. The blunted effect in the presence of beta-blockade for the primary efficacy endpoint and for pVO_2 may be a chance finding, but a true interaction cannot be ruled out.

- Mavacamten treatment was superior to placebo for all secondary endpoints:

Continuous secondary endpoints (Change from baseline at Week 30)	Between groups difference (95%CI)	P value
Change in postexercise LVOT gradient (mmHg)	-35 (-43.2, -28.1)	p < 0.0001
Change in pVO_2 (mL/kg/min)	1.4 (0.6, 2.1)	p = 0.0006
Change in KCCQ-23 CSS[a]	9.1 (5.5, 12.7)	p <0.0001
Change in HCMSQ SoB[b]	-1.8 (-2.4, -1.2)	p <0.0001

[a]The KCCQ-23 CSS is composed of the physical limitations and total symptom burden scores of the KCCQ-23. The KCCQ-23 CSS ranges from 0 to 100, with higher scores representing better health status.
[b]The HCMSQ SoB domain score measures frequency and severity of shortness of breath. The HCMSQ SoB domain score ranges from 0 to 18, with lower scores representing less shortness of breath.

- For the categorical secondary endpoint, a statistically greater proportion of patients with improvement of ≥ 1 NYHA class was observed in patients on mavacamten vs. placebo (65.0% vs. 31.3%, p < 0.0001).
- The main efficacy review issue was missing secondary endpoint data of KCCQ-23 CSS and HCMSQ-SoB scores both at baseline (22% and 14% for KCCQ-23 CSS and HCMSQ SoB, respectively) and at week 30 (12% and 25% for KCCQ-23 CSS and HCMSQ SoB, respectively). Our analysis showed that the missing data had no impact on the PRO efficacy conclusions.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Safety evaluation was primarily based on the data obtained in the EXPLORER-HCM trial (N=251 receiving at least one dose of study drug; n=123 in the mavacamten group and n=128 in the placebo group). This study provided controlled data with a median exposure of 7 months. Long-term safety is supported by the ISS dataset, which included a total of 5 phase 2/3 studies and 2 ongoing extension studies. With the updated safety data through May 05, 2021, the median exposure for all mavacamten treated patients was about 17 months including 214 patients with at least 1-year of treatment. The size of the safety database is acceptable. • Safety evaluation focused on the on-target effects of mavacamten, whereby reduction of contractility could increase the risk of heart failure with reduced ejection fraction. Other clinical events of special interest included atrial fibrillation (AF), other arrhythmias, and syncopal-related events. o There was a small mean decrease in LVEF (~4% with SD of 8%) during 30 weeks of mavacamten treatment compared with placebo. LVEF appeared reversible with discontinuation of drug therapy. o The incidence of cardiac failure AEs and other clinical events of special interest were as follows: ▪ Cardiac failure (2.4%) compared with placebo (3.9%) ▪ Arrhythmia (13.8%) compared with placebo (12.5%) ▪ AF (8.1%) compared with placebo (7.8%) ▪ Syncope (5.7%) compared with placebo (1.6%); syncope was largely associated with dizziness. o A greater incidence of dizziness (27% vs. 18%) was reported in patients on mavacamten vs. placebo. o No other off-target adverse events were identified • In the ISS, the incidence of a SAE of HF with systolic dysfunction and/or LVEF ≤ 30% was 8/314 (2.5%) in patients on mavacamten compared to 1/147 (0.7%) in patients on placebo; the corresponding event rate was 1.7 and 0.99 per 100 pt-yrs, respectively. Six of these patients experienced new or worsening AF, worsening HF symptoms and/or elevated N-terminal pro b-type natriuretic peptide (NT-proBNP) prior to the event. The safety profile of mavacamten from the ISS was generally consistent with that in the EXPLORER-HCM.	The principal safety concern of mavacamten is the risk of HF due to systolic dysfunction resulting from an excessive pharmacologic effect of mavacamten, particularly in patients who are poor CYP2C19 metabolizers and in patients taking concomitant prescription and non-prescription drugs that inhibit mavacamten's metabolism. In EXPLORER-HCM in which thorough PK/PD monitoring was implemented, the risk of HF and/or systolic dysfunction was low during 30 weeks of treatment. The risk remained similar and acceptable in the ongoing extension study with PD monitoring. The risk of HF due to systolic dysfunction will be clearly described in labeling including a boxed warning and Medication Guide. Labeling language which clearly conveys the final dosing regimen, dosing instructions as well as drug-drug interaction management is essential to help mitigate the risks of mavacamten due to excessive exposure. However, careful monitoring in the real world is not expected to be as rigorous as in the clinical trials, and labeling alone will not ensure that prescribers appropriately titrate mavacamten, obtain echocardiograms at appropriate time points, or ensure patients are informed about the importance of avoiding interacting medications, including non-prescription medications. Hence an ETASU REMS (which includes prescriber and pharmacy certification) is required to assure safe use and ensure that the benefits of mavacamten outweigh the risks of HF/systolic dysfunction. Other risks include dizziness and syncope, which can be adequately managed through labeling. In addition, because of the observed non-clinical teratogenicity findings, labeling will include a Warning and Precaution for embryo-fetal toxicity and recommend the use of contraception in females of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The dosing strategy in EXPLORER-HCM was based on frequent monitoring of both PK and PD (LVOT and LVEF assessed with echocardiography) markers. However, the approved dosing strategy for mavacamten is based on PD monitoring alone. The main concern with a PD-based monitoring scheme is that mavacamten is predominantly metabolized by CYP2C19. There are limited clinical data in patients who are poor CYP2C19 metabolizers (2% of patient population), but the risk of systolic dysfunction is expected to be higher among these patients due to increased mavacamten exposures if the dose is too high. • We identified a dosing strategy that involves starting all patients on a low dose of mavacamten and then basing titration, treatment interruption, and discontinuation decisions on echocardiography (LVOT and LVEF) assessments at regular intervals to adequately mitigate the risk of excessive mavacamten exposure-related HF/systolic dysfunction. Healthcare providers should also consider patients' clinical status (e.g., AF, HF symptoms). With this approach, determining the CYP2C19 genotype of the patient is not required for the effective and safe use of mavacamten. • Concomitant use of CYP2C19 inhibitors or strong CYP3A4 inhibitors with mavacamten may increase mavacamten exposures and increase the risk of systolic dysfunction and/or HF. Patients will need to avoid prescription and nonprescription drugs that are moderate-to-strong CYP2C19 inhibitors or strong CYP3A4 inhibitors. • There are some uncertainties regarding the potential for an adverse PD interaction between mavacamten and other drugs that also reduce cardiac contractility. The safety of concomitant use of mavacamten with disopyramide, or with the combination of calcium channel blockers with beta blockers is unknown and should be discouraged. • A concentration-dependent increase in the QTc interval was observed in healthy volunteers but not in HCM patients. The reason for these differences between healthy volunteers and HCM patients is unclear but may be related to an adaptive response to marked LV depression from healthy hearts. • Teratogenicity was observed in nonclinical studies in two animal species at clinically relevant exposures based on the maximum recommended human dose of 15 mg/day. There were no pregnancies reported in patients exposed to mavacamten in the clinical trials.	reproductive potential. We are also requiring a worldwide post marketing descriptive study that collects prospective and retrospective data in women exposed to mavacamten during pregnancy and/or lactation. This study will assess the risk of pregnancy and maternal complications, and adverse effects on the developing fetus, neonate and infant. Infant outcomes will be assessed through at least the first year of life. Lastly, we will issue a postmarketing requirement (PMR) for the ongoing rodent 2-year carcinogenicity study to ensure timely completion and receipt of the study report. Based on the unmet need for this rare disease, we determined that this carcinogenicity study can be completed post-approval. Other available data have not identified a carcinogenicity concern but these additional data are required.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Mavacamten has a high probability of being a teratogen when administered during gestation.	

Conclusions Regarding Benefit-Risk

To assess benefit-risk, we calculated the number needed to treat (NNT) and the number needed to harm (NNH) based on the primary efficacy result in EXPLORER-HCM and the estimated risk of HF and/or systolic dysfunction SAEs from the integrated safety data, respectively. It should be noted that the NNH was derived based on the difference in the *event rate* of HF and/or systolic dysfunction SAEs between groups to account for longer exposures in patients on mavacamten as compared to placebo from the integrated safety data. One can translate the calculated NNT and NNH approximately as follows: for every 140 patients treated, 28 will achieve clinical improvement of the efficacy primary outcome (based on ~30 weeks of treatment) and 1 person will experience an SAE of HF and/or systolic dysfunction (based on ~1 year of treatment) (see Table 3).

The review team considered several factors when assessing the benefit-risk profile of mavacamten. First, oHCM is a serious, progressive disease and there is an unmet need for a disease-specific drug. Furthermore, patients can have clinically meaningful improvements in functional status and symptom relief with mavacamten as shown on a variety of endpoints in EXPLORER-HCM, including NYHA Class, LVOT gradient, and fit-for-purpose instruments that measured signs and symptoms that are meaningful to patients with the disease. Patients who do not experience meaningful improvements of their symptoms with mavacamten would be expected to discontinue the drug given the complex monitoring. While there is a risk of HF and systolic dysfunction associated with excessive pharmacokinetic exposures to mavacamten, this risk can be managed and mitigated using the available regulatory tools. Implementation of an ETASU REMS that requires certification of prescribers accomplishes the following: 1) ensures that only certified healthcare providers prescribe mavacamten; 2) includes strict monitoring of PD effects (LVOT an LVEF on echocardiography); and 3) informs prescribers and patients to avoid drug-drug interactions. This increases the chance of a positive benefit-risk profile. With the restricted access and the regulatory requirements to ensure safe use, we expect that mavacamten would only be used in selected patients for whom the benefit justifies the complexities of taking the drug, particularly among those with limited therapeutic options. Based on these considerations, the clinical team recommends approval of mavacamten for the treatment of patients with symptomatic oHCM, and the signatory authority concurs. In addition, none of the other review disciplines identified any approvability issues.

Table 3 The Number Needed to Treat and The Number Needed to Harm for Mavacamten

Benefits			Risks		
Primary Efficacy endpoint in EXPLORER-HCM	Treatment Effect (%) Mavacamten vs. Placebo	NNT		Rate difference[3] (per 100 pt-yrs) Mavacamten vs. Placebo	NNH
A Composite of Functional Endpoint[1]	19.4	5.2	Heart Failure and/or Systolic Dysfunction SAE[2]	0.71	140.8

1. The endpoint was defined as an improvement of ≥ 1.5 mL/kg/min in pVO_2 and a reduction ≥ 1 NYHA class, or an improvement of ≥ 3.0 mL/kg/min in pVO_2 with no worsening in NYHA class.
2. Heart failure and/or systolic dysfunction SAE was defined as any SAE of cardiac failure (SMQ, narrow), systolic dysfunction (preferred term) or any LVEF ≤ 30%
3. Using updated integrated safety data through May 2021 (section 0)
Reviewer's Table, Source: Table 10 and Table 40 in the body of review
Abbreviations: NNT, number needed to treat; NNH, number needed to harm

II. Interdisciplinary Assessment

3. Introduction

The Applicant has submitted a single, Phase 3 trial (EXPLORER-HCM) in support of an NDA for mavacamten for the following indication:

> *"Camzyo is indicated for the treatment of New York Heart Association (NYHA) class II-III symptomatic obstructive hypertrophic cardiomyopathy (HCM) in adults to improve functional capacity,* (b) (4) *and symptoms."*

The Applicant also has on-going extension studies to evaluate the long-term safety and tolerability of mavacamten in patients with HCM.

Disease Background

Hypertrophic cardiomyopathy (HCM) is a common autosomal dominant genetic heart disease that affects men and women globally and is characterized by left ventricular (LV) hypertrophy, hyperdynamic contraction and impaired relaxation. The prevalence of asymptomatic HCM among young adults in the United States has been estimated at 1/200 to 1/500, with symptomatic HCM based on medical claims data being less common (estimated at (b) (4) (1). A large percentage of patients are asymptomatic and/or undiagnosed. Two HCM phenotypes are recognized based on the presence or absence of obstruction in the LVOT, obstructive HCM (oHCM) and non-obstructive HCM (nHCM), where obstruction is defined as a peak LVOT gradient ≥ 30 mmHg at rest or ≥ 50 mmHg with provocation (e.g., Valsalva maneuver). Approximately 70% of individuals diagnosed with HCM have oHCM (2). The prevalence of symptomatic oHCM is estimated to be between 2 and 5 per 10,000 people. The health impacts of HCM are variable with a wide range of symptom presentations and disease courses.

Many patients experience minimal or few symptoms and minor or no limitations in daily activities; however, others suffer significant debilitating consequences and high symptom burden, most frequently shortness of breath, chest pain and palpitations with profound effects on their lives. The presence of LVOT obstruction is an important prognostic factor in HCM (3). Over the course of the disease, many patients develop other cardiac comorbidities; Atrial fibrillation (AF) is common in oHCM patients. HCM-related adverse outcomes include sudden death, progressively limiting symptoms caused by diastolic dysfunction and/or LVOT obstruction, HF caused by systolic dysfunction, and thromboembolic complications.

There are currently no approved disease-specific or sarcomere-targeted therapies for oHCM. Current guidelines for the pharmacologic management of HCM recommend the use of negative inotropic agents, including beta-blockers, non-dihydropyridine calcium channel blockers, and disopyramide. Only the beta-blocker propranolol carries an approved indication for improving NYHA functional class based on an uncontrolled series of 13 subjects. Current pharmacologic

treatments may improve LVOT obstruction, but they offer limited and variable relief in symptoms and functional status. The gold standard treatment for oHCM is septal myectomy. As an alternative to this open-heart surgical procedure, patients may opt for percutaneous transluminal septal myocardial ablation (PTSMA), which is a cardiac catheterization procedure whereby concentrated alcohol is infused into a target septal artery that feeds the thickened septal wall. The resulting iatrogenic myocardial infarction reduces the septal thickness and thus decreasing the LVOT gradient. Although this procedure is effective, there are potential procedural complications, such as spill-over (alcohol infusion into other arteries thus causing an expanded myocardial infarction), disruption of electrical conduction causing blocks and potential pacemaker requirements, and resurgence of LVOT obstruction requiring a repeat procedure.

Therefore, the development of mavacamten was seen as important in the treatment paradigm for this condition, especially for patients who are not surgical candidates and patients who prefer not to undergo open heart surgery or PTSMA.

There continues to be an unmet need for a disease-specific drug to treat HCM.

Drug Class

Mavacamten is a first-in-class, small molecule, allosteric inhibitor of cardiac myosin. Mavacamten modulates the number of myosin heads that can enter “on actin” (power-generating) states, thus reducing the probability of force-producing (systolic) and residual (diastolic) cross-bridge formation. Mavacamten shits the overall myosin population towards an energy-sparing, recruitable, super-relaxed state and reduces cardiac contractility. Excess cross-bridge formation between myosin and actin and dysregulation of the super-related state are mechanistic hallmarks of HCM. By targeting the underlying sarcomere hypercontractility, mavacamten reduces sarcomere force production and myocardial contractility which results in smaller excursions of the hypertrophied basal septum into an already narrow LVOT. The reduction in myocardial contractility attenuates the force of ejection flow and lessens the venturi effect responsible for anterior mitral valve leaflet displacement into the LVOT and worsening of LVOT obstruction. In HCM patients, myosin inhibition with mavacamten reduced dynamic LVOT obstruction and improved cardiac filling pressures.

3.1. Approach to the Review

This was a joint review. Preston Dunnmon and Cherry Liu focused on the data supporting efficacy, and Tzu-Yun McDowell focused on the data supporting safety.

Table 4. Main Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for Mavacamten

Trial Identifier	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints
MYK-461-005 (EXPLORER-HCM)	Patients with symptomatic oHCM (LVEF ≥55% and LVOT gradient with Valsalva maneuver ≥50 mmHg)	Phase 3 Randomized, parallel-group, placebo-controlled, double-blind, multicenter study	Drug: Mavacamten 2.5, 5, 10 or 15 mg or placebo once daily Number treated: Mavacamten:123 Placebo: 128 Duration 30 wk	Primary: Composite functional endpoint with pVO2 and NYHA class Secondary: -Change in postexercise LVOT peak gradient -Change in pVO_2 -≥1 class of improvement in NYHA -KCCQ-23 CSS -HCMSQ-SoB
MYK-461-004 (PIONEER-HCM):	Patients with symptomatic oHCM	Phase 2, open label Uncontrolled clinical study	Drug: Mavacamten 2, 5, 10, 15, or 20 mg once daily 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 Part A and B may have had dose adjustments beginning Week 4 Number treated: Part A: 11 Part B: 10 Duration 12 weeks	Primary: Change in postexercise peak LVOT gradient from baseline to Week 12 Secondary: - LVOT gradient response of < 30 mmHg -change in pVO_2 - PK and PD markers

Trial Identifier	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints
MYK-461-006 (MAVERICK-HCM)	Patients with symptomatic nHCM	Phase 2 Randomized, double blind, placebo-controlled study	Drug: Mavacamten 2.5, 5, 10, or 15 mg or placebo once daily Number treated: Mavacamten: 40; placebo: 19 Duration 16 weeks	Primary objective: To evaluate the safety and tolerability of 16-week course of mavacamten Exploratory efficacy endpoints: -Change in pVO_2 -Change in NT-proBNP -≥1 class of improvement in NYHA - PK and PD markers
MYK-46-008 (PIONEER-OLE)	Patients with symptomatic oHCM	Phase 2 Uncontrolled clinical study	Drug: Mavacamten 5, 10 and 15 mg. Individualized target dose was determined based on PK at Week 6 Number treated: 13 Duration 156 Weeks	Primary: To assess long-term safety and tolerability of mavacamten Exploratory efficacy endpoints: -NYHA class -KCCQ -NT-proBNP -PD markers

Trial Identifier	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints
MYK-461-007 (MAVA-LTE) Ongoing	Patients with oHCM who have completed EXPLORER HCM or patients with nHCM who have completed MAVERIC HCM	Phase 2/3 extension Uncontrolled clinical study	Drug: Mavacamten 2.5, 5, 10, or 15 mg once daily Number treated: EXPLORER-HCM cohort: 180 MAVERICK-LTE Cohort: 43 Duration Up to 5 years	Primary: To assess long-term safety and tolerability of mavacamten Exploratory efficacy endpoints: -Change in LVOT gradient -Change in NYHA class - Change in NT-proBNP

Source: Reviewer's table
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
Abbreviations: BID, twice daily; DB, double-blind; LTE, long-term extension study; MC, multi-center; N, number of subjects; OL, open-label; PC, placebo-controlled; PG, parallel group; R, randomized.

4. Patient Experience Data

The EXPLORER-HCM trial collected data on patient's perception of their symptoms and health status at baseline and various timepoints using the Kansas City Cardiomyopathy Questionnaire (23-item version) (KCCQ-23) Clinical Summary Score (CSS) and Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ) shortness of breath (SoB) domain score.

Table 5. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☒	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☒	Patient-focused drug development meeting summary	PFDD The Voice of the Patient Report (m5.3.5.4)
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (but Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Evidence of Benefit (Assessment of Efficacy)

5.1. Assessment of Dose and Potential Effectiveness

The Applicant conducted an open-label, dose-ranging study in patients with oHCM (PIONEER-HCM) to inform the dosing in the Phase 3 study. The study explored the PK/PD relationship and identified concentration (Ctrough) dependent decreases in LVOT gradient and LVEF. The PK/PD modeling was also used to inform the starting dose (i.e., 5 mg once daily) and target trough concentration to maintain normal ejection fraction (i.e., LVEF >50%) while achieving a relevant decrease in LVOT gradient for the subsequent Phase 3 study (see Section 5.2.3).The safe dosing of mavacamten has been the central review issue for this application. For extensive details on exposure-response and PBPK modeling, see the Clinical Pharmacology reviews dated 18 October 2021 and 24 February 2022. PIONEER-HCM is also a proof-of-concept study to evaluate the effect of 12 weeks of mavacamten treatment on reducing post-exercise peak LVOT gradient in subjects with symptomatic oHCM (see Table 4 for the trial design). In this 2-part study, the Applicant utilized higher starting doses based on body weight (i.e., 10 or 15 mg based on body weight) in Part A of the study where baseline therapy or concomitant therapy with beta-blocker were not permitted (N=11). Part B utilized a lower starting dose (i.e., 2 mg) and patients were permitted to take concomitant therapy with beta-blockers (N=10). Dose titration was allowed at Week 4 in both Part A (up to 20 mg) and Part B of the study (to 5 mg) based on LVEF or LVOT.

The primary endpoint of the study was the change in post-exercise peak LVOT gradient from baseline to Week 12. Large, statistically significant reductions in post-exercise peak LVOT gradient (as well as resting LVOT gradient, and Valsalva post LVOT gradient) were observed in both Part A and Part B (Table 6), a finding that would not be expected to occur spontaneously to this extent as demonstrated by the modest LVOT changes with placebo in EXPLORER-HCM. PIONEER-HCM also evaluated a range of functional endpoints and parameters such as pVO_2, NYHA functional class, KCCQ, and NT-proBNP. In general, an improvement or a trend for improvement in these endpoints from baseline to Week 12 was observed (Appendix III.10.1), although these endpoints cannot readily be interpreted without a control arm.

PIONEER-HCM demonstrated sizeable hemodynamic effects of mavacamten, which are not expected to occur spontaneously and which are expected to be translated into some degree of clinical benefits on functional improvements and symptom relief in patients with oHCM. While recognizing the limitations of an open-label, uncontrolled and small trial, the large effect on LVOT gradient in PIONEER-HCM together with the highly statistically significant and robust results of EXPLORER-HCM on a variety of efficacy endpoints provide substantial evidence of effectiveness of mavacamten.

Table 6 Left Ventricular Outflow Tract Gradient Changes from Baseline at Week 12, PIONEER-HCM,

	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: PIONEER-HCM CSR Table 15

5.2. Design of Clinical Trials Intended to Demonstrate Benefit to Patients

5.2.1. Trial Design

EXPLORER-HCM is a Phase 3, double-blind, randomized, placebo-controlled, multicenter, international, parallel group study to evaluate the safety, tolerability, and efficacy of mavacamten compared with placebo in participants with symptomatic oHCM. Approximately 220 eligible participants were planned to be randomized in 1:1 ratio to receive mavacamten or placebo, in which ~80 participants (~40 per treatment group) might participate in a cardiac magnetic resonance imaging (CMR) substudy at selected sites. Randomization was stratified according to New York Heart Association (NYHA) functional classification (II or III), current treatment with β-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 expected study duration was approximately 43 weeks: up to 5 weeks for screening, a 30-week treatment period, and an 8-week post-treatment follow-up period (±7 days).

Primary efficacy endpoint: The primary efficacy endpoint was the composite functional endpoint at Week 30 defined as:

1. An improvement of ≥ 1.5 mL/kg/min in pVO_2 as determined by cardiopulmonary exercise testing (CPET) and a reduction ≥ 1 NYHA class, **or**

2. An improvement of ≥ 3.0 mL/kg/min in pVO_2 with no worsening in NYHA class.

Reviewer's comment:

During the End of Phase 2 meeting, the Division agreed that change in pVO_2 during exercise testing is an appropriate measure of exercise and functional capacity to serve as a primary endpoint to support clinical benefit in patients with symptomatic oHCM. Due to limited data in the HCM population, there were some uncertainties regarding the subjectivity of the proposed threshold of 1.5 mL/kg/min and 3 mL/kg/min. However, an improvement of 1 mL/kg/min in pVO_2 was associated with improved CV outcomes in patients with HF (see section 5.4.2). Furthermore, adding NYHA class as a component of the primary endpoint strengths the validity of clinical response. Hence, the Division agreed that the improvements defined in the composite endpoint of NYHA functional class and pVO_2 could support approval.

Secondary efficacy endpoints:

- Change from baseline to Week 30 in postexercise LVOT peak gradient
- Change from baseline to Week 30 in pVO_2 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[1]
- Change from baseline to Week 30 in subject-reported severity of HCM symptoms as assessed by the HCMSQ SoB domain score[2]

Reviewer's Comment: *The Division had consulted the Clinical Outcome Assessments (COA) team regarding the Applicant's proposal to include KCCQ-23 and HCMSQ SoB as secondary endpoints in their clinical studies. In general, the Division and COA had no major objection to these two patient reported outcomes (PROs); however, we informed the applicant that the completed qualitative and quantitative data to evaluate content validity and other measurement properties for the KCCQ-23 and HCMSQ SoB in patients with oHCM would be reviewed at the time of NDA submission (COA review dated 23 March 2020).*

In addition, the Division and COA recommended using the KCCQ-23 CSS or total symptom scores (TSS) instead of the KCCQ-23 overall summary score (OSS) as they measure concepts that may be more responsive to treatment (e.g., core disease symptoms, physical function). The Division also agreed that shortness of breath is one of the main clinical manifestations of HCM, and therefore agreed that it is acceptable to evaluate HCMSQ SoB as a secondary endpoint. The Division recommended the Applicant to consider additional concepts to measure treatment benefit (e.g., chest pain, fatigue) but acknowledged that it is the Applicant's choice for endpoint selection.

[1] The KCCQ-23 CSS is composed of the physical limitations and total symptom burden scores of the KCCQ-23. The KCCQ-23 CSS ranges from 0 to 100, with higher scores representing better health status.

[2] The HCMSQ SoB domain score measures frequency and severity of shortness of breath. The HCMSQ SoB domain score ranges from 0 to 18, with lower scores representing less shortness of breath.

Exploratory efficacy endpoints:

- Proportion of subjects achieving a post-exercise LVOT peak gradient < 50 mmHg at Week 30
- Proportion of subjects achieving a post-exercise LVOT peak gradient < 30 mmHg at Week 30
- Proportion of subjects with any decrease in post-exercise LVOT peak gradient from baseline to Week 30
- Proportion of subjects achieving complete response (NYHA Class I and LVOT peak gradient < 30 mmHg for all 3 types of gradients: resting, Valsalva, and post-exercise) at Week 30
- Changes from baseline to Week 30 in cardiopulmonary function as assessed by CPET
- Changes from baseline to Week 30 in echocardiographic indices of cardiac structure (e.g., LV ventricular wall thickness, atrial and ventricular chamber size and volumes), as well as systolic and diastolic function
- NT-proBNP concentration over time
- Perceived health status/health-related QoL as assessed by the EuroQol 5-dimensions 5-levels questionnaire (EQ-5D-5L) scores
- Work productivity and activity impairment as assessed by the Work Productivity and Activity Impairment Questionnaire-Specific Health Problem (WPAI-SHP) scores
- Perceived severity of symptoms as assessed by Patient Global Impression of Change (PGIC) and Patient Global Impression of Severity (PGIS) scores
- Health-related QoL as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score and overall summary score
- Severity of HCM symptoms as assessed by the Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ) total score and the 2 domain sub scores of tiredness and cardiovascular (CV) symptoms
- Proportion of subjects who had clinically meaningful changes in KCCQ-23 scores
- Proportion of subjects who had clinically meaningful changes in HCMSQ scores
- Changes from baseline to Week 30 in daily step count and other accelerometer parameters
- Change from baseline to Week 30 in high-sensitivity cardiac troponin-I

5.2.2. Eligibility Criteria

Key Inclusion Criteria:

- 18 years old at Screening
- Weight greater than 45 kg at Screening
- Acoustic windows to enable accurate transthoracic echocardiograms (TTEs)
- Diagnosed with oHCM consistent with current American College of Cardiology Foundation (AACF)/American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines, satisfying both of the following criteria (criteria to be documented by the echocardiography core laboratory):
    - Has unexplained LV hypertrophy with nondilated ventricular chambers in the absence of other cardiac causes (e.g., 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
    - Has LVOT peak gradient ≥50 mmHg during Screening as assessed by echocardiography at rest, after Valsalva maneuver, or post-exercise (confirmed by echocardiography core laboratory interpretation)
- LVEF ≥55% by echocardiography core laboratory read of Screening TTE at rest
- LVOT gradient with Valsalva maneuver at Screening TTE of ≥30 mmHg, determined by echocardiography core laboratory
- NYHA Functional Class II or III symptoms at Screening
- Oxygen saturation at rest ≥90% at Screening
- Able to perform an upright CPET and has a respiratory exchange ratio (RER) ≥1.0 at Screening per central reading; if the respiratory exchange ratio is between 0.91 and 1.0, the participant may be enrolled only if it is determined by the central CPET laboratory that peak exercise has been achieved in the subject (the only permitted reasons for subpeak performance are [1] a decrease in systolic blood pressure (SBP) or [2] severe angina)

Key Exclusion Criteria:

- Previously participated in a clinical study with mavacamten
- Known infiltrative or storage disorder causing cardiac hypertrophy that mimics oHCM, such as Fabry disease, amyloidosis, or Noonan syndrome with LV hypertrophy
- Syncope within 6 months prior to screening or history of sustained ventricular tachyarrhythmia with exercise within 6 months prior to Screening
- 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 is allowed)
- Paroxysmal, intermittent AF with AF present per the investigator's evaluation of the participant's ECG at the time of Screening
- Persistent or permanent AF not on anticoagulation for at least 4 weeks prior to Screening and/or not adequately rate controlled within 6 months of Screening
- 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 β-blockers and verapamil or a combination of β-blockers and diltiazem
- For individuals on β-blockers, verapamil, or diltiazem, any dose adjustment of that medication <14 days prior to Screening or an anticipated change in treatment regimen using these medications during the study
- Successfully treated with invasive septal reduction (surgical myectomy or percutaneous alcohol septal ablation) within 6 months prior to Screening or plans to have either of these treatments during the study
- ICD placement or pulse generator change within 2 months prior to Screening or planned new ICD placement during the study
- Has QT interval with Fridericia correction (QTcF) >500 ms at Screening or any other ECG abnormality considered by the investigator to pose a risk to participant safety (e.g., second-degree atrioventricular block type II)

- Documented obstructive coronary artery disease (>70% stenosis in one or more epicardial coronary arteries) or history of myocardial infarction
- Known moderate or severe (as per investigator's judgment) aortic valve stenosis at Screening
- Pulmonary disease that limits exercise capacity or systemic arterial oxygen saturation
- Body size–adjusted estimated glomerular filtration rate less than 30 mL/min/1.73 m^2
- Positive serologic test at Screening for infection with human immunodeficiency virus, hepatitis C virus, or hepatitis B virus
- Has taken within 14 days prior to Screening, a prohibited medication, such as a cytochrome P450 (CYP) 2C19 inhibitor (e.g., omeprazole or esomeprazole), a strong CYP 3A4 inhibitor, or St. John's Wort
- Prior treatment with cardiotoxic agents such as doxorubicin or similar

5.2.3. Selection of Doses

Mavacamten dosing in EXPLORER-HCM utilized a dosing algorithm based on measurement of mavacamten plasma concentrations and PD markers measured by echocardiography (i.e., LVOT gradient and LVEF) (see Section 5.1). EXPLORER-HCM was designed to target a mavacamten plasma trough concentration < 700 ng/mL and use PD responses to guide dose adjustments in individual subjects. The criteria for mavacamten dose adjustment (dose increase, dose decrease, no change) during 30 weeks of daily treatment in EXPLORER-HCM are summarized in Appendix III.10 (Table 46 and Table 47**).** All dose adjustments were blinded and occurred via an interactive response system (IXRS).

5.2.4. Pre-Specified Criteria for Study Drug Discontinuation

Pre-specified dosing discontinuation criteria in EXPLORER-HCM are summarized below:

Permanent Discontinuation

Per protocol, the following reasons would lead to permanent treatment discontinuation:

- Pregnancy
- LVEF ≤ 30%
- New or worsening HF associated with systolic dysfunction
- If all the criteria are met for possible drug-induced liver injury (DILI)

Temporary Discontinuation

Per protocol, at any time during the treatment period, dosing could be temporarily discontinued in the case of exaggerated systolic dysfunction, a higher-than-expected plasma concentration of mavacamten, or excessive QTcF prolongation listed below:

- Resting LVEF <50%
- Plasma drug concentration ≥1000 ng/mL
- If QRS is narrow (<120 ms), QTcF prolongation is defined as a 15% increase from baseline QTcF or QTcF ≥520 ms
- If QRS is wide (≥120 ms), QTcF prolongation is defined as a 15% increase from baseline QTcF or QTcF ≥550 ms

If LVEF, plasma drug concentration and/or QTcF improved and did not meet the above hold criteria at the follow-up visit (2 to 4 weeks after temporary discontinuation), then the study drug would be restarted at a lower dose for the remainder of the study. If LVEF, plasma drug concentration and/or QTcF persisted out of range at the follow-up visit, then study drug would be permanently discontinued.

5.2.5. Statistical Analysis Plan

Sample Size

Approximately 220 participants were planned to be randomized in 1:1 ratio to receive mavacamten or placebo. Randomization was stratified for NYHA class (II or III), current treatment with β-blocker (yes/no), type of ergometer (treadmill or exercise bicycle), and consent for the CMR substudy (yes or no). The proposed sample size was determined to provide 96% power to detect a treatment effect of 25% in achieving the primary efficacy endpoint at the 2-sided 5% statistical significance level, assuming a 50% responder rate in the mavacamten group and 25% responder rate in the placebo group, based on the PIONEER-HCM trial.

Statistical Analysis

1. Primary efficacy endpoint: The Cochran-Mantel-Haenszel (CMH) test stratified by the randomization strata was used to test the statistical significance of the association between clinical response status (responder vs. non-responder) and treatment group (mavacamten vs. placebo). Unstratified analysis using a Chi-square test was performed as a sensitivity analysis.

2. Secondary efficacy endpoints:

- Endpoints of LVOT gradient and pVO2 were analyzed using analysis of covariance (ANCOVA) that includes treatment group, baseline value of the corresponding endpoint of interest, and the 3 stratification factors (beta blocker use, NYHA class, ergometer type) as fixed effects.
- Endpoints of KCCQ-23 CSS and HCMSQ SoB were analyzed using a mixed model for repeated measurements (MMRM) that includes treatment group, baseline value of the corresponding endpoint of interest, time point (as a categorical variable), the interaction between treatment and time point, and the 3 stratification factors (beta blocker use, NYHA class, ergometer type) as fixed effects. Subject were treated as a random effect, and compound symmetric variance covariance component was used.
  Endpoint of at least 1 class of improvement in NYHA was analyzed using the CMH test.

Multiplicity Control

A sequential testing procedure was used for multiplicity control. Contingent upon significance in the primary endpoint, each of the secondary efficacy endpoints was tested sequentially in the following order, at a 2-sided alpha level of 0.05:

- Change from baseline to Week 30 in post-exercise LVOT peak gradient

- Change from baseline to Week 30 in pVO2 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 patient-reported health-related QoL as assessed by the KCCQ-23 CSS
- Change from baseline to Week 30 in patient-reported severity of HCM symptoms as assessed by the HCMSQ SoB sub score

Missing Data

1. For a mixed model repeated-measure analyses, missing data were handled implicitly by the model.
2. For the responder analysis of primary and secondary endpoints, participants whose response status at Week 30 was missing were classified as non-responders.
3. Missing Data for KCCQ-23 CSS and HCMSQ SoB: The impact of the missing data was assessed in 2 ways:
   - Analyses to determine whether there was any evidence suggesting certain patterns of missing data (i.e., missing-not-at-random)
   - Sensitivity analyses to assess whether the analyses were robust when imputing the missing data with favorable outcomes for the placebo group and unfavorable outcomes for the mavacamten group.

5.3. Results of Analyses of Clinical Trials/Studies Intended to Demonstrate Benefit to Patients

5.3.1. Disposition of Subjects

A total of 429 subjects were screened, and 183 (42.7%) subjects met at least 1 screen failure criterion. The most common reasons for screen failure were not meeting the oHCM diagnosis criteria consistent with current guidelines (10%) and other echocardiogram-related inclusion criteria (e.g., adequate acoustic window, LVOT gradient, LVEF) (19%). Five of the 183 subjects were randomized into the study prior to learning that they had met screen failure criteria. A total of 251 subjects were randomized, per the table below:

Table 7 Patient Screening and Randomization, EXPLORER-HCM

Disposition	N
No. of patients screened	429
No. of patients not randomized	178
No. of patients failed in screening	183
No. of patients randomized	251

Source: Table 6 in CSR, confirmed by statistical reviewer

Of the 251 subjects that were randomized, 123 subjects were assigned to the mavacamten group and 128 subjects to the placebo group. Overall, 97.2% subjects completed 30 weeks of treatment

and 70.9% completed the study. About 27% of subjects (67 of 251) were unable to attend on-site study visits at Week 38 (End of study) due to the COVID-19 pandemic and completed that visit via a telephone conversation with site personnel, per the disposition table below:

Table 8 MYK-461-005: Subject Disposition, EXPLORER-HCM, 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)
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)
Completed Study	88 (71.5)	90 (70.3)	178 (70.9)
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)

a: Subjects may have discontinued treatment and remained on study.
b: In the context of COVID-19, 67 subjects 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%).
Source: Table 8 in CSR, confirmed by statistical reviewer

5.3.2. Subject Demographics and Baseline Characteristic

Demographics and baseline characteristics were generally similar for the mavacamten and placebo groups. The mean age of subjects was 59 years, and the majority of subjects were in the age group of 50-64 years (45.4%). More subjects were male (59.4%), white (91.2%), and non-Hispanic or Latino (92.8). A slightly higher proportion of subjects was recruited from outside the US.

Body Mass Index (BMI), body surface area (BSA), heart rate and blood pressure measurements were similar in the two groups. More subjects were normal CYP2C19 metabolizers (36.7%), NYHA class II (72.9%), and using beta-blocker therapy (75.3%) at baseline. Baseline NT-proBNP was higher in the mavacamten treated subjects compared with the subjects in the placebo, per the demographics table below (FDA Biometrics):

Table 9 Subject Demographics and Baseline Characteristics, EXPLORER-HCM, ITT Population

Demographics and Baseline Characteristics	**Mavacamten (N = 123)**	**Placebo (N = 128)**	**Overall (N = 251)**
Age (Years)			
Mean (SD)	58.5 (12.2)	58.5 (11.8)	58.5 (11.9)
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)
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 (4.9)	29.2 (5.6)	29.4 (5.3)
Range	20.8, 51.9	15.9, 50.1	15.9, 51.9
BSA (m^2)			
Mean (SD)	1.96 (0.2)	1.97 (0.2)	1.97 (0.2)
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)
Mean (SD) Blood Pressure (mmHg)			
Systolic	128.4 (16.2)	128.4 (14.6)	128.4 (15.4)
Diastolic	75.5 (10.8)	76.1 (9.9)	75.8 (10.3)

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)
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, n (%)			
II	88 (71.5)	95 (74.2)	183 (72.9)
III	35 (28.5)	33 (25.8)	68 (27.1)
Background HCM Therapy, n (%)			
Beta-Blocker	94 (76.4)	95 (74.2)	189 (75.3)
Calcium Channel Blocker	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)	690 (130.8)
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

Source: Table 10 in CSR, confirmed by statistical reviewer

5.3.3. Efficacy Results

5.3.3.1. Primary efficacy endpoint:

A greater proportion of subjects in the mavacamten group achieved the primary efficacy endpoint compared to the placebo group (36.6% vs 17.2%, respectively). The difference in proportion of responders between mavacamten and placebo groups was statistically significant per the table below:

Table 10 Primary Efficacy Analysis: Composite Functional Endpoint at Week 30, ITT Population

	Achieved Composite Functional Endpoint n (%)		Difference in Proportion of Subjects who Achieved the Composite Function Endpoint (95% CI)	Odds Ratio (95% CI)	P-value
	Mavacamten (N = 123)	**Placebo (N = 128)**			
Stratified Analysis[a]	45 (36.6)	22 (17.2)	19.4 (8.7, 30.1)	2.74 (1.51, 5.45)	0.0005
Unstratified Analysis[b]				2.78 (1.54, 5.00)	0.0005

a: The analysis was based on Cochran-Mantel-Haenszel method stratified on NYHA class, beta-blocker use, and exercise type (based on IXRS). P-value and 95% CI were derived using the exact method.
b: Unstratified analysis is performed as a sensitivity analysis. P-value and 95% CI is derived from Pearson's Chi-square test.
(Source: Table 15 in CSR, confirmed by statistical reviewer)

Of note, the extent of missing data for the primary efficacy endpoint was low: 2.4% for pVO_2 and 1.6% for NYHA class. Data were imputed as follows to assess the clinical response status at Week 30:

- If Week 30 pVO_2 was missing, the participant was considered a non-responder.
- If pVO_2 was available but NYHA class was missing at Week 30, the NYHA class at Week 30 was imputed with the NYHA class at Week 26, if available.
- If the response status at Week 30 was missing, the patient was classified as a non-responder.

Based on the low amount of missing data and the conservative assumptions regarding missing data, there are no concerns with the robustness of the primary efficacy endpoint results.

Additional analyses were performed for the components of primary efficacy endpoint. Similarly, a greater proportion of subjects in the mavacamten group achieved the components of the primary efficacy endpoint compared to the placebo group (Table 11).

Table 11 Additional Primary Efficacy Analysis: Composite Functional Endpoint at Week 30, EXPLORER-HCM, ITT Population

		Achieved Composite Functional Endpoint n (%)		Difference in Proportion of Subjects who Achieved the Composite Function Endpoint (95% CI)	Odds Ratio (95% CI)	P-value
		Mavacamten (N = 123)	Placebo (N = 128)			
$PVO_2 \geq 1.5$ mL/kg/min and a reduction ≥ 1 NYHA class	Stratified Analysis	41 (33.3)	18 (14.1)	19.3 (9.0, 29.5)	2.92 (1.58, 6.21)	0.0006
	Unstratified Analysis				3.06 (1.58, 6.06)	0.0003
$PVO_2 \geq 3.0$ mL/kg/min with no worsening in NYHA class	Stratified Analysis	29 (23.6)	14 (10.9)	12.6 (2.4, 22.3)	2.49 (1.19, 5.38)	0.013
	Unstratified Analysis				2.51 (1.20, 5.44)	0.008

Source: Reviewer's Analysis

5.3.3.2. Secondary efficacy endpoints:

- Continuous secondary efficacy endpoints of LVOT peak gradient, pVO_2, KCCQ-23 CSS and HCMSQ SoB: The results showed that baseline values were similar for the mavacamten and placebo groups for each of the endpoints. Subject treated with mavacamten showed a statistically significant improvement compared to subjects in the placebo group for all the endpoints, per the table below.

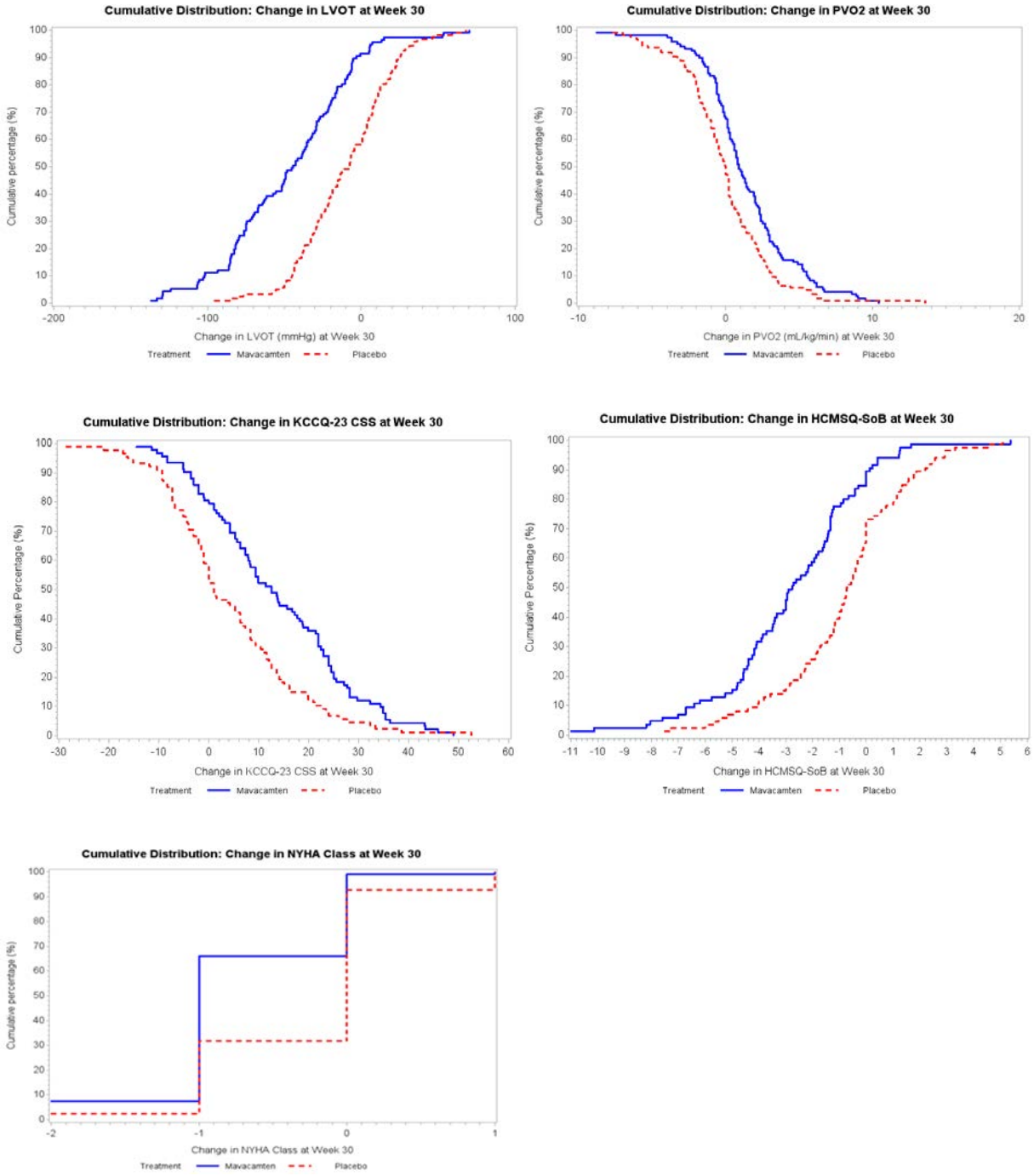
Table 12 Continuous Secondary Efficacy Endpoint Analyses, EXPLORER-HCM, ITT Population

Endpoint	Time Point		Treatment		LS Mean Difference in Change from Baseline (95% CI)	P-value
			Mavacamten (N = 123)	**Placebo (N = 128)**		
Change from Baseline to Week 30 in Post-exercise LVOT Peak Gradient (mmHg)	Baseline	n	122	127	-35 (-43.2, -28.1)	< 0.0001[a]
		Mean (SD)	86 (34.3)	84 (35.7)		
	Week 30	n	118	123		
		Mean (SD)	38 (32.1)	73 (34.9)		
Change from Baseline to Week 30 in pVO_2 (mL/kg/min)	Baseline	n	123	128	1.4 (0.6, 2.1)	0.0006[a]
		Mean (SD)	18.9 (4.9)	19.9 (4.9)		
	Week 30	n	120	125		
		Mean (SD)	20.4 (5.4)	19.9 (5.4)		
Change from Baseline to Week 30 in KCCQ-23 CSS	Baseline	n	99	97	9.1 (5.5, 12.7)	< 0.0001[b]
		Mean (SD)	71.1 (16.3)	70.6 (19.1)		
	Week 30	n	108	113		
		Mean (SD)	82.0 (16.5)	73.0 (20.3)		
Change from Baseline to Week 30 in HCMSQ SoB Domain Score	Baseline	n	108	109	-1.8 (-2.4, -1.2)	< 0.0001[b]
		Mean (SD)	4.9 (2.5)	4.5 (3.2)		
	Week 30	n	92	97		
		Mean (SD)	2.0 (2.6)	3.7 (3.0)		

α: The LS mean difference estimate, its 95% CI, and p-values are from the ANCOVA which controls for treatment group, baseline value of the corresponding endpoint of interest, and the 3 stratification factors (beta-blocker use, NYHA class, ergometer type based on IXRS).
b: The LS mean difference estimate, its 95% CI, and p-values are from a mixed model for repeated measurements (MMRM) which controls for treatment group, baseline value of the corresponding endpoint of interest, time point (as a categorical variable), the interaction between treatment and time point, and the 3 stratification factors (beta blocker use, NYHA class, ergometer type).
Source: Table 16 in CSR, confirmed by statistical reviewer

The cumulative distributions of change from baseline at Week 30 for LVOT, pVO_2, NYHA class, KCCQ-23 CSS and HCMSQ SoB were compared between mavacamten and placebo groups. There is a clear separation in cumulative distribution functions (CDFs) between treatment groups. At any given values of LVOT, pVO_2, NYHA class, KCCQ-23 CSS score and HSCMSQ SoB score, a greater proportion of subjects in the mavacamten group achieved improvement compared with the subjects in the placebo group, per the figure below:

Figure 1 Cumulative Distribution of Secondary Endpoints, EXPLORER-HCM, ITT Population



Source: Reviewer's analysis

- Categorical secondary efficacy endpoint of improvement ≥ 1 NYHA class: The proportion of subjects with improvement ≥ 1 NYHA class in the mavacamten group was significantly larger than that in the placebo group (65.0% vs 31.3%, for mavacamten and placebo, respectively; p<0.0001, per the table below). Among the subjects who had

improvement in NYHA class, most showed an improvement of 1 NYHA class (89% and 93% for the mavacamten and placebo groups, respectively), and very few subjects showed an improvement of 2 NYHA class (11% and 7% for the mavacamten and placebo groups, respectively).

Table 13 Proportion of Subjects with Improvement ≥ 1 NYHA Class from Baseline to Week 30, EXPLORER-HCM, ITT Population

	Improved by ≥ 1 NYHA Class from Baseline to Week 30[c] n (%)		Difference in Proportion of Subjects Improved by ≥ 1 NYHA Class (95% CI)	Odds Ratio (95% CI)	P-value
	Mavacamten (N = 123)	**Placebo (N = 128)**			
Stratified Analysis[a]	80 (65.0)	40 (31.3)	33.8 (22.2, 45.4)	4.3 (2.5, 8.0)	< 0.0001
Unstratified Analysis[b]				4.1 (2.4, 6.9)	< 0.0001

a: The analysis was based on Cochran-Mantel-Haenszel method stratified on NYHA class, beta-blocker use, and exercise type (based on IXRS). P-value and 95% CI were derived using the exact method.
b: Unstratified analysis is performed as sensitivity analysis. P-value and 95% CI is derived from Pearson's Chi-square t est.
c: Missing NYHA class at Week 30 was imputed using available NYHA at Week 26. After imputation, subjects whose response status at Week 30 was still missing were classified as non-responders.
Source: Table 17 in CSR, confirmed by statistical reviewer

Reviewer's Comment: While all secondary endpoints in EXPLORER-HCM were statistically significant, whether the improvements demonstrated in these endpoints were clinically meaningful are review issues and briefly discussed below:

LVOT gradient change: Mavacamten associated decreases in LVOT gradient are the expected PD effect. The magnitude of the observed changes was on top of beta-blocker use in 75% of subjects in EXPLORER-HCM and comparable to what was observed with the treatment of beta-blocker alone in the literature (4). An LVOT peak gradient ≥ 30 mmHg is the criterion that defines obstruction in the HCM population. Among patients with postexercise LVOT peak gradient ≥ 30 mmHg at baseline, 64 of 113 subjects (57%) in the mavacamten group compared to 8 of 114 subjects (7%) in the placebo group achieved LVOT peak gradient < 30 mmHg at Week 30. The observed changes in LVOT gradient are expected to be translated into some degree of clinical benefits on functional improvements and symptom relief, which was demonstrated by the results of other clinical endpoints in EXPLORER-HCM.

pVO_2: There were some uncertainties regarding clinical significance of the small change in pVO_2 (i.e., Δ pVO_2 of 1.4 mL/kg/min). However, the totality of data suggests that this modest increase in pVO_2 could be related to meaningful clinical outcomes. See section 5.4.2 for further discussion on pVO_2.

KCCQ-23 CSS and HCMSQ-SoB: The COA team was consulted to assess the adequateness of using these two PROs in patients with oHCM and the proposed labeling claim (COA review dated 30 September 2021). In brief, COA concluded that both KCCQ-23 CSS and HCMSQ-SoB are fit-for-purpose to support its context of use in patients with oHCM and the evidence provided

by the Applicant generally supports the proposed labeling claims. See section 5.3.3.6 for further discussion on clinical meaningfulness of these two PROs.

NYHA Functional Class: The Division considers that a change in NYHA Class of 1 or more represents a clinically meaningful improvement. Thus, mavacamten treatment was associated with a statistically significant and clinical meaningful improvement in NYHA functional class.

5.3.3.3. Missing data in secondary endpoints

- pVO_2 and Post-exercise LOVT peak gradient:
  Missingness was low for pVO_2 (2.4%) and LVOT gradient (4.8%). The reviewer performed sensitivity analyses to assess the impact of missing data and verify the robustness of the analyses of pVO_2 and LVOT gradient using the completers. The subjects who had missing pVO_2 or LVOT gradient values at baseline and/or week 30 were assigned a zero value for the change from baseline at week 30.

  Similar results were shown in sensitivity analyses. Subjects treated with mavacamten had a greater improvement on pVO_2 (difference of 1.3 [95% CI: 0.6, 2.1] and LVOT gradient (difference of -34 [95% CI: -42, -27]) compared with subjects in the placebo group.

- Patient Report Data of KCCQ-23 CSS and HCMSQ SoB

  There were substantial missing data for KCCQ-23 CSS and HCMSQ SoB. Approximately, 30% of patients had missing data either at baseline (22% and 14% for KCCQ-23 CSS and HCMSQ SoB, respectively) or week 30 (12% and 25% for KCCQ-23 CSS and HCMSQ SoB, respectively). The impact of missing data was assessed using the following analyses:

  1) Assess mechanism of missing data by:
     - Comparing the missingness between mavacamten and placebo groups. The missingness appeared similar in both treatment groups: 31/123 (25%) subjects in the mavacamten group versus 40/128 (31%) in the placebo group for KCCQ-23 CSS scores; and 38/123 (31%) in the mavacamten group versus 42/128 (33%) in the placebo group for HMCSQ SoB scores.

     - Comparing the distribution of the baseline demographic and disease characteristics between mavacamten and placebo groups. The distributions of most selected baseline demographics and disease characteristics were similar between the missing group and the non-missing group within each treatment group. Some imbalances were noted in a few baseline demographics and disease characteristics between the missing group and the non-missing group. It appears that more KCCQ CSS missing data were observed in females and patients with NYHA class II; and more HCMSQ missing data were observed in the US patients and patients with NYHA class III in the mavacamten group. However, there was no systematic pattern of missingness observed, per the table below:

Table 14 Summary of Baseline Demographics and Disease Characteristics by Subjects with Missing versus Non-missing KCCQ-23 CSS, EXPLORER-HCM, ITT Population

Characteristic	Mavacamten (N = 123)		Placebo (N = 128)	
	Nonmissing Group (n=92)	Missing Group (n=31)	Nonmissing Group (n=88)	Missing Group (n=40)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	57.8 (12.7)	60.6 (10.3)	58.5 (11.5)	58.4 (12.5)
Female, n (%)	40 (43.5)	17 (54.8)	29 (33.0)	16 (40.0)
White race, n (%)	86 (93.5)	29 (93.5)	80 (90.9)	34 (85.0)
US Region, n (%)	42 (45.7)	11 (35.5)	36 (40.9)	19 (47.5)
BMI (kg/m^2)	30.0 (5.0)	28.7 (4.2)	29.5 (5.7)	28.6 (5.4)
Heart rate (beat/min)	62.4 (10.7)	64.4 (7.7)	62.2 (10.2)	62.7 (11.4)
Systolic blood pressure (mmHg)	129.6 (15.7)	124.7 (17.2)	128.2 (14.7)	128.8 (14.4)
Diastolic blood pressure (mmHg)	75.5 (10.7)	75.4 (11.2)	75.6 (9.8)	77.2 (10.0)
NYHA Class, n(%)				
II	64 (69.6)	24 (77.4)	65 (73.9)	30 (75.0)
III	28 (30.4)	7 (22.6)	23 (26.1)	10 (25.0)
Beta-blocker use, n(%)	73 (79.3)	21 (67.7)	62 (70.5)	33 (82.5)
NT-proBNP (ng/L), median (Q1, Q3)	804.5 (366.0, 1755.0)	669 (403.0, 1764.0)	643 (389.0, 1132.0)	751 (227.0, 1602.0)
Resting LVEF (%)	74.0 (5.9)	74.5 (5.8)	74.5 (5.6)	73.5 (6.5)
Resting LVOT gradient (mmHg)	54.0 (29.5)	44.9 (28.7)	50.3 (30.7)	52.7 (34.9)
Valsalva LVOT gradient(mmHg)	75.5 (31.0)	63.0 (32.4)	73.6 (31.7)	74.7 (33.1)
Septal wall thickness (mm)	16.7 (2.5)	17.1 (2.7)	17.1 (2.7)	15.8 (2.9)
Posterior wall thickness (mm)	11.8 (2.5)	11.4 (2.1)	11.4 (2.3)	11.4 (2.6)
Max LV wall thickness (mm)	19.9 (3.7)	19.7 (3.8)	20.0 (3.2)	18.9 (3.4)
LAVI (mL/m^2)	41.4 (12.0)	37.2 (12.0)	41.3 (13.8)	38.8 (13.9)

BMI = body mass index; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; NT-proBNP = N-terminal pro b-type natriuretic peptide; NYHA = New York Heart Association

Source: Table 1 in DOCUMENTATION OF STATISTICAL METHODS

Table 15 Summary of Baseline Demographics and Disease Characteristics by Subjects with Missing versus Non-missing HCMSQ-SoB Domain Scores, EXPLORER-HCM, ITT Population

Characteristic	Mavacamten (N=123)		Placebo (N=128)	
	Nonmissing Group (n=85)	Missing Group (n=38)	Nonmissing Group (n=86)	Missing Group (n=42)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	58.3 (11.9)	58.9 (13.0)	59.7 (11.8)	55.9 (11.4)
Female, n (%)	41 (48.2)	16 (42.1)	30 (34.9)	15 (35.7)
White race, n (%)	83 (97.6)	32 (84.2)	79 (91.9)	35 (83.3)
US Region, n (%)	34 (40.0)	19 (50.0)	32 (37.2)	23 (54.8)
BMI (kg/m^2)	30.0 (5.1)	28.8 (4.2)	29.0 (5.2)	29.7 (6.4)
Heart rate (beat/min)	62.6 (10.3)	63.6 (9.5)	61.6 (10.8)	63.9 (10.0)
Systolic blood pressure (mmHg)	130.7 (16.7)	123.2 (13.7)	129.8 (15.6)	125.6 (11.9)
Diastolic blood pressure (mmHg)	76.0 (10.3)	74.2 (11.8)	76.5 (9.5)	75.3 (10.7)
NYHA Class, n (%)				
II	64 (75.3)	24 (63.2)	63 (73.3)	32 (76.2)
III	21 (24.7)	14 (36.8)	23 (26.7)	10 (23.8)
Beta-blocker Use, n (%)	67 (78.8)	27 (71.1)	64 (74.4)	31 (73.8)
NT-proBNP (ng/L), median (Q1, Q3)	793 (380.0, 1781.0)	679 (322.0, 1343.0)	791 (442.0, 1431.0)	480 (227.0, 1052.0)
Resting LVEF (%)	73.7 (5.5)	75.1 (6.6)	73.9 (6.2)	74.7 (5.4)
Resting LVOT gradient (mmHg)	54.5 (30.3)	45.4 (26.7)	50.5 (31.4)	52.2 (33.3)
Valsalva LVOT gradient(mmHg)	75.6 (32.5)	65.1 (29.0)	73.1 (31.7)	75.7 (32.9)
Septal wall thickness (mm)	16.7 (2.6)	17.0 (2.6)	16.8 (2.9)	16.5 (2.7)
Posterior wall thickness (mm)	11.7 (2.4)	11.7 (2.4)	11.4 (2.4)	11.4 (2.4)
Max LV wall thickness (mm)	19.8 (3.8)	19.9 (3.6)	19.8 (3.3)	19.3 (3.3)
LAVI (mL/m^2)	40.8 (12.2)	39.1 (12.1)	40.8 (13.4)	40.1 (14.8)

BMI = body mass index; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; NT-proBNP = N-terminal pro b-type natriuretic peptide; NYHA = New York Heart Association

Source: Table 2 in DOCUMENTATION OF STATISTICAL METHODS

2) Sensitivity analyses to verify the robustness of secondary endpoint analyses
   - Method: Sensitivity analyses were conducted to assess the impact of deviation from the assumption of missing at random. A conservative approach (worse-case scenario) was applied for imputation in the sensitivity analyses with favorable outcomes for the placebo group and unfavorable outcomes for mavacamten group.
     - For the KCCQ-23 CSS, as a greater increase indicates a better response, the missing values in change from baseline to Week 30 were imputed with greater-than-average increases (third quartile [Q3] of the observed changes) in the placebo group and lower-than average increases (first quartile [Q1] of the observed changes) in the mavacamten group. In addition, 2 different imputation scenarios were considered for missing scores at baseline: (1) missing at random (i.e., use of median of each treatment group) and (2) missing not at random (i.e., use of Q3 of the observed changes for mavacamten and Q1 of the observed changes for placebo).
     - For the HCMSQ SoB, as a greater decrease indicates a better response, the missing values in the change from baseline to Week 30 were imputed with greater-than-average decreases (Q1 of the observed

changes) in the placebo group and lower-than-average decreases (Q3 of the observed changes) in the mavacamten group. In addition, 2 different imputation scenarios were considered for missing scores at baseline: (1) missing at random (i.e., use of median of each treatment group) and (2) missing not at random (i.e., use of Q1 of the observed changes for mavacamten and Q3 of the observed changes for placebo).

- A multiple imputation (MI) was performed using a Mixed-Effect Model Repeated Measure (MMRM) model to derive the estimates of treatment effect and the estimates of treatment effect are then combined based on Rubin's rule.

- Results: There was no tipping point found in the sensitivity analyses. The conclusion of treatment benefit of mavacamten remained unchanged. A greater improvement was shown in the mavacamten treated subjects compared to those receiving placebo. However, the treatment effect in the KCCQ CSS sensitivity analysis appears smaller (5.3; 95% CI: 1.7, 8.8) compared to that based on the primary analysis (9.1; 95% CI: 5.5, 12.7) when we assume that baseline is not missing at random, per the table below:

Table 16 Sensitivity Analysis of PRO scores (KCCQ-CSS and HCMSQ SoB Domain Score) Change from Baseline to Week 30, EXPLORER-HCM, ITT Population

	Imputed Mean Value for Missing data		Diff. Mavacamten vs Placebo in Change from Baseline to Week 30 (95% CI)	p-value
	Mavacamten	Placebo		
KCCQ-CSS				
Scenario 1: Baseline missing at random	Baseline: median (73) Change from baseline: Q1 (2.3)	Baseline: median (72) Change from baseline: Q3 (12.2)	4.9 (1.3, 8.4)	0.0072
Scenario 2: Baseline missing not at random	Baseline: Q3 (82) Change from baseline: Q1 (2.3)	Baseline: Q1 (58) Change from baseline: Q3 (12.2)	5.3 (1.7, 8.8)	0.0038
HCMSQ-SoB Domain Score				
Scenario 1: Baseline missing at random	Baseline: median (4.9) Change from baseline: Q3 (-1.29)	Baseline: median (4.6) Change from baseline: Q1 (-2.0)	-1.2 (-1.8, -0.6)	0.0002
Scenario 2: Baseline missing not at random	Baseline: Q1 (3.3) Change from baseline: Q3 (-1.29)	Baseline: Q3 (6.0) Change from baseline: Q1 (-2.0)	-1.2 (-1.8, -0.6)	<0.0001

HCMSQ SoB = Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness of Breath (domain score); KCCQ-23 CSS = Kansas City Cardiomyopathy Questionnaire 23-item version clinical summary score
Imputed values were random samples from normal distributions with means at the value defined for each scenario, and standard deviations equal to the observed standard deviations of the corresponding treatment group.

Source: Table 5 in Appendix 16.1.9, confirmed by statistical reviewer

3) We issued an IR (dated June 15, 2021) to request clarification as to why so much baseline data were missing. The applicant responded that missing baseline data of KCCQ-23 CSS and HCMSQ SoB were primarily due to operational challenges:
   - Subjects and/or site staff were in the learning stage to perform the electronic clinical outcome assessment (eCOA) device operation
   - Many subjects forgot to bring their eCOA device on the Day 1 visit for collecting baseline data or the site did not appropriately change the subject status on the eCOA device
   - Completing the HCMSQ SoB questionnaire daily was burdensome.

Reviewer's Comment: Based on the assessment of missing data, this reviewer concluded:

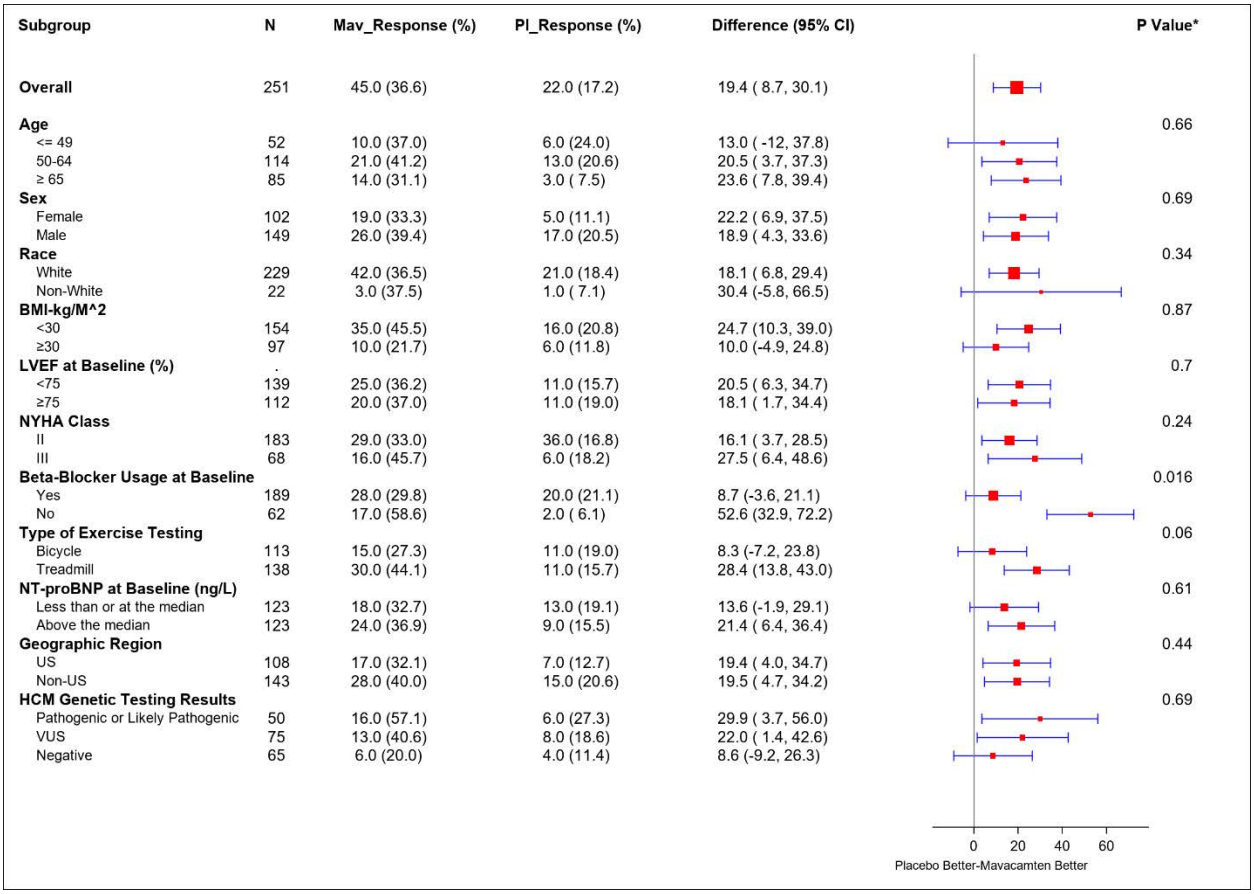
- *There were no certain patterns of missing data. The missingness of KCCQ-23 CSS and HCMSQ-SoB data appeared similar for the mavacamten and placebo treatment groups. The distributions of most selected baseline demographics and disease characteristics were similar between the missing group and the non-missing groups within each treatment group. Although some imbalances were noted in a few baseline demographics and disease characteristics between the missing group and the non-missing group, there was no systematic pattern of missingness observed.*
- *The conclusion of treatment benefit of mavacamten remained unchanged based on the sensitivity analysis with imputation using the worse-case scenario assumption. However, the estimated treatment effect was smaller.*
- *Missing data appear unrelated to treatment.*

See Section 5.4.1 for further discussion of the missing data.

5.3.3.4. Subgroup Analysis

Subgroup analyses of the primary endpoint were performed by stratification factors and pre-specified demographics and baseline characteristics. The benefit of mavacamten treatment was consistent across all subgroups, per the figure below (FDA Biostatistics). A nominally statistically significant interaction of treatment by beta-blocker use at baseline was found (p=0.016). The treatment effect of mavacamten was much larger in the patients who were not on beta-blocker therapy at baseline.

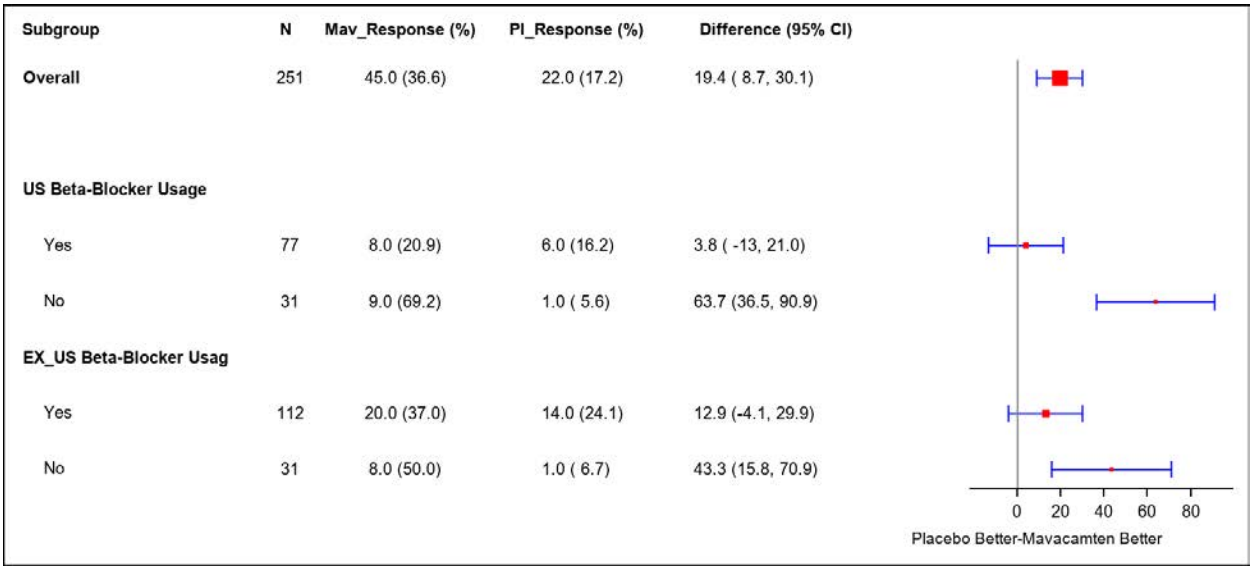
Figure 2 Subgroup Analysis of Primary Endpoint by Baseline Characteristics and Stratification Factors, EXPLORER-HCM, ITT Population



Source: Reviewer's analysis

The impact of beta-blocker usage was compared between regions (US vs. ex-US). It was consistent that a larger mavacamten effect was shown in subjects who were not on beta-blocker therapy at baseline in both regions. Subjects taking beta-blockers appeared to show little evidence of efficacy with the addition of mavacamten therapy, per the figure below. The results from the subgroup analysis should be interpreted with caution. The subgroup analysis may not have enough power to detect a treatment effect as no formal sample size calculation was performed for individual subgroups. See Section 5.4.3 for further discussion of these results.

Figure 3 Subgroup Analysis of Primary Endpoint by Beta-Blocker Usage at Baseline, EXPLORER-HCM, ITT Population



Source: Reviewer's analysis

5.3.3.5. Cardiac Biomarker Endpoints

Data of biomarkers [N-terminal pro b-type natriuretic peptide (NT-proBNP) and high sensitive cardiac troponin-I (hs-cTn-I)] were examined. At Week 30, the reduction of geometric mean ratio from baseline after mavacamten treatment was 80% greater than placebo for NT-proBNP and 41% greater than placebo for hs-cTn-I, per the tables below:

Table 17 Between-Group Comparisons of Changes from Baseline in NT-proBNP at Week 30, EXPLORER-HCM, ITT Population

Serum Concentration (ng/L)	Baseline Geometric Mean (CV%)		Week 30 Ratio to Baseline (Geometric Mean [%CV])				Mavacamten vs. Placebo Proportion of Week 30 Geometric Mean Ratio (95% CI) P-Value
	Mavacamten	Placebo	n	Mavacamten	n	Placebo	
NT-proBNP	777.4 (136.34)	615.7 (108.43)	116	0.20 (266.91)	121	1.02 (55.80)	0.20 (0.17, 0.24) $p < 0.0001$

%CV = percent coefficient of variation; NT-proBNP = N-terminal pro b-type natriuretic peptide
The proportion of the Week 30-to-baseline geometric mean ratio between the mavacamten and placebo groups, the corresponding 95% CI, and p-values are estimated from a mixed model for repeated measurement with data up to Week 30 fitted with log-transformed baseline NT-proBNP value, treatment group, time, interaction between treatment group and time, and the 3 stratification factors (beta-blocker use, NYHA class, and exercise type based on IXRS) as fixed effects, and subject as a random effect.

Source: Table 28 in CSR, confirmed by statistical reviewer

Table 18 Between-Group Comparisons of Changes from Baseline in NT-proBNP at Week 30, EXPLORER-HCM, ITT Population

Serum Concentration (ng/L)	Baseline Geometric Mean (CV%)		Week 30 Ratio to Baseline (Geometric Mean [%CV])				Mavacamten vs. Placebo Proportion of Week 30 Geometric Mean Ratio (95% CI) P-Value
	Mavacamten	Placebo	n	Mavacamten	n	Placebo	
hs-cTn-I	12.5 (207.75)	12.5 (372.80)	114	0.58 (49.17)	111	0.99 (143.34)	0.59 (0.50, 0.69) $p < 0.0001$

%CV = percent coefficient of variation; hs-cTn-I = high-sensitivity cardiac troponin-I
The proportion of the Week 30-to-baseline geometric mean ratio between the mavacamten and placebo groups, the corresponding 95% CI, and p-values are estimated from a mixed model for repeated measurement with data up to Week 30 fitted with log-transformed baseline NT-proBNP value, treatment group, time, interaction between treatment group and time, and the 3 stratification factors (beta-blocker use, NYHA class, and exercise type based on IXRS) as fixed effects, and subject as a random effect.

Source: Table 29 in CSR, confirmed by statistical reviewer

Reviewer's Comment: Although the clinical significance of these findings is unknown, the greater reduction of NT-proBNP in patients on mavacamten compared to placebo is likely related to the reduction in myocardial wall stress resulting from attenuation of the hypercontractile state described with mavacamten use. Hence, the changes of NT-proBNP are relevant PD effects associated with mavacamten treatment in the target population. Summary of NT-proBNP results will be included in the label, Section 12.

5.3.3.6. Meaningful Change for HCMSQ and KCCQ

FDA's Clinical Outcome Assessments (COA) team requested the Biometrics team to verify the Applicant's analyses of thresholds for meaningful change for HCMSQ-SoB and KCCQ-23 CSS.

1. Methods

   Anchor-based methods were primarily used to establish thresholds for meaningful change, supplemented with distribution-based methods, CDFs, and probability density function curves (PDFs) to provide supportive information. The Patient Global Impression of Change questionnaire (PGIC) at Week 30 and Patient Global Impression of Severity questionnaire (PGIS) change from Baseline to Week 30 were used as anchors. In this review, only the anchor-based analyses and CDFs results were verified.

2. Results

   - Anchor-based analysis: A clinically meaningful change threshold is the mean change scores in the "improved" PGIC responses (including very much improved, much improved, minimally improved), and the mean change scores in a sample of patients who improved at least 1 level on PGIS represent a second estimate of responder threshold. These thresholds were determined based on the pooled data from the two treatment arms. The results showed that the thresholds ranged from 13.5 (PGIC anchor) to 16.6 (PGIS anchor) for KCCQ-23 CSS and -2.5 (PGIC anchor) to -3.4 (PGIS anchor) for HCMSQ SoB, per the table below (FDA Biostatistics).

Table 19 Clinically Meaningful Threshold: Collapsed * Change from Baseline at Week 30, EXPLORER-HCM, ITT Population

Domain	Anchor-Based Approach	
	PGIC Improved Week 30 (n=127)	PGIS Improved Week 30 (n=81)
KCCQ-23 CSS	13.5	16.6
HCMSQ SoB	-2.5	-3.4

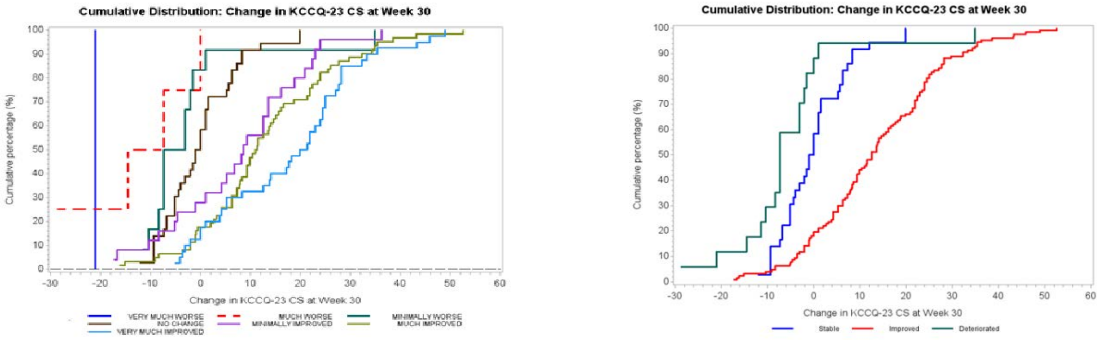
*Include categories of minimally improved, much improved and very much improved

Source: Reviewer Analysis

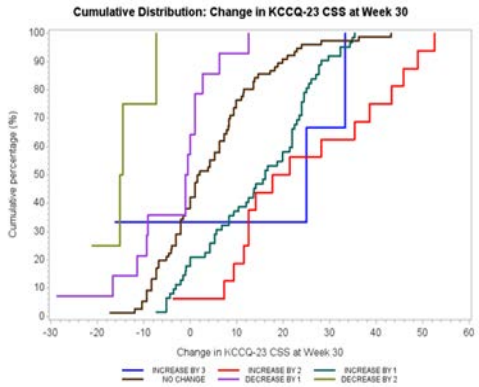
- eCDFs: eCDF plots were generated to supplement the anchor-based methods, using both un-collapsed (including VERY MUCH WORSE, MUCH WORSE, MINIMALLY WORSE, NO CHANGE, VERY MUCH IMPROVED, MUCH IMPROVED, MINIMALLY IMPROVED) and collapsed (including STABLE, IMPROVED, DETERIORATED) categories of improvement, stability, and worsening. For these analyses, data from the two treatment arms were pooled. There is a clear separation of KCCQ-23 CSS/HCMSQ SoB change scores by PGIC and PGIS anchor levels in the curves of collapsed categories (per the figure below). The median change on KCCQ-23 CSS was 12.5, -0.5 and -7.3 for patients who were improved, stable and deteriorated on PGIC, respectively; the median change on KCCQ-23 CSS was 16.7, 1.8 and -4.2 for patients who were improved, stable and deteriorated on PGIS, respectively. The median change on HCMSQ SoB was -2.2, -0.8 and 0.9 for patients who were improved, stable and deteriorated on PGIC, respectively; the median change on HCMSQ SoB was -2.9, -0.7 and 1.2 for patients who were improved, stable and deteriorated on PGIS, respectively.

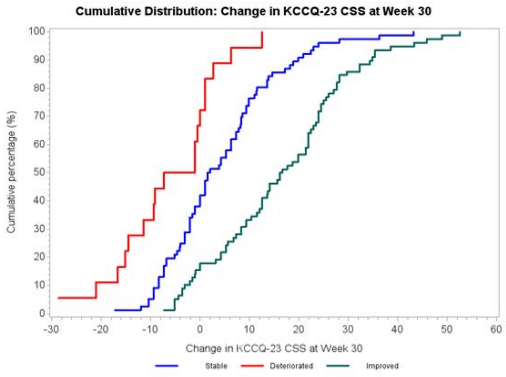
Figure 4 CDF Curves from Baseline to Week 30 using Un-collapsed and Collapsed Categories of PGIC and PGIS, EXPLORER-HCM, ITT Population

KCCQ-23 CSS PGIC

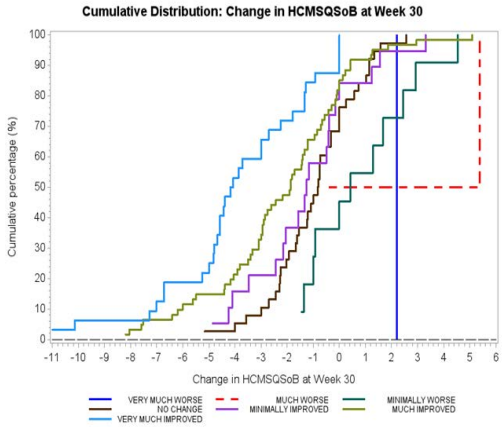


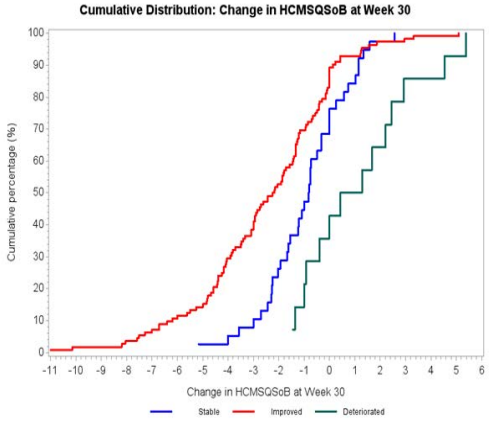
KCCQ-23 CSS PGIS



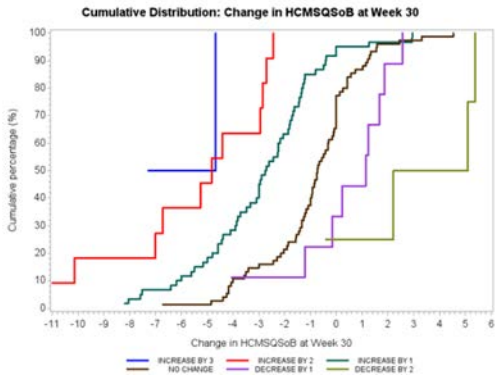


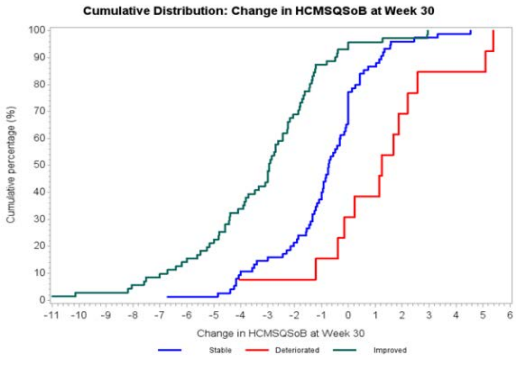
HCMSQ SoB PGIC





HCMSQ SoB PGIS





Source: Reviewer Analysis

The applicant proposed an increase from baseline of ≥10 points as the threshold for a within-subject clinically meaningful response in KCCQ-23 CSS. This threshold took into account the anchor-based analysis using the data from the EXPLORER-HCM study and results from the literature, with the latter reporting a KCCQ-23 CSS change of 5-10 points as a small improvement, a change of 10-20 points as a moderate improvement, and a change greater than 20 points as a large improvement (Spertus, 2005). For the HCMSQ SoB, the applicant proposed a decrease from baseline of ≥ 2.5 points as the threshold for a within-subject clinically meaningful response in the HCMSQ SoB domain score using the anchor-based analysis of the data from the EXPLORER-HCM study.

Reviewer's Comment: The thresholds derived from the PGIC and PGIS analyses were comparable. The CDF plots show fairly good separations among categories of response. The statistical reviewer verified the analyses and agreed that the proposed thresholds of clinically meaningful within patient change in KCCQ-23 CSS and HCMSQ-SoB were reasonable.

The COA reviewer pointed out that the PGIS and PGIC are not ideal anchor scales to interpret meaningful changes in HCMSQ-SoB and KCCQ-23 CSS scores given that they are not specific and use a different recall period. However, the anchor-based analysis using these two scales are still considered informative given the heterogeneity of HCM symptoms. Overall, the COA team concurred with the acceptance of the proposed clinical responder thresholds for KCCQ-23 CSS and HCMSQ-SoB based on the totality of evidence provided by the applicant (e.g., CDF, distribution-based analysis, anchor-based analysis and literature review).

*The percentage of subjects with clinically meaningful changes in the KCCQ-23 CSS and HCMSQ SoB domain score were evaluated as exploratory efficacy endpoints in EXPLORER-HCM. At Week 30, 54% of subjects in the mavacamten group achieved a clinically meaningful improvement of at least 10 points from baseline in KCCQ-23 CSS compared with 34% in the placebo group. Similarly, 50% of subjects in the mavacamten group achieved a clinically meaningful improvement of a decrease from baseline ≥ 2.5 points in HCMSQ SoB compared with 21% in the placebo group. In addition, the CDFs for the KCCQ-23 CSS and HCMSQ SoB show a clear separation between groups indicating a greater proportion of subjects in the mavacamten group achieved improvement compared with the subjects in the placebo group at any given values of these two PROs (*Figure 1*). The COA team confirmed that the data provided by the Applicant appear to support the proposed labeling claims for HCMSQ-SoB score and KCCQ-23 CSS.*

5.4. Review Issue Relevant to the Evaluation of Benefit

5.4.1. Missing Data of KCCQ-23 CSS and HCMSQ SOB

The efficacy of mavacamten was demonstrated in the improvement of exercise capacity and clinical symptoms in subjects with symptomatic oHCM. A greater proportion of subjects in the mavacamten group met the pre-specified components of the composite functional primary

endpoint (36.6% vs 17.2%, respectively; p=0.0005) compared to the placebo group. A greater improvement was also shown in the mavacamten group compared to the placebo group for all secondary endpoints, including reduction of LVOT gradients (-47 vs -10 mmHg; $p < 0.0001$), increase in pVO2 (1.4 vs -0.1 mL/kg/min; p=0.0006), improvement of ≥ 1 NYHA class (65% vs 31%; $p<0.0001$) and patient report health status measured by KCCQ-23 CSS (LS mean difference of 9.1; $p<0.0001$) and HCMSQ SoB domain score (LS mean difference of -1.8; $p<0.0001$).

One main issue for the application was missing data in the secondary endpoints of KCCQ-23 CSS and HCMSQ-SoB. There were approximately 30% of patients with missing data for KCCQ-23 CSS and HCMSQ SoB scores, either at baseline (22% and 14% for KCCQ-23 CSS and HCMSQ SoB, respectively) or week 30 (12% and 25% for KCCQ-23 CSS and HCMSQ SoB, respectively). Based on the assessments to evaluate the impact of missing data, we conclude that:

- Missing data appeared unrelated to treatment, but mainly due to operational errors from use of the eCOA device, especially missing data for the baseline measurement.
- No tipping point was found in the sensitivity analysis. The conclusion of treatment benefit of mavacamten remained unchanged, even using the worse-case scenario assumption in the analysis.
- For KCCQ 23 CSS, the estimated treatment effect based on the worst-case scenario was approximately half of the size of the effect based on the primary analysis (~5 and 9.1, respectively). Given that the missing data at baseline was due to operational errors, the sensitivity analysis likely provided a conservative estimate of the treatment effect. The real treatment effect is probably closer to the estimate from the primary analysis based on the ITT population.

5.4.2. Clinical Relevance of Small Absolute Increases in pVO_2

In EXPLORER-HCM, pVO_2 was part of a functional composite primary endpoint at prespecified thresholds combined with the change in NYHA functional class. Separately, pVO_2 was analyzed on its own as a secondary point. The results of both the primary composite endpoint and the secondary endpoint of pVO_2 were statistically significant (Table 10- Table 12). However, the mean difference in change from baseline of pVO_2 by 1.4 mL/kg/min is of questionable clinical significance.

In HCM, pVO_2 is associated with clinical prognosis and death (5,6). However, the relationship between a change in pVO_2 and clinical outcomes is not extensively studied or well defined. The HF-ACTION trial – a multicenter, randomized controlled trial assessed the incremental effect of aerobic exercise training over the standard of care, among 2331 patients with HF and reduced ejection fraction and NYHA functional class II -IV symptoms. The study findings revealed that every 6% increase in pVO_2 (~1 mL/kg/min) from baseline was associated with a 5% lower risk of all-cause mortality or all-cause hospitalization ($p<0.001$), a 4% lower risk of CV mortality or CV hospitalization, and a 7% lower risk of all-cause mortality (7). It is unclear whether the described association of pVO_2 on CV outcomes in patients with HFrEF with LVEF $\leq$ 35% can be extrapolated to the HCM population with preserved LV systolic function at baseline and patients who have a reasonably normal life expectancy overall. In HCM, an increase of 1 mL/kg/min in pVO_2 was also found to be predictive of reduced risk of death from HF and need for heart transplantation (6). However, this study was a retrospective observational study from a single center, and the generalizability of the study findings is uncertain. Overall, while there is some evidence indicating that a modest increase in pVO_2 is related to better clinical outcomes in HF and HCM patients, current evidence is insufficient to quantify the magnitude of clinical benefit associated with a small increase in pVO_2 in patients with HCM.

Despite the uncertainties, it should be noted that improvement with mavacamten treatment was observed across a broader range of CPET parameters including VE/VCO_2 slope, a strong predictor of CV outcomes in the HF population (Table 20) (8). The observed consistent results from CPET parameters support that mavacamten treatment increases exercise tolerance and capacity to some extent.

In addition, treatment with mavacamten in EXPLORER-HCM resulted in significant improvements compared with placebo across a range of diverse clinical endpoints including NYHA class, PROs (KCCQ-23 CSS and HCMS) and PD markers (LVOT gradient and cardiac biomarkers). The magnitude of benefit observed with mavacamten on some endpoints including KCCQ is not trivial. For example, using the $\geq$10-point change from baseline threshold in KCCQ-23 in EXPLORER-HCM, 54% of subjects in the mavacamten group achieved a clinically meaningful improvement from baseline in KCCQ-23 CSS compared with 34% in the placebo group. A sensitivity analysis demonstrated that the proportion of subjects who achieved a $\geq$ 15-point change from baseline in KCCQ-23 CSS was 52% for the mavacamten group and 22% for the placebo group. The internal consistency of these efficacy results cannot be overlooked. It is also important to note that some patients can have more sizeable improvements in pVO_2, as evidenced for example, by the proportion of patients with $\geq$3.0 mL/kg/min improvement without worsening in NYHA class. Approximately 24% of mavacamten-treated patients met this component of the primary efficacy endpoint compared to 11% of patients treated with placebo

(p=0.013). Overall, EXPLORER-HCM provides sufficient evidence demonstrating the beneficial effect of mavacamten compared to placebo in improving functional capacity and symptoms.

Table 20 Changes from Baseline to Week 30 for Exploratory CPET Endpoints, EXPLORER-HCM, ITT Population

	Mavacamten				Placebo				LS Mean Difference (95% CI)	p-value
	Baseline		Change at Week 30		Baseline		Change at Week 30			
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.

Source: Table 18 in EXPLORER CSR

5.4.3. Lack of Efficacy on a Background on Beta-Blocker Therapy

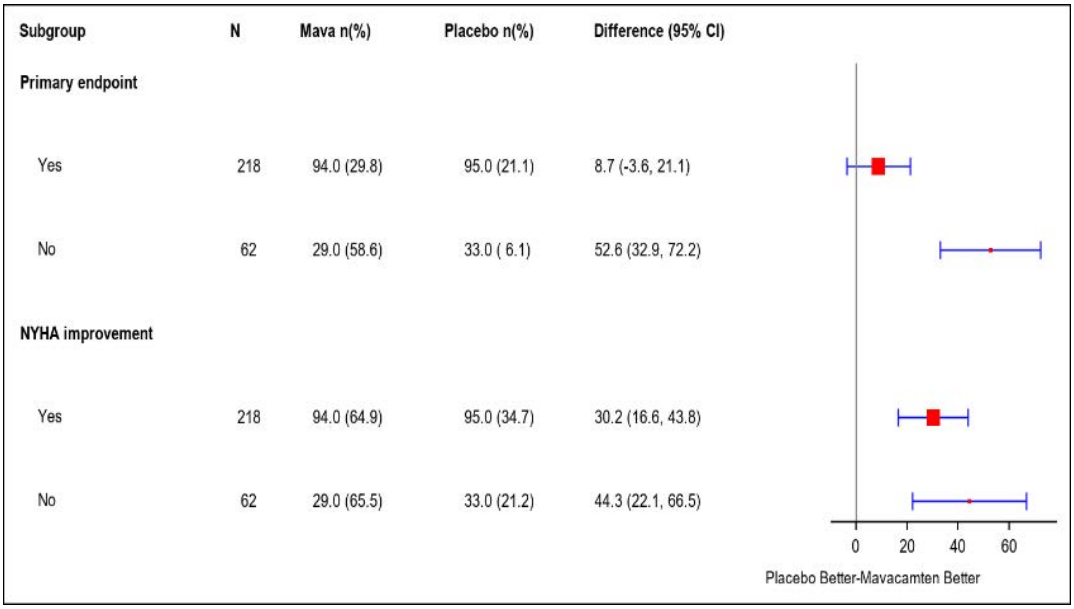
There appears to be an attenuated clinical effect of mavacamten therapy when it is administered to patients on background beta-blocker therapy, as previously discussed for the primary efficacy endpoint (Figure 3). Figure 5 shows subgroup analyses in key efficacy endpoints by beta-blocker use at baseline. The mean pVO_2 change was slightly lower for subjects on beta-blockers compared with those who were not on beta-blockers (Δ=1.1 vs. 2.2 mL/kg/min, respectively). The other secondary endpoints, including change in post-exercise LVOT peak gradient, NYHA class, and both PROs (KCCQ-23 CSS and HCMSQ SoB) showed largely consistent benefits of mavacamten compared with placebo, irrespective of beta-blocker use (Figure 5). The cumulative distribution function plot for Valsalva LVOT peak gradient also demonstrates a consistent improvement in hemodynamic status in mavacamten-treated patients regardless of beta-blocker use.

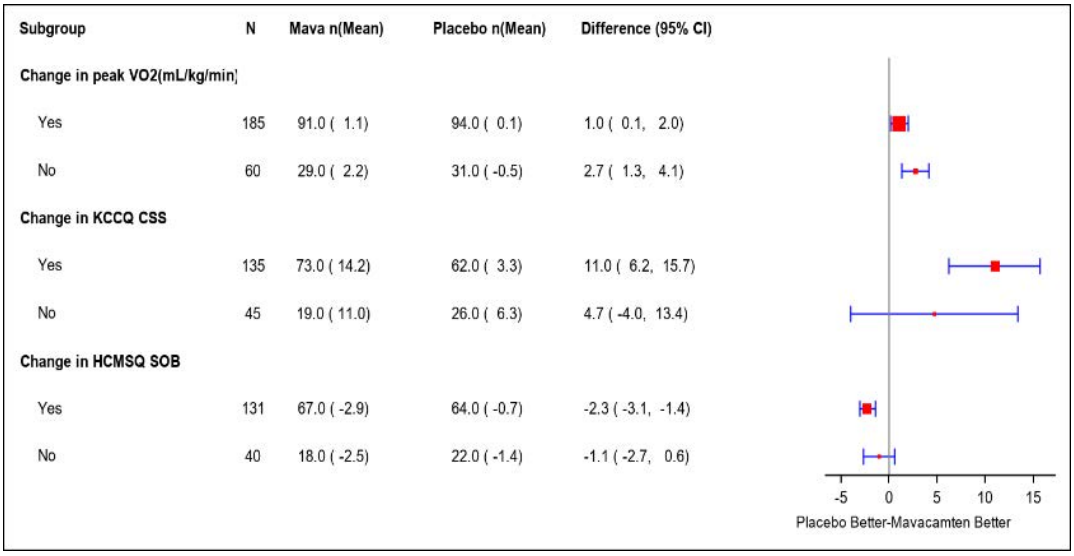
The Applicant attributed the observed subgroup findings to the described "blunting effect" of beta-blocker use on CPET performance (9, 10), likely resulting from negative chronotropic effects of beta-blockers. They pointed out that as expected, the mean peak heart rate (HR) with exercise at baseline was lower for patients with beta-blocker use compared to those without (118 bpm vs. 138 bpm, respectively). However, to what extent this potential HR effect of beta-blockers impacted the observed differential efficacy in patients with or without beta-blocker use is unclear.

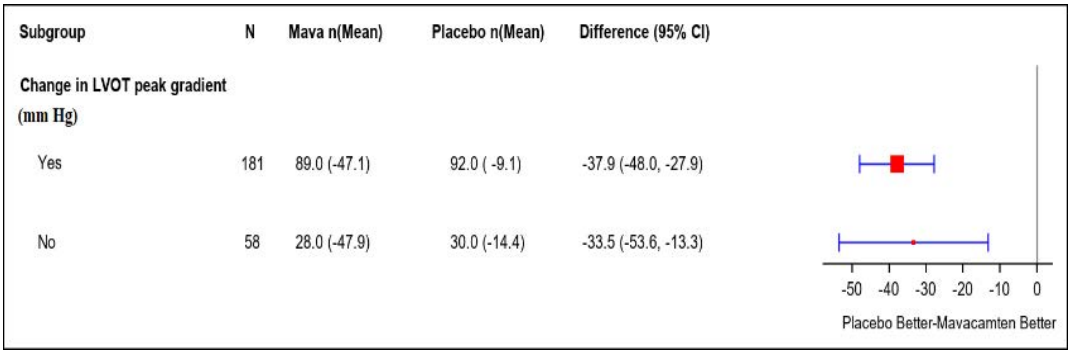
It should be noted that other CPET parameters that are heart rate independent such as VE/VCO_2 slope (a prognostic marker of ventilatory efficiency), peak VE/VCO_2 and ventilatory power improved with mavacamten treatment relative to placebo, irrespective of beta-blocker use. The mean VE/VCO_2 slope change was -2.5 (95% CI: -3.7, -1.4) in the beta-blocker subgroup compared with -2.5 (95% CI: -4.8, -0.2) in the non-beta-blocker subgroup (Table 21 and Table 22).

Overall, the totality of evidence suggests that clinical improvements associated with mavacamten treatment were generally preserved in subjects receiving beta blockers despite the subgroup findings for the primary efficacy endpoint.

Figure 5 Subgroup Analysis in Efficacy Endpoints by Beta-Blocker Use at Baseline, EXPLORER-HCM, ITT Population

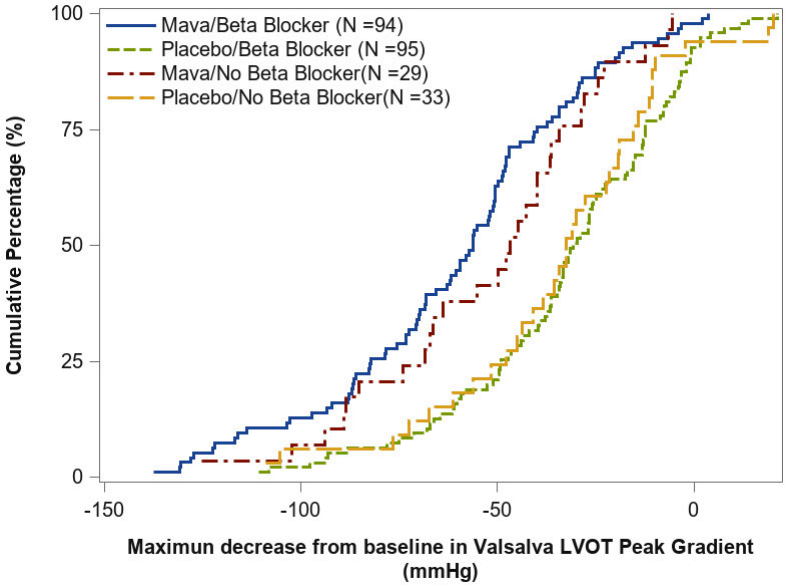






Source: Reviewer' Figure
Abbreviations: Yes = subgroup using beta-blockers; No = subgroup not using beta-blockers;
NYHA = New York Heart Association; LVOT = left ventricular outflow tract; VO2 = oxygen consumption; KCCQ CSS = Kansas City Cardiomyopathy Questionnaire, clinical summary score; HCMSQ SoB = Hypertrophic Cardiomyopathy Symptom Questionnaire, shortness of breath

Figure 6 Cumulative Distribution for Maximum Decrease in Valsalva LVOT Peak Gradient (mmHg) by Beta-Blocker Use at Baseline



Source: Reviewer's Figure

Table 21 Changes from Baseline to Week 30 for Exploratory CPET Endpoints for Subjects Who Were Using Beta-Blockers at Baseline, EXPLORER-HCM, ITT Population

	Mavacamten				Placebo				LS Mean Difference (95% CI)	p-value
	Baseline		Change at Week 30		Baseline		Change at Week 30			
Parameter	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)		
Peak VE/VCO_2	94	35.1 (5.16)	91	-1.8 (3.84)	95	33.8 (5.25)	94	0.5 (3.76)	-2.0 (-2.98, -0.92)	0.0003
VE/VCO_2 Slope	94	33.3 (6.19)	91	-2.4 (4.50)	95	31.9 (5.88)	94	0.6 (4.06)	-2.5 (-3.68, -1.36)	< 0.0001
Peak Circulatory Power	93	2973.6 (1082.13)	90	321.0 (920.49)	94	3184.1 (1120.71)	92	42.6 (904.55)	210.2 (-40.58, 461.02)	0.0999
Ventilatory Power	93	4.9 (1.30)	90	0.63 (1.34)	94	5.2 (1.52)	92	0.003 (1.28)	0.5 (0.15, 0.88)	0.0054
Peak Mets	94	5.3 (1.4)	91	0.3 (0.89)	95	5.6 (1.34)	94	0.02 (0.91)	0.3 (0.00, 0.52)	0.0497
Peak RER	94	1.1 (0.09)	91	0.02 (0.09)	95	1.1 (0.09)	94	-0.002 (0.09)	0.02 (-0.01, 0.04)	0.1560
Percent predicted VO_2	94	75.9 (21.03)	91	6.5 (11.56)	94	75.1 (20.72)	94	-0.5 (12.81)	7.2 (3.85,10.54)	< 0.0001
Ventilatory Threshold	86	11.4 (2.4)	79	0.63 (2.50)	93	11.5 (2.54)	87	-0.15 (2.51)	0.67 (-0.01, 1.35)	0.0531

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 LS means (95% CI) and the p-values are 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.
Beta-blocker use at baseline is based on information captured on eCRF.

Source: Table 19 in EXPLORER-HCM CSR

Table 22 Changes from Baseline to Week 30 for Exploratory CPET Endpoints for Subjects Who Were Not Using Beta-Blockers at Baseline, EXPLORER-HCM, ITT Population

	Mavacamten				Placebo				LS Mean Difference (95% CI)	p-value
	Baseline		Change at Week 30		Baseline		Change at Week 30			
Parameter	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)		
Peak VE/VCO2	29	36.1 (5.27)	29	-2.3 (3.09)	33	35.2 (6.27)	31	0.42 (4.09)	-2.63 (-4.49, -0.77)	0.0065
VE/VCO_2 Slope	29	34.5 (6.44)	29	-2.7 (4.94)	33	33.9 (6.85)	31	-0.1 (4.39)	-2.5 (-4.76, -0.20)	0.0337
Peak Circulatory Power	29	3451.3 (1356.16)	29	703.0 (1083.46)	31	3590.2 (1291.76)	29	-209.8 (726.33)	850.1 (403.50, 1296.66)	0.0004
Ventilatory Power	29	5.1 (1.69)	29	0.80 (1.56)	31	5.3 (1.62)	29	-0.14 (1.04)	0.85 (0.24, 1.45)	0.0071
Peak Mets	29	5.8 (1.42)	29	0.64 (0.87)	33	5.9 (1.58)	31	-0.13 (0.67)	0.74 (0.35, 1.14)	0.0004
Peak RER	29	1.1 (0.09)	29	0.03 (0.11)	33	1.1 (0.10)	31	0.002 (0.076)	0.02 (-0.02, 0.066)	0.3417
Percent predicted VO2	29	81.4 (19.86)	29	11.5 (16.73)	33	82.4 (25.14)	31	-0.95 (9.75)	12.0 (5.01,18.92)	0.0011
Ventilatory Threshold	28	12.15 (2.02)	27	0.88 (2.51)	32	11.6 (2.88)	29	0.90 (2.74)	0.06 (-1.24, 1.36)	0.9256

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 LS means (95% CI) and the p-values are 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.
Beta-blocker use at baseline is based on information captured on eCRF.

Source: Table 20 in EXPLORER-HCM CSR

6. Risk and Risk Management

6.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Consistent with mavacamten's mechanism of action and primary pharmacological activity, cardiac toxicities including dose-dependent reduction in cardiac contractility and reduced systolic function by echocardiogram assessment culminating in cardiac failure or unintended deaths were observed in animals. Mavacamten has demonstrated a steep concentration to LVEF relationship in preclinical models. Both rat and dog studies show that the drug has a very narrow therapeutic index, with only a ~3-fold safety margin between the NOAEL and the dose that caused HF and mortality. However, patients with oHCM have a hypercontractile myocardium and would likely tolerate a reduction in cardiac contractility to a greater extent than animals or humans with normal cardiac contractility. Modest and reversible QTc prolongation was also observed in dogs.

Based on animal studies, mavacamten may cause fetal harm when administered to a pregnant woman. Administration of mavacamten to pregnant rats and rabbits during organogenesis resulted in decrease in mean fetal body weight and increases in visceral and skeletal malformations. Increases in post-implantation loss were also observed in rats.

6.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Mavacamten is a cardiac myosin inhibitor and NME. The most likely risks are those associated with higher exposures resulting in an excessive decrease in cardiac contractility (reduced LVEF),

which could result in the development of signs or symptoms of HF. In addition, mavacamten has a complex PK profile in the setting of drug interactions and CYP2C19 metabolizer polymorphisms which raise safety concerns regarding therapeutic management for DDIs as well as the necessity of differential dosing based on CYP2C19 genotype (see section 7 and Clinical Pharmacology review dated 18 October 2021 and 24 February 2022).

6.3. Potential Safety Concerns Identified Through Postmarket Experience

Mavacamten is not approved in the United States or in any foreign market.

6.4. FDA Approach to the Safety Review

FDA's safety evaluation focused on the data obtained in the EXPLORER-HCM. This pivotal study provides controlled data to evaluate the safety profile of mavacamten under PK/PD based dosing and monitoring strategies in oHCM patients. As agreed, the sponsor also provided an integrated safety summary (ISS) that pooled safety data from the EXPLORER-HCM and 4 other clinical studies including 2 ongoing long-term extension studies (see section 6.5). The pooled data from these studies were used as supportive safety data to evaluate the safety topics of interest. The ongoing extension study MAVA-LTE provides long-term safety data.

The JumpStart Service was consulted to review data quality for this NDA. The overall data and submission quality are reasonable. Adverse events (AE) were analyzed by Medical Dictionary for Regulatory Activities (MedDRA; Version 21.0 for EXPLORER-HCM and Version 23.1 for ISS) preferred term and by pooling AEs with a similar medical concept (referred to as the MedDRA SMQ or FDA MedDRA Query [FMQ]). The Applicant's translations of verbatim terms to MedDRA preferred terms for the events reported in EXPLORER-HCM were reviewed and found to be acceptable. All AEs henceforth presented and discussed are treatment-emergent AEs unless specified otherwise. Given the long half-life of mavacamten (i.e., 8 days for normal metabolizer of CYP2C19 and longer for patients with a slower metabolizing rate), treatment-emergent AEs are defined as any AE with onset date on or after first dose of study treatment, or with worsening on or after first dose of study treatment up through 56 days after the last dose of study treatment.

FDA's safety review focused on categorizing the on-target effects of mavacamten on decreasing ejection fraction and increasing the risk of cardiac failure. Clinical events of special interest included AF and other arrhythmias as well as syncope-related events. Other safety evaluations included the analyses of exposure, AEs, echocardiographic data, laboratory data and vital signs.

SAS version 9.4 and the Office of Computational Science table builder tool were used for most analyses; MedDRA Adverse Event Diagnosis and JMP Clinical were also used.

6.5. Adequacy of the Clinical Safety Database

Pivotal clinical safety data supporting the proposed indication were derived from the Phase 3 placebo-controlled study MYK-461-005 (EXPLORER-HCM). Per agreement with the FDA, the

integrated safety data from 5 efficacy and safety studies in subjects with HCM (either oHCM or nHCM) treated with mavacamten were provided supporting the application (see the list of the clinical studies in Appendix III.10 Table 48). These data are referred to as the ISS. A brief summary of the characteristics of the 5 studies is listed below:

- Pivotal Phase 3 study, MYK-461-005 (EXPLORER-HCM): a randomized, double-blind, placebo-controlled study in subjects with symptomatic oHCM (safety population N =251; 123 patients randomized to mavacamten and 128 randomized to placebo).
- Supporting Phase 2 study, MYK-461-004 (PIONEER-HCM): an open-label efficacy, PK, PD, and safety study in subjects with symptomatic oHCM (safety population N = 21).
- Supporting Phase 2 study, MYK-461-006 (MAVERICK-HCM): a randomized, double-blind, placebo-controlled study in subjects with symptomatic nHCM (safety population N=56; 39 patients randomized to mavacamten and 19 randomized to placebo).
- Supporting Phase 2/3 extension study, MYK-461-007 (MAVA-LTE): an ongoing long-term safety extension study in subjects with oHCM who completed Phase 3 study EXPLORER-HCM and subjects with nHCM who completed MAVERICK-HCM (safety population N = 180; 137 patients with oHCM and 43 patients with nHCM). The cut-off date for the ISS is May 27th, 2020.
- Supporting Phase 2 extension study, MYK-46-008 (PIONEER-OLE): an ongoing open-label extension study in subjects with symptomatic oHCM who were previously enrolled in PIONEER-HCM (safety population N = 13). The cut-off date for the ISS is January 29th, 2020.

The ISS data consisted of a total of 330 unique subjects who received at least one dose of study treatment; this includes 263 subjects dosed with mavacamten (All Mavacamten) and 67 subjects who received placebo. Of the mavacamten-treated subjects, 209 had oHCM and 54 had nHCM. The duration of treatment exposure in the EXPLORER-HCM, MAVA-LTE and the pooled safety dataset with all subjects treated with mavacamten is summarized in Table 23

Table 23. Duration of Exposure, EXPLORER-HCM and ISS, Safety Population

	EXPLORER-HCM		MAVA-LTE[4] (EXPLORER Cohort)	ISS
Parameter	**Mavacamten N=123**	**Placebo N=128**	**Mavacamten N = 137[5]**	**All Mavacamten N=263**
Duration of treatment (months)[1]				
Mean (SD)	6.9 (0.8)	6.9 (0.6)	5.3 (3.0)	9.3 (5.3)
Median (min, max)	7.0 (0.3, 9.3)	7.0 (1.4, 7.7)	4.2 (0.9, 13.3)	8.3 (0.3, 23.5)
Adjusted duration of treatment[2]				
Mean (SD)	6.8 (0.8)	6.8 (0.8)	5.2 (3.0)	9.2 (5.3)
Median (min, max)	7.0 (0.3, 9.3)	7.0 (1.4, 7.7)	4.1 (0.9, 12.5)	8.1 (0.3, 23.5)
Patients treated, by duration[3], n (%)				
Any duration (at least 1 dose)	123 (100%)	128 (100%)	137 (100%)	263 (100%)
<1 month	1 (0.8%)	0 (0%)	2 (1.5%)	3 (1.1%)
≥1 month	122 (99.2%)	128 (100%)	135 (98.5%)	260 (98.9%)
≥3 months	121 (98.4%)	127 (99.2%)	106 (77.4%)	233 (88.6%)
≥6 months	120 (97.6%)	125 (97.7%)	49 (35.8%)	196 (74.5%)
≥12 months	0 (0%)	0 (0%)	3 (2.2%)	69 (26.2%)
≥18 months	0 (0%)	0 (0%)	0 (0%)	21 (8.0%)
≥24 months	0 (0%)	0 (0%)	0 (0%)	0 (0%)

1.Duration of treatment is defined as (last dose date - first dose date + 1 day) within a single study, regardless of intermittent discontinuation.
2. Adjusted duration of treatment excludes time off drug due to temporary interruptions
3. Cumulative duration of treatment. Duration of exposure in MAVA-LTE does not include prior exposure in EXPLORER-HCM.
4. MAVA-LTE, an on-going long-term extension trial with a data cutoff date of May 27, 2020 for the NDA submission
5. Patients who completed EXPLORER-HCM in either treatment group were eligible to participate in MAVA-LTE
Source: Reviewer's table, data: ISS adex
Abbreviations: N, number of subjects in group; n, number of subjects with given treatment duration; SD, standard deviation; min, minimum; max, maximum

Reviewer's Comment: The median exposure for all mavacamten treated patients was about 9 months at the time of the NDA submission and has extended to about 17 months with the ongoing extension studies including >200 patients who have been received at least 1-year of treatment (see section 0 Safety Updates Table 37). This exposure and size of safety data is considered acceptable given the prevalence of this disease. However, there are still limited data for long-term exposure ≥24 months under the proposed dosing algorithm.

6.6. Safety Findings and Safety Concerns Based on Review of the Clinical Safety Database

6.6.1. Discontinuations and Dose Reductions due to Protocol-Specified Criteria

To ensure safety, protocol-specified criteria for dosing discontinuation and reductions based on key PK and PD markers were in place in the mavacamten clinical trials (see the criteria for EXPLORER-HCM in section 5.2.4 and for all studies in the ISS in Appendix III.10 Table 49)

6.6.1.1. Permanent Discontinuation

There were no subjects in either treatment group in EXPLORER-HCM who permanently discontinued study treatment due to the protocol specified criteria (e.g., LVEF < 30%). One subject (Subject (b) (6) in the mavacamten group in EXPLORER-HCM had LVEF < 30% after the completion of study treatment (see section 6.6.6.1). In the ISS, there were a total of 8 mavacamten-treated subjects (3%), all with nHCM, who met the protocol-specified criteria for permanent treatment discontinuation. Six subjects were in the randomized, controlled trial for patients with nHCM (MAVERICK-HCM) and 2 subjects were in the extension trial (MAVA-LTE).

In MAVERICK-HCM, the protocol-specified criteria for permanent discontinuation included LVEF ≤ 45% and plasma trough concentration ≥ 1,000 ng/mL. Five subjects (13%) met LVEF ≤ 45% and two of them had high trough concentrations (one with Ctrough > 1,000 ng/mL and the other with Ctrough > 800 ng/mL). One subject (3%) met the plasma trough concentration ≥ 1,000 ng/mL without a decrease in LVEF (concurrent LVEF = 60%). Four of these six subjects also reported concurrent AEs of cardiac failure and/or systolic dysfunction at the time of permanent discontinuation (see Section 6.6.8.1). No placebo-treated subjects in MAVERICK-HCM permanently discontinued study treatment due to protocol-specified criteria.

One of the two nHCM patients in MAVA-LTE who met the criteria for permanent discontinuation had LVEF ≤ 30% concurrent with Ctrough > 1,000 ng/mL, which was also an AESI (see section 6.6.6.1). The other patient experienced LVEF <50% twice during treatment without concurrent high PK (Ctrough <200 ng/mL); the first event resulted in dose reduction from 5 mg to 2.5 mg (Ctrough: 152 ng/mL, LVEF 45%, concurrent mild AEs of palpitations and fatigue) and the second event occurring about a month later led to permanent discontinuation (Ctrough: 18 ng/mL, LVEF 49% concurrent AE of dyspnea exertional).

Reviewer's Comment: It should be noted that mavacamten dosing in MAVERICK-HCM was designed to achieve pre-specified plasma trough concentration targets (200 ng/mL or 500 ng/mL) and there was no prespecified criterion for temporary discontinuation based on LVEF <50%, a safety measure used in EXPLORER-HCM to mitigate the risk of excessive mavacamten exposure (see section 6.6.1.2). A high incidence of subjects meeting the permanent discontinuation criteria in MAVERICK-HCM is likely due to the dosing strategies implemented in the study, which is not an approach recommended in the proposed USPI.

Regardless of the different dosing strategies used across studies, all subjects who met the LVEF criterion that led to permanent discontinuation of treatment generally had improvements on subsequent LVEF measurements, usually measured 4 weeks after stopping treatment. One subject's LVEF did not return to >50% over 9 weeks after discontinuation of treatment. This subject experienced ongoing and worsening AF during treatment. His LVEF was back to baseline (LVEF =79%) 2 weeks after cardiac ablation for AF (about 15 weeks after treatment discontinuation).

6.6.1.2. Temporary Discontinuations and Dose Reductions

The protocol-specified criteria for temporary discontinuation of study treatment were primarily applied to EXPLORER-HCM and the ongoing extension studies. In EXPLORER-HCM, 7

subjects in the mavacamten arm vs. 2 subjects in the placebo arm met criteria for temporary discontinuation of study treatment due to LVEF <50% (median LVEF 48%, range 35-49%) (Table 24). Three of the 7 mavacamten-treated subjects also had concurrent Ctrough > 700 ng/mL at the time when LVEF <50% occurred. Four of the 7 subjects' LVEF values that met the discontinuation threshold were measured at the end of treatment visit at Week 30 (two of them had concurrent Ctrough > 700 ng/mL). The remaining 3 subjects underwent temporary discontinuation of study treatment and subsequently resumed dosing (one with a dose reduction and two with the same dose) and completed the study. The Kaplan-Meier plot for the event of LVEF <50% is listed in Appendix III.10 Figure 22. Of note, in 3 of the 7 patients on mavacamten, LVEF reductions were detected without other clinical manifestations/symptoms. Among the 4 subjects with clinical manifestations, 2 had concurrent SAEs of stress cardiomyopathy, which is thought not to be related to mavacamten (see section 6.6.4) and the other two had ongoing non-serious AF during treatment prior to the event of LVEF <50% including the complex case who subsequently experienced LVEF < 30% while off treatment during the follow-up period (see section 6.6.6.1, Subject (b) (6)

Overall, LVEF reductions meeting criteria for temporary discontinuation in these studies were reversible based on subsequent LVEF values except for the aforementioned subject (Subject (b) (6)) who had a partial recovery to LVEF 50%.

Three subjects in each group met QTcF prolongation criteria for temporary treatment discontinuation; all subjects in the mavacamten group had Ctrough within the therapeutic range (<700 ng/mL) and with a stable LVEF prior to temporary discontinuation (Table 24). No subjects in EXPLORER-HCM met the temporary discontinuation criteria for mavacamten plasma trough concentration ≥ 1,000 ng/mL or hepatoxicity.

Reviewer's Comments: In EXPLORER-HCM, no up-titration was allowed after Week 14. The late onset of LVEF <50% (i.e., at EOT Week 30) accompanied with high Ctrough >700 ng/mL in two subjects raised concern regarding the potential late effect (accumulative effect) of mavacamten on systolic function. Mavacamten has a long half-life that depends on CYP2C19 genotype. One of the two subjects who had late onset of LVEF <50% accompanied with high concentration is a CYP2C19 poor metabolizer (see narrative for Subject (b) (6) *. Nevertheless, LVEF < 50% could occur at any time during treatment and could be asymptomatic thus routine surveillance with echocardiogram is necessary to mitigate the potential risk associated with mavacamten-related systolic dysfunction.*

In EXPLORER-HCM, as specified in the protocol, if a subject had a mavacamten plasma trough concentration ≥ 700 ng/mL to < 1,000 ng/mL at any time during 30 weeks of treatment, the dose was reduced by 1 level (i.e., 5 mg to 2.5 mg, 10 mg to 5 mg, 15 mg to 10 mg) 2 weeks later. A total of 17 subjects (14%) met the criterion for dose reduction (Ctrough range: 703 to 844 ng/mL) and for 3 of the 17 subjects (2% of the mavacamten-treated patients), a concurrent LVEF <50% was measured with increased concentrations (Table 24). The median time for these events was about 19 weeks (min: 7 weeks and max: 21 weeks). In all cases, mavacamten plasma concentrations decreased to < 700 ng/mL following dose reduction.

The comparison between EXPLORER-HCM (PK/PD monitoring) and MAVA-LTE (PD monitoring) regarding the number of subjects meeting these criteria for temporary discontinuation is discussed in section 6.7.

Table 24 Number of Subjects with Protocol-Specified Criteria for Temporary Treatment Discontinuation or Dose Reduction Other Than Due to Adverse Event, EXPLORER-HCM, Safety Population

Protocol-Specified Criteria	EXPLORER-HCM	
	Mavacamten (N=123) n (%)	Placebo (N=128) n (%)
Temporary Treatment Discontinuation		
Resting LVEF < 50%[1]	7 (5.7)	2 (1.6)
QT prolongation	3 (2.4)	3 (2.3)
Ctrough ≥ 1000 ng/mL	0 (0)	---
Dose Reduction due to Ctrough (700-<1000 ng/mL)[2]	17 (13.8)	---
Resting LVEF < 50%	3 (2.4)	---

[1] Based on central-read data
[2] Number of subjects who met the PK criterion for dose reduction. A total of 13 subjects (10.6%) had actual dose reduction.
Source: Reviewer's Table, data: ISS adsl, adcv and adpc, SCS Table 8 and CSC Table 36
Abbreviations: N, number of subjects in group; n, number of subjects with the event of interest; LVEF, left ventricular ejection fraction; Ctrough, trough plasma concentration

6.6.2. Overall Adverse Event Summary

The overall incidence of AEs and SAEs was generally similar between treatment groups in EXPLORER-HCM (Table 25). The two AEs leading to discontinuation of study drug in the mavacamten group were syncope and AF (see section 6.6.5).

Table 25. Overview of Adverse Events,[1], Safety Population

Event	EXPLORER-HCM		ISS
	MYK-461 (N=123) n (%)	Placebo (N=128) n (%)	All Mavacamten (N=263) n (%)
Any TEAE	108 (87.8)	104 (81.2)	215 (81.7)
Moderate or severe AEs (Grade 3-5)	12 (9.8)	14 (10.9)	24 (9.1)
Any SAE	14 (11.4)	12 (9.4)	28 (10.6)
Any SAE with a fatal outcome	0	1 (0.8)	0
AE leading to discontinuation of study drug	2 (1.6)	0	9 (3.4)
AE leading to interruption of study drugs	3 (2.4)	6 (4.7)	14 (5.3)

[1] Includes treatment-emergent AE defined as any AE with onset date on or after first dose of study treatment, or with worsening on or after first dose of study treatment up through 56 days after the last dose of study treatment
Source: Reviewer's table; data: ISS adsl and adae
Abbreviations: TEAE, treatment emergent adverse event; SAE, serious adverse event; N, number of subjects in group; n, number of subjects with at least one event.

6.6.3. Deaths

In EXPLORER-HCM, there was one fatal event of sudden death in the placebo group. No death occurred in the mavacamten group during treatment. No additional deaths were reported in the ISS at the time of the NDA submission.

With the updated safety data through May 2021 (see section 0), there were 3 deaths in mavacamten-treated patients in the ongoing extension study MAVA-LTE (1 endocarditis bacterial, 1 cardiac arrest and 1 sudden cardiac death, see narratives in Appendix III.11.1). The cumulative incidence rate of all-cause death was 0.65 and 0.99 per 100 pt-yrs in patients on mavacamten and placebo, respectively.

Reviewer's Comment: The observed death rate in all mavacamten-treated patients in the ISS up to May 2021 is within the background rate for this patient population and narrative review of the cases did not indicate a direct role of mavacamten in the cause of death. One death case (cardiac arrest) occurred in the setting of worsening AF and post-procedure of AF ablation. Mavacamten treatment was continued during hospitalization and until the time of death (the subject's NT-proBNP was 2,800 pg/mL during hospitalization, significantly increased from the previous value of 200 pg/mL). The subject's LVEF was stable in the range of 50-55%. Although the causality cannot be established in this case, it raised concern that mavacamten should not be continued in patients experiencing worsening clinical status including worsening arrhythmia. The risk seems to outweigh benefit in these settings when patients may have significant hemodynamic shifts, have conditions predisposing them to systolic dysfunction and have the potential for initiating some interacting medications. The same concern was raised during narrative review of cases with HF/systolic dysfunction SAE (see section 6.7.1). The potential risk of mavacamten on systolic dysfunction in these clinical settings should be clearly described in the USPI and additional dosing adjustment may be considered in patients experiencing worsening clinical status including new or worsening arrhythmia.

6.6.4. Serious Adverse Events

Overall, the incidence of SAEs was similar between groups in EXPLORER-HCM. Narrative review of the cases in the mavacamten group did not reveal major safety concerns, and the majority of these events were likely related to subjects' underlying conditions. Two SAEs (AF and syncope, see section 6.6.5) in the mavacamten group resulted in discontinuation of treatment. SAEs that met the criteria for adjudicated cardiovascular events are summarized in section 6.6.7. Two cases with a stress cardiomyopathy SAE in the mavacamten group continued treatment after the event and completed the study without recurrence of any cardiac AEs. Both subjects were enrolled into the ongoing extension study with about additional 60 weeks of mavacamten exposure provided by the updated safety data. No additional SAE or similar event were reported by these two cases during their participation in the extension study (see narrative for subject (b) (6) and subject (b) (6) in Appendix III.11.1). The ISS data showed similar SAE results. Systolic dysfunction, AF, and syncope are clinical events of interest which are discussed in section 6.6.8.1, 6.6.8.2 and 6.6.8.3, respectively.

Table 26. Serious Adverse Events[1], Safety Population

	EXPLORER-HCM		ISS
Serious Adverse Event[2]	**MYK-461 (N=123) n (%)**	**Placebo (N=128) n (%)**	**All Mavacamten (N=263) n (%)**
SAE	14 (11.4)	12 (9.4)	28 (10.6)
Atrial f brillation	3 (2.4)	5 (3.9)	6 (2.3)
Syncope	3 (2.4)	1 (0.8)	3 (1.1)
Stress cardiomyopathy	2 (1.6)	0	2 (0.8)
Systolic dysfunction	1 (0.8)	0	2 (0.8)
Urinary tract infection	0	2 (1.6)	0

[1] This table only lists preferred term reported by more than 1 patient in either group or ISS
[2] Coded as MedDRA preferred terms,
Source: Reviewer's table, data: ISS adsl and adae
Abbreviations: N, number of subjects in group; n, number of subjects with an event; ISS, integrated summary of safety

6.6.5. Dropouts and/or Discontinuations Due to Adverse Events

Two subjects (1.6%) in the mavacamten group discontinued study drug and study due to AEs in EXPLORER-HCM. One subject who had no history of syncope had a first SAE of syncope (leading to treatment interruption) on Day 68 (see narrative for subject (b) (6) in Appendix III.11.1). The event of syncope was considered resolved on the same day, but the subject was hospitalized for observation. The event was thought to be related to use of metoprolol due to the subject's low heart rate (low 40's bpm). The metoprolol dose was consequently reduced. The subject resumed mavacamten treatment two days after the event. The subject had a recurrence of syncope after two weeks which resulted in study discontinuation. Normal rate and cardiac rhythm were observed at the day of the event. The subject subsequently underwent a myectomy procedure. Both events were plausibly related to the subject's underlying and progressive oHCM but the role of mavacamten in these events cannot be ruled out due to the temporal relationship.

The other subject had multiple occurrences of AF (none were categorized as an SAE) during the study. The subject was diagnosed with HCM in (b) (6) The first AF (new onset) occurred about 1 month after the first dose of mavacamten, and the event did not resolve until 3 weeks later. There was no action taken with the study drug. The subject subsequently had the mavacamten dose up-titrated to 10 and 15 mg. The second event occurred several days after mavacamten was up titrated to 15 mg, which resulted in study drug discontinuation. The subject's LVEF was in the range of 60 to 70% during treatment. The role of mavacamten in these events cannot be ruled out due to the observed temporal relationship. No subjects in the placebo group discontinued the study due to AEs.

6.6.6. Adverse Event of Special Interest

Three adverse events of special interest (AESI) were specified in the clinical program based on pharmacologic on-target effects and findings from mavacamten nonclinical studies: LVEF ≤ 30%, overdose, and pregnancy. Table 27 summarizes the incidence of AESIs in EXPLORER-

HCM and the ISS. No pregnancies have been reported for female subjects or female partners of male subjects treated with mavacamten, thus there are no clinical safety data for embryofetal toxicity with mavacamten. Detailed discussions of the other two AESIs are summarized in sections 6.6.6.1 and 6.6.6.2.

Table 27 Summary of Adverse Events of Special Interest

	EXPLORER-HCM		ISS
	Mavacamten (N=123) n (%)	Placebo (N=128) n (%)	All Mavacamten (N=263) n (%)
LVEF at resting ≤ 30%[1]	1 (0.8)	0	2 (0.8)
Overdose	18 (14.6)	29 (22.7)	49 (18.6)
Symptomatic	0	0	2 (0.8)

1 LVEF ≤ 30% measured at study sites and/or external locations
Source: Reviewer's Table
Abbreviations: N, number of subjects in group; n, number of subjects with an event; ISS, integrated summary of safety; LVEF, left ventricular ejection fraction

6.6.6.1. LVEF ≤ 30%

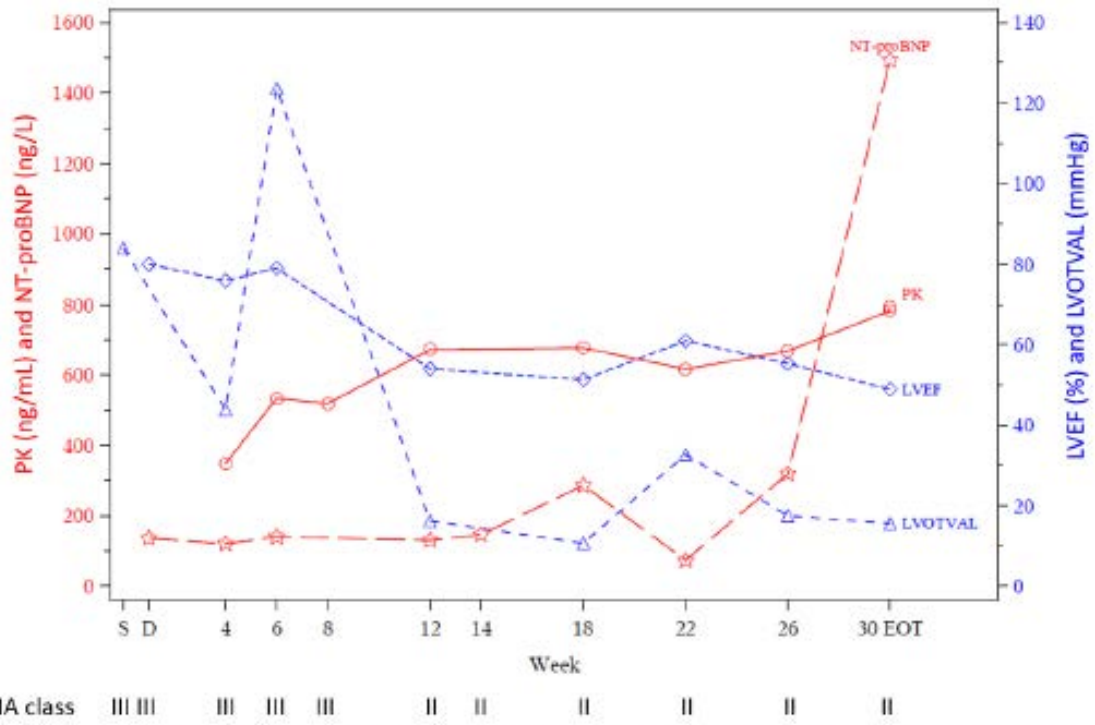
The AESI of LVEF ≤ 30% was originally defined based on site-read echocardiograms. To evaluate all possible cases with LVEF ≤ 30%, FDA's analysis of LVEF ≤ 30% also included cases with LVEF measured during hospitalization or at external locations of clinical care (Table 27). In EXPLORER-HCM, there was one case who had LVEF of 49% at the Week 30 (EOT visit) and later experienced LVEF ≤ 30% in the post-treatment period. In the ISS, one additional subject with nHCM experienced an AESI of LVEF ≤ 30% during the chronic treatment phase in the extension study MAVA-LTE (about 47 weeks after the first dose of mavacamten).

A brief summary of these two cases is described as below:

- Subject (b) (6) This case is a 35-year-old Caucasian male with oHCM, baseline NYHA Class III and a CYP2C19 poor metabolizer. He has a family history of sudden cardiac death and had a prior history of AF (once every 4-5 months, lasting about 30 mins). Prior to randomization, he had moderate LV hypertrophy, mild to moderate mitral and tricuspid regurgitation, good systolic function (LVEF = 65%) and good right ventricular function. He received mavacamten (5 mg) in EXPLORER-HCM and experienced AF on Day 9 through end of the study (2 times per week). There was no change in treatment due to the AF AE. The subject was hospitalized for recurrent AF (SAE) on Day 64 and suffered from more frequent episodes of AF with a longer duration. The AF SAE was resolved in two days. There was no action taken with the study drug as a result of this SAE. The investigator attributed the event to the subject's underlying condition of oHCM. At the Week 30 visit (Day 214), the subject had LVEF 49% (55% at Week 26) and NT-proBNP of 1494 ng/L (319 ng/L at Week 26) (Figure 7). He received the last dose of mavacamten on Day 225. The subject was on mavacamten 5 mg during the entire study and his Ctrough was generally in the range of 400-700 ng/mL, but increased to a peak of 782 ng/mL measured at Week 30 (Figure 7). During the washout period on study Day 235 (10 days after the last dose of mavacamten), the subjects was admitted for abdominal pain (SAE), a rapid irregular

pulse and dyspnea. On Day 240, the subject experienced persistent AF with rapid ventricular response (RVR). He was treated with multiple concomitant medications including beta blockers (bisoprolol and metoprolol) and high doses of verapamil and amiodarone. Abdominal computerized tomography (CT) scan showed moderate to large right side pleural effusion possibly associated with HF, and free fluid in the abdomen. On Day 242 (17 days after the last dose of mavacamten), the subject was admitted to a different hospital for tachycardia (120 beats/min) induced systolic dysfunction. Echocardiogram on Day 242 revealed severely reduced global contractility with LVEF of 20%, enlarged right ventricle with moderate decrease in function and regurgitation in multiple valves. On the same day, the subject had a cavotricuspid isthmus and left atrial catheter ablation. After the procedure, the echocardiogram demonstrated moderate to severe pericardial effusion and severe decline in both ventricles (LVEF = 20% on Day 243, LVEF =15% on Day 244). On Day 245, the subject developed severe hypoxia and experienced ischemic stroke and developed facial palsy, dysarthria, left hemiplegia and detachment. The subject underwent an emergent cerebral catheterization. He then developed HF, desaturation, difficulty in oxygenation, and low blood pressure. The subject was given vasopressors and was returned to the cardiac ICU. Transesophageal echocardiography (TEE) revealed an atrial septal defect, which the sponsor stated was a complication that occurred during the ablation procedure. The subject was put on ECMO for a few days and LVEF declined to 5% on Day 246. The subject experienced worsening HF and cardiogenic shock. Follow-up echocardiogram on Day 249, Day 251 and Day 258 revealed LVEF of 28%, 45%, 50% respectively. The SAEs of systolic dysfunction and HF were considered resolved on Day 261.

Figure 7 Clinical Map for Subject [redacted] (b) (6) from Day 1 to Week 30, EXPLORER-HCM



Abbreviations: D = Day 1; EOT = End of Treatment; LVEF = left ventricular ejection fraction; LVOTVAL = LVOT Valsalva gradient; NT-proBNP = N-terminal pro B-type natriuretic peptide; S = Screening
Note: Week 30 (EOT) NT-proBNP sample obtained prior to exercise testing.

Source: Sponsor's response to clinical IR dated May 28, 2021, Figure 10

Reviewer's Comment: As previously mentioned in section 6.6.1.2, this case raised concern about the potential late effect (accumulative effect) of mavacamten on systolic function. Ctrough was at its peak at the last treatment visit despite a constant dose of 5 mg throughout the study. Although SAEs of HF and systolic dysfunction occurred during the post-treatment period, it is expected that Ctrough would remain at a considerable level in this subject considering the long half-life of mavacamten, particularly in a CYP2C19 poor metabolizer. There were multiple confounding factors that may have impacted LV function. It is noted that the patient was treated with high doses of multiple medications that have the potential to adversely impact LV systolic function. However, the role of mavacamten in this case of LVEF < 30% cannot be ruled out. Of note, the subject also experienced a significant elevated NT-proBNP level as well as worsening AF preceding the SAE of HF and systolic dysfunction. A similar phenomenon was also observed in other mavacamten-treated subjects who developed HF/systolic dysfunction SAEs (see section 6.7.1).

- Subject [redacted] (b) (6): This case is a 41-year-old Caucasian woman with nHCM, baseline NYHA Class III and a CYP2C19 rapid metabolizer. Relevant medical history included HF (ongoing since [redacted] (b) (6) and ICD/pacemaker insertion [redacted] (b) (6) She received placebo in the Phase 2 study and was treated with mavacamten in the extension study MAVA-LTE (starting dose 5 mg). The mavacamten dose was increased to 10 mg on Day 49. The LVEF was 58% on Day 249. The subject experienced worsening fatigue and dyspnea

(both non-serious Grade 2) and was diagnosed with worsening HF on Day 266. Her dose of furosemide was increased from 20 mg to 40 mg but there was no improvement in her symptoms. The mavacamten dose was not changed due to this event, and the subject continued 10 mg mavacamten until Day 329. On Day 330, the subject had LVEF 29% per core lab (LVEF 20% at the local site) and mavacamten was permanently discontinued due to protocol specified criteria. The mavacamten plasma concentration was 1,400 ng/mL on Day 330. The subject had improvement in her symptoms within 2 days post discontinuation. There was subsequent improvement of LVEF values measured 2 weeks and 4 weeks after study drug discontinuation (see Table 28).

Table 28 Key PK and PD parameters for subject (b) (6) in the extension study MAVA-LTE

Age/Sex/Race	NYHA	CYP2C19 metabolizer	Visit	Dose	Ctrough (ng/mL)	LVEF (%)	VLVOT (mmHg)	NT-proBNP (ng/L)
41 / F / WHITE	Class III	Rapid	Baseline (Day 1)	0	NA	64.557	11.022	1191
			Week 4 (Day 28)	5	197	65.086	NA	486
			Week 8 (Day 63)	10	418	70.379	NA	425
			Week 12 (Day 80)	10	509	67.361	NA	373
			Week 16 (Day 119)	10	847	56.229	NA	NA
			Week 24 (Day 176)	10	537	61.627	NA	350
			Week 36 (Day 249)	10	511	57.609	NA	331
			Week 48 (Day 330)	10	1400	29.1	NA	1800
			Week 48 (Day 344)	NA	579	43.388	5.382	1168
			Week 48 (Day 358)	NA	NA	68.418	NA	847

Source: Reviewer's Table, data: ISS adsl, adpc, adex, and adcv
Abbreviations: NYHA, New York Heart Association; PK, pharmacokinetic (trough concentration); LVEF, left ventricular ejection fraction; VLVOT, Valsalva left ventricular outflow tract, NT-proBNP, N-terminal pro b-type natriuretic peptide

Reviewer's Comment: It is not clear why the mavacamten concentration increased drastically between week 36 and week 48 while the dose remained unchanged. There was no evidence of concomitant interacting medications in this event based on available data. Worsening HF was diagnosed at around Week 38 based on the subject's worsening clinical signs and symptoms and the mavacamten dose was not changed due to the event. Low LVEF and high NT-proBNP subsequently measured at week 48 consistent with the HF event. LVEF reduction seems reversible after drug discontinuation at week 48 (LVEF = 43% two weeks after discontinuation and LVEF = 68% one month after discontinuation). This case raises concern regarding potential alteration of mavacamten exposure due to unidentified issues.

There are 2 additional cases with LVEF ≤ 30% in the ongoing MAVA-LTE extension study that occurred after NDA data cut, which are summarized in Section 0 Safety Updates.

6.6.6.2. Overdose

No symptomatic overdose was reported in either group in EXPLORER-HCM. There were 2 subjects in the ISS who experienced an AESI of symptomatic overdose; both occurred in subjects with nHCM in the extension study. Both subjects reported accidently taking 1 extra pill of study drug. Associated AEs included bradycardia/anxiety in one case and lethargy in another case. These AEs were mild in severity and resolved on the same day without medical intervention.

During this NDA review, there was a safety report regarding a case of accidental ingestion and overdose which occurred in a 10-month-old male infant of a (b) (6) subject participating in the extension study (MAVA-LTE). The infant ingested three 15 mg capsules of his father's mavacamten study medication on (b) (6) A mobile ICU arrived at the child's home about two hours after the ingestion of capsules. Cardiac arrest with asystole was witnessed by the mobile ICU team. Extracorporeal cardiopulmonary resuscitation (ECPR) was initiated and after 90 minutes of low flow CPR, the electrical rhythm was 80 bpm with no mechanical activity or ventricular ejection. Norepinephrine and milrinone and charcoal chelation were given, and hemodialysis was started. The infant's status worsened with signs of severe neurological impairment, multi-organ failure and no activity on EEG the next day. The child was pronounced dead on (b) (6)

Reviewer's Comment: This fatal case demonstrated that overdose in humans can be life-threatening and result in asystole refractory to any medical interventions. The risk of overdose should be included in the USPI.

6.6.7. Adjudicated Cardiovascular Events

All deaths and hospitalizations in EXPLORER-HCM were adjudicated by an independent clinical event adjudication committee (Table 29). A slightly higher incidence of major adverse cardiovascular events (MACE) was found in subjects on mavacamten vs. placebo (4.1% vs. 2.3%, a difference of only 2 events between treatment arms, limiting conclusions). All adjudicated myocardial infarctions (MIs) in the study were non-ST elevation MIs (type II MI); the reported term for two of the cases in the mavacamten group was stress cardiomyopathy SAE (see section 6.6.4). Narrative review of these cases did not suggest a contributary role of mavacamten in these events (see Appendix III.11.1), and the number of MI events was low (3 with mavacamten vs. 1 with placebo), limiting conclusions. Treatment with mavacamten is not associated with an increase in troponin-I (Table 18 and Appendix III.11.3 Figure 24). There were no additional MIs in the MAVA-LTE extension study. Except for HF, there is no mechanistic basis for other major CV events such as MI and stroke as a result of mavacamten therapy. Overall, there are no major safety concerns for important non-heart-failure-related CV events as a consequence of mavacamten therapy.

Table 29 Overview of Adjudicated Cardiovascular Hospitalizations or Cardiovascular Death, EXPLORER-HCM, Safety Population

Cardiovascular Events	Mavacamten N=123 n (%)	Placebo N=128 n (%)
CV hospitalization	8 (6.5%)	6 (4.7%)
MACE[1]	5 (4.1%)	3 (2.3%)
MI	3 (2.4%)[2]	1 (0.8%)
Heart failure	3 (2.4%)[2]	1 (0.8%)
CV death	0	1 (0.8%)
Non-MACE	3 (2.4%)	3 (2.3%)
Atrial fibrillation	2 (1.6%)	3 (2.3%)
Syncope	1 (0.8%)	0

[1] MACE is defined as a composite of CV death, stroke, MI and heart failure hospitalization
[2] One subject with MI also had HF
Source: Reviewer's Table, SCS Figure 2
Abbreviations: N, number of subjects in group; n, number of subjects with an event; CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction; CV, cardiovascular

6.6.8. Clinical Events of Special Interest

6.6.8.1. Cardiac failure and systolic dysfunction

Cardiac failure as a clinical event of interest was defined based on the narrow MedDRA SMQ "cardiac failure" in the sponsor's analysis. FDA's analysis added in an additional term "systolic dysfunction" in the search. Table 30 summarizes cardiac failure related events by preferred terms in the EXPLORER-HCM and ISS.

The incidence of cardiac failure related AEs was similar between the two groups in EXPLORER-HCM. Two out of three cardiac failure AEs in the mavacamten group did not have concurrent systolic dysfunction (i.e., LVEF > 65% in both cases) including one event (non-serious, Grade 1, LVEF 70%) that occurred on Day 1 that was not likely related to the study drug. The third case had a SAE of cardiac failure (with concurrent SAEs of cardiogenic shock and systolic dysfunction) that occurred during the follow-up period after the subject completed the study treatment. This subject (Subject (b) (6)) has been previously discussed in section 6.6.6.1.

There was a total of 17 cardiac failure AEs in mavacamten-treated patients in the ISS. One additional SAE of systolic dysfunction (LVEF =45%) occurred in a patient with nHCM that led to study drug discontinuation. It should be noted that mavacamten dosing was different across studies in the ISS. An individual dosing approach based on PK and/or PD criteria was implemented in the pivotal trial EXPLORER-HCM and its extension study (the EXPLORER cohort in MAVA-LTE) (See Section 6.7.1). Other clinical studies in patients with nHCM and oHCM determined mavacamten dose based on a dosing-finding approach (e.g., initiating dose based on weight or titrating dose based on targeted mavacamten trough concentration), which is not an approach recommended in the proposed labeling. Given various disease courses and comorbidities in these patients and different dosing strategies across studies, there is limited

generalizability to these events. Some of these cases clearly demonstrated excess on-target effect of systolic dysfunction which is accompanied with high Ctrough. This is more obvious in the studies with nHCM population, in which the dosing was not based on individualized PK and/or PD markers. For cases with systolic dysfunction, LVEF decline seemed reversible in all cases after study drug interruption or permanent discontinuation except for a few cases where LVEF did not immediately bounce back after drug discontinuation because of concurrent medical conditions.

Table 30 Incidence of cardiac failure related AE, Safety Population

	EXPLORER-HCM		ISS
	Mavacamten (N=123) n (%)	Placebo (N=128) n (%)	All Mavacamten (N=263) n (%)
Cardiac failure related AEs[1]	3 (2.4)	5 (3.9)	17 (6.5)
Cardiac failure	3 (2.4)	3 (2.3)	8 (3.0)
Cardiac failure acute	0	2 (1.6)	0
Cardiac failure congestive	0	1 (0.8)	0
Cardiac failure chronic	0	0	1 (0.4)
Cardiogenic shock	1 (0.8)	0	1 (0.4)
Ejection fraction decreased	0	0	8 (3.0)
Systolic dysfunction	1 (0.8)	0	2 (0.8)
Cardiac failure related SAEs	1 (0.8)	1 (0.8)	2 (0.8)

[1]Cardiac failure related AEs was defined as MedDRA SMQ "cardiac failure" narrow plus a preferred term of systolic dysfunction.
Subject could have more than one reported preferred terms for a single event.
Source: Reviewer's Table, data: ISS adsl and adae
Abbreviations: N, number of subjects in group; n, number of subjects with an event; ISS, integrated summary of safety; AE, adverse event, SAE, serious adverse event

After NDA data cut, there were an additional 5 SAEs of HF or systolic dysfunction in the long-term extension study MAVA-LTE (see Section 0 Safety Updates).

6.6.8.2. Atrial Fibrillation and other arrhythmias

Atrial fibrillation (AF) as a clinical event of interest was defined as any AE with preferred term "atrial fibrillation" or "atrial flutter" by the sponsor. To assess AF and other arrhythmia related AEs, we used the FMQ "arrythmia" narrow for our search.

Overall, the incidence of arrythmia related AEs including AF was similar between the groups in EXPLORER-HCM. There were 3 subjects (2%) who experienced AF SAEs in the mavacamten group compared to 5 (4%) in the placebo group. All three cases in the mavacamten group have a history of AF and two of the three AF SAEs occurred during the 8-week post-treatment washout period.

Consistent with the arrythmia AE findings, data from cardiac rhythm monitoring also did not indicate safety concerns for mavacamten (Section 6.6.12).

Table 31 Incidence of Arrythmia AE, EXPLORER-HCM and ISS, Safety Population

	EXPLORER-HCM		ISS
	Mavacamten (N=123) n (%)	Placebo (N=128) n (%)	All Mavacamten (N=263) n (%)
Arrythmia AEs (FMQ, Narrow)	17 (13.8)	16 (12.5)	48 (18.3)
Atrial f brillation	10 (8.1)	10 (7.8)	21 (8.0)
Atrial flutter	0	1 (0.8)	2 (0.8)
Atrial tachycardia	0	1 (0.8)	0
Bradycardia	1 (0.8)	1 (0.8)	2 (0.8)
Cardiac flutter	2 (1.6)	0	5 (1.9)
Extrasystoles	0	0	1 (0.4)
Sinus bradycardia	0	2 (1.6)	0
Sinus tachycardia	1 (0.8)	0	1 (0.4)
Supraventricular tachycardia	0	0	2 (0.8)
Tachycardia	0	0	1 (0.4)
Ventricular extrasystoles	1 (0.8)	1 (0.8)	3 (1.1)
Ventricular tachycardia	2 (1.6)	2 (1.6)	10 (3.8)
Arrythmia SAEs (FMQ, Narrow)	3 (2.4)	5 (3.9)	6 (2.3)
Atrial fibrillation	3 (2.4)	5 (3.9)	6 (2.3)
Ventricular tachycardia	0	1 (0.8)	0

Source: Reviewer's Table, data: ISS adsl and adae
Abbreviations: N, number of subjects in group; n, number of subjects with an event; ISS, integrated summary of safety; AE, adverse event; SAE, serious adverse event; FMQ, FDA MedDRA Query

6.6.8.3. Syncope

In EXPLORER-HCM, a slightly higher incidence of syncope AE was reported in patients on mavacamten compared to placebo (6% vs. 2%). A total of 3 subjects (2.4%) in the mavacamten group and 1 subject (0.8%) in the placebo group experienced a SAE of syncope. Two SAEs in the mavacamten group occurred during treatment; proximate plasma trough concentrations were relatively low for these two cases (one was < 200 ng/mL and the other was 32 ng/mL). The third SAE in the mavacamten group occurred 25 days after treatment completion; the trough concentration at the end of treatment was < 450 ng/mL (see narrative review in Appendix III.11.1).

The sponsor examined syncope AEs by combining syncope and presyncope AEs, which yields a similar incidence between groups (6.5% vs. 5.5%). In the ISS, no subjects with nHCM in the mavacamten group experienced events of syncope or presyncope.

Using a broad definition, the incidence of syncope (FMQ, broad) was higher in patients on mavacamten compared to placebo (24.4% vs. 19.5%) and the imbalance was primarily driven by dizziness AE, which was more frequently reported in the mavacamten group.

Table 32 Incidence of syncope , EXPLORER-HCM, Safety Population

	EXPLORER-HCM		ISS
	Mavacamten (N=123) n (%)	Placebo (N=128) n (%)	All Mavacamten (N=263) n (%)
FMQ syncope (Narrow) AE			
Syncope	7 (5.7)	2 (1.6)	7 (5.7)
SAE	3 (2.4)	1 (0.8)	3 (2.4)
FMQ syncope (Broad) AE			
Syncope	30 (24.4)	25 (19.5)	47 (17.9)
Dizziness	26 (21.1)	17 (13.3)	42 (16.0)
Syncope	7 (5.7)	2 (1.6)	7 (2.7)
Presyncope	2 (1.6)	5 (3.9)	5 (1.9)
Hypotension	1 (0.8)	3 (2.3)	1 (0.4)
Orthostatic Hypotension	1 (0.8)	0	2 (0.8)

Source: Reviewer's Table, ISS adsl and adae
Abbreviations: N, number of subjects in group; n, number of subjects with an event; ISS, integrated summary of safety; AE, adverse event, SAE, serious adverse event, FMQ, FDA MedDRA Query

Reviewer's Comment: Although the syncope AE was reported more frequently in patients on mavacamten compared to placebo, the difference was modest. Syncope is a common symptom in patients with oHCM. The majority of syncope cases in both groups had a history of syncope/presyncope or dizziness. Narrative review of SAEs did not reveal particular safety concerns and it appeared that syncope was likely related to the patients' underlying condition of oHCM. Three of the 7 subjects in the mavacamten group who experienced syncope also experienced dizziness during the study. Notably, there were a total of 4 on-treatment syncope events including 2 SAEs in the mavacamten group; all occurred at the lower range of plasma trough concentrations (< 200 ng/mL). Three syncope events including one SAE occurred during the follow-up/washout period. Considering that there is no difference in arrythmia AEs between groups (see Section 6.6.8.2) and mavacamten is not associated with blood pressure decrease/hypotension from both AE and vital sign data, a higher incidence of syncope AEs could be a chance finding or potentially attributed to dizziness, which is considered an adverse reaction of mavacamten (Section 6.6.9). Given that syncope could be attributed to dizziness, the imbalanced findings of syncope AE should be included in labeling.

6.6.9. Treatment-Emergent Adverse Events

Dizziness was the most common AE reported in EXPLORER-HCM and it was reported more frequently in the mavacamten group compared to placebo (27% vs.18%) (*Table 33*). The majority of dizziness AEs in both groups were reported as mild. Only one dizziness AE in the mavacamten group was reported as severe. There was no dizziness SAE in either group.

Dyspnea is another common HCM symptom, and it was reported more frequently in patients on mavacamten than placebo. None of the dyspnea events were reported as severe or serious. It should be noted that the observed imbalance can be largely attributed to occurrence of dyspnea during the follow-up period after planned treatment completion (between Week 30 and Week

38). There was no difference in dyspnea AEs between groups during treatment (7% vs. 8% in the mavacamten group vs. placebo). Treatment of mavacamten was associated with the reduction of NT-proBNP (Table 17 and Appendix III.11.3 Figure 23) and NT-proBNP levels returned to baseline at Week 38, following 8 weeks of study drug washout. It is likely that the imbalance is primarily due to a recurrence of symptoms after treatment discontinuation in the mavacamten group thus safety data did not support that dyspnea is an on-treatment effect of mavacamten.

Numerical imbalance of headache, back pain, arthralgia, pyrexia and cough was also observed in EXPLORER-HCM; however, the frequency of these AEs was overall low, and the differences between groups were small (< 5%). These events were generally reported to be mild in severity. Due to the nature of the events, the significance of these results in mavacamten-treated patients is unclear and the imbalance may be due to chance. Evaluation of syncope is discussed previously in section 6.6.8.3. The ISS data are generally consistent with the findings in EXPLORER-HCM and did not reveal additional safety signals of concern. Dizziness with a >5% higher frequency reported in the mavacamten group compared to placebo will be included as an adverse reaction in the label. Given that syncope could be attributed to dizziness, the imbalanced findings of syncope AE will also be included in the label.

Table 33. Adverse Events[1] Occurring at ≥ 4% with Higher Frequency in Treatment Arm Than Comparator Arm, EXPLORER-HCM, Safety Population

FMQ (Narrow)	**Mavacamten (N=123) n (%)**	**Placebo (N=128) n (%)**	**RD (95% CI)**
Dizziness[1]	33 (26.8)	23 (18.0)	8.9 (-1.4, 19.1)
Headache	18 (14.6)	13 (10.2)	4.5 (-3.7, 12.6)
Back pain	13 (10.6)	8 (6.3)	4.3 (-2.5, 11.2)
Arthralgia	7 (5.7)	2 (1.6)	4.1 (-0.5, 8.8)
Syncope	7 (5.7)	2 (1.6)	4.1 (-0.5, 8.8)
Pyrexia	6 (4.9)	1 (0.8)	4.1 (0, 8.20)
Preferred Term			
Dyspnea	18 (14.6)	13 (10.2)	8.9 (-1.4, 19.1)
Cough	10 (8.1)	4 (3.1)	5.0 (-0.7, 10.7)

[1]Dizziness includes the following PTs: dizziness, dizziness postural, vertigo, dizziness exertional, presyncope, balance disorder, vertigo positional.
Source: Reviewer's table, data: EXPLORER adsl and adae
Abbreviations: CI, confidence interval; N, number of subjects; n, number of subjects with an event; FMQ, FDA MedDRA Query; RD, risk difference; CI, confidence interval

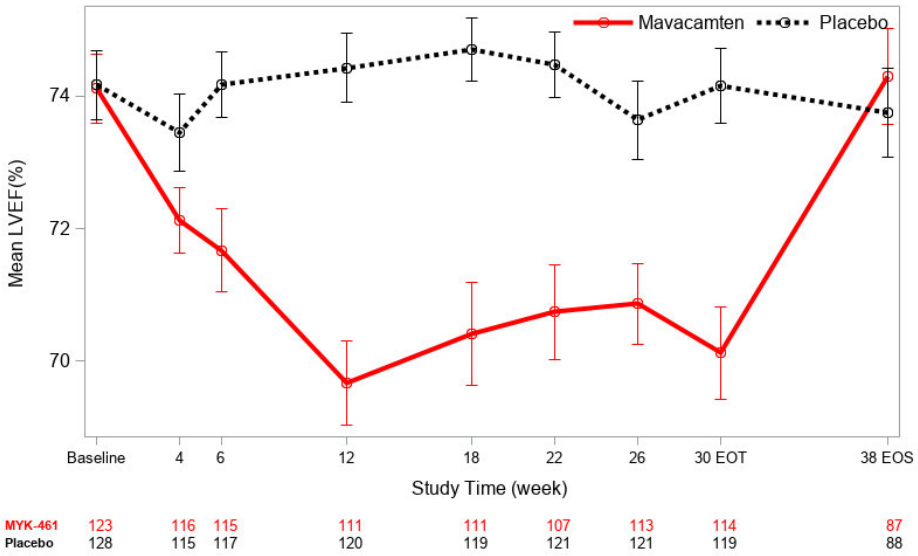
6.6.10. Echocardiograms-LVEF

Consistent with the mavacamten mechanism of action, there was a small mean decrease in LVEF (~4% with SD of 8%) during 30 weeks of mavacamten treatment compared with placebo. Mean LVEF returned to baseline at Week 38, following the 8-week washout period (Figure 8).

Considering the efficacy subgroup finding by beta blocker use (Figure 3), CDFs of maximum decreases in LVEF from baseline by beta-blocker use at baseline was conducted (Figure 8). There is no evidence of greater LVEF decreases among mavacamten-treated subjects who received a beta-blocker at baseline.

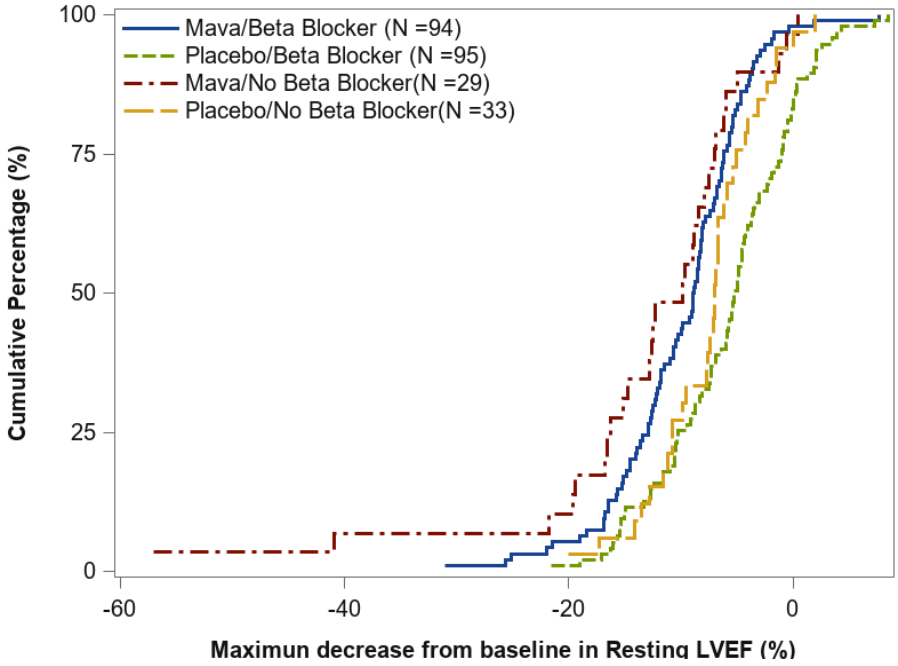
Reviewer's Comment: It is reassuring that mavacamten-induced LVEF reduction is not greater among subjects who were on a beta-blocker given the modest benefit observed in this subgroup and the potential additive negative inotropic effects of mavacamten and beta-blockers.

Figure 8 Mean LVEF across time, EXPLORER-HCM, Safety Population



Source: Reviewer's Figure, data: EXPLORER adsl and adcv

Figure 9 Cumulative Distribution of Maximum Decrease in LVEF from Baseline by Beta Blocker Subgroup, EXPLORER-HCM, Safety Population



Source: Reviewer's Figure, data: EXPLORER adsl and adcv

6.6.11. QT evaluation

A Thorough QT study was not conducted for mavacamten due to safety concerns. The effect of mavacamten on the QTc interval was evaluated in multiple clinical trials in healthy volunteers and in HCM patients. The Interdisciplinary Review Team (IRT) was consulted regarding the applicant's QT evaluation and the proposed labeling claim. In brief, IRT does not expect a QT prolonging effect of mavacamten in the clinically relevant exposure range (<1,000 ng/mL) in the HCM patient population despite some QT effects observed in animals and healthy volunteers (IRT review dated 19 July 2021).

Safety monitoring of potential QT prolongation was implemented in mavacamten clinical trials. No major safety concern was raised from this evaluation. All mavacamten-treated patients meeting the predefined QT prolongation criteria for temporary discontinuation in EXPLORER-HCM and its extension study (N = 10, Table 39) had a relative increase in QTcF (15% increase from baseline) and not an absolute increase above the prespecified thresholds (e.g., QTcF > 520 ms with a narrow QRS interval). The QT prolongation in these mavacamten-treated patients occurred in a wide range of mavacamten plasma concentrations from as low as < 100 ng/mL to >1,000 ng/mL, which suggests an idiopathic nature of these events. Only one patient with QT prolongation (QTcF = 455 ms, 16% increase from baseline QTcF of 392 ms) had a simultaneous elevated Ctrough of 1,330 ng/mL beyond the therapeutic range of > 700 ng/mL. This patient was asymptomatic with a concurrent LVEF of 55% and no reported AEs. A positive relationship between Ctrough and ΔQTcF change cannot be ruled out in this patient.

Mavacamten concentration-dependent QT prolongation was detected at doses up to 25 mg QD in healthy volunteers. However, it should be noted that the same concentration-dependent increase in the QTc interval was not observed in HCM patients. The clinical trial experience showed a trend for lower ΔQTcF with increasing mavacamten concentration in an exposure range up to 1,500 ng/mL. The reason for the differential concentration-QT effects between healthy volunteers and HCM patients is unclear but thought to be related to an adaptive response to marked LV depression from healthy hearts.

Overall, the clinical data suggest that QT is not prolonged with mavacamten treatment in HCM patients within the therapeutic range. A potential risk for QT prolongation would also be mitigated given that a significant reduction of LVEF exceeding a safety threshold (i.e., LVEF <50%) and/or presence of worsening clinical symptoms is to result in interruption of therapy before mavacamten exposure potentially reaches a level that might result in a significant QT prolongation in HCM patients.

6.6.12. Cardiac Rhythm Monitoring

Subjects were provided a cardiac monitoring device to collect continuous heart rate (HR) and rhythm data for approximately 48 hours at baseline, Week 12, and Week 26 in EXPLORER-HCM. Table 34 shows the summary of cardiac rhythm monitoring data. Overall, the incidence of AF or nonsustained ventricular tachycardia (NSVT) is similar between groups at all visits. Mean maximum HR was slightly higher in the mavacamten group compared with the placebo group at Week 26.

Table 34 Cardiac Rhythm Monitoring Results in EXPLORER-HCM, Safety Population

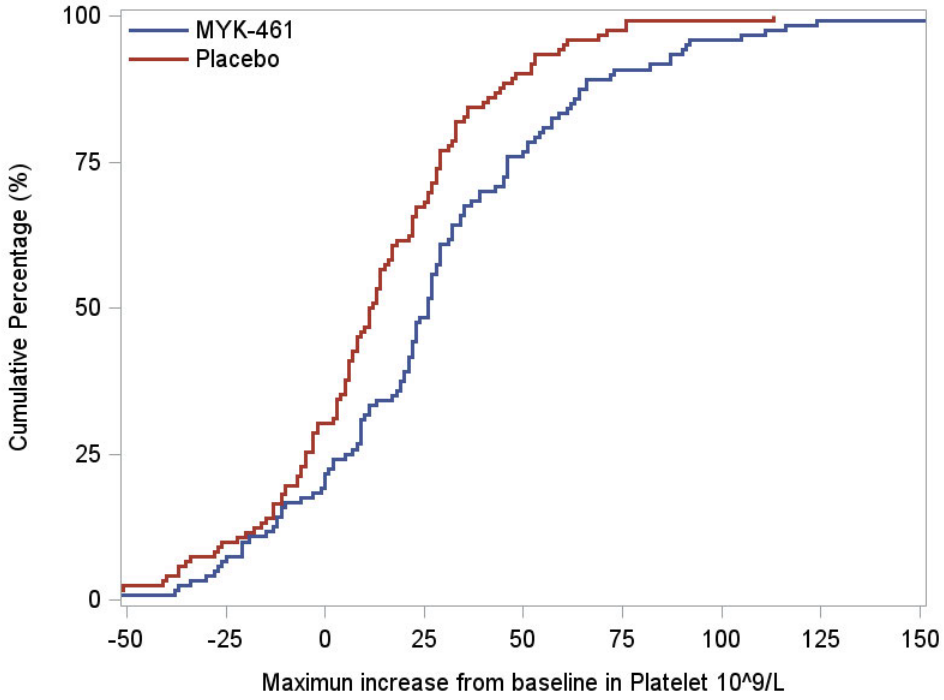
Parameter/Visit	n	Mavacamten (N=123)	n	Placebo (N = 128)
Atrial Fibrillation, n (%)				
Baseline	117	2 (1.7)	122	1 (0.8)
Week 12	99	2 (2.0)	96	2 (2.1)
Week 26	113	4 (3.5)	117	4 (3.4)
NSVT, n (%)				
Baseline	117	36 (30.8)	122	35 (28.7)
Week 12	99	26 (26.3)	96	33 (34.4)
Week 26	113	36 (31.9)	117	38 (32.5)
Maximum Heart Rate (beats/min), mean (SD)				
Baseline	117	117 (19.2)	122	118 (19.3)
Week 12	99	116 (17.4)	96	117 (17.0)
Week 26	110	121 (19.4)	117	115 (19.0)

NSVT = nonsustained ventricular tachycardia
Source: Reviewer's Figure, CSR Table 51 and Table 14.3.4.8, dataset: adsl & adeg

6.6.13. Laboratory Findings

Analyses of laboratory data from the EXPLORER-HCM study did not raise major safety concerns. Median changes from baseline to the end of treatment were similar between the groups for the majority of clinical chemistry and hematology parameters collected in the study. Subjects in the mavacamten group had a greater increase in platelet counts from baseline at Week 30 (median change from baseline of 22 x 10^9/L and 6 x 10^9/L in the mavacamten and placebo groups, respectively). Platelet count was measured at baseline, Week 30 and Week 38 in EXPLORER-HCM. Figure 10 shows the CDF of maximum changes from baseline in platelet counts. No subjects in either group had platelet count > 450 10^9/L at Week 30 (2 subjects in the mavacamten group had platelet count >400 10^9/L) but more subjects in the mavacamten group compared to placebo had >30% increase in platelet count from baseline. No corresponding AE findings were observed in the EXPLORER-HCM and ISS.

Figure 10 Cumulative Distribution of Maximum Increase from Baseline in Platelet Count, EXPLORER, Safety Population



Source: Reviewer's figure, data: EXPLORER adlb
Abbreviations: MYK-461, mavacamten

Table 35. Patients Meeting Platelet Abnormality Criteria, EXPLORER-HCM, Safety Population

	Mavacamten n (%)	Placebo n (%)
Platelet	N=119[1]	N=121[1]
>400-<450 $10^9$9/L	2 (2%)	0 (0%)
>30% increase from baseline	21 (18%)	4 (3%)

Source: Reviewer's analysis EXPLORER datasets adlb
[1] Number of subjects who had a baseline measure and at least one postbaseline measure at Week 30 or Week 38
Abbreviations: N, number of subjects; n, number of subjects with abnormality.

Liver toxicity was assessed by elevations in serum alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) and total bilirubin (TBL). Review of liver enzyme tests demonstrated that no subject met the criteria for drug-induced liver injury assessed by concurrent ALT or AST > 3x ULN and TBL > 2 x ULN (i.e., possible Hy's Law cases). Shift table analysis for liver enzymes also did not reveal major safety concerns (see Appendix III.11.4).

6.6.14. Vital Signs and Physical Examination Findings

Analyses of vital signs data from EXPLORER-HCM found small increases in blood pressure (BP) and HR in the mavacamten group compared to the placebo group (Table 36, Figure 11). No other notable changes were found for other physical examination findings.

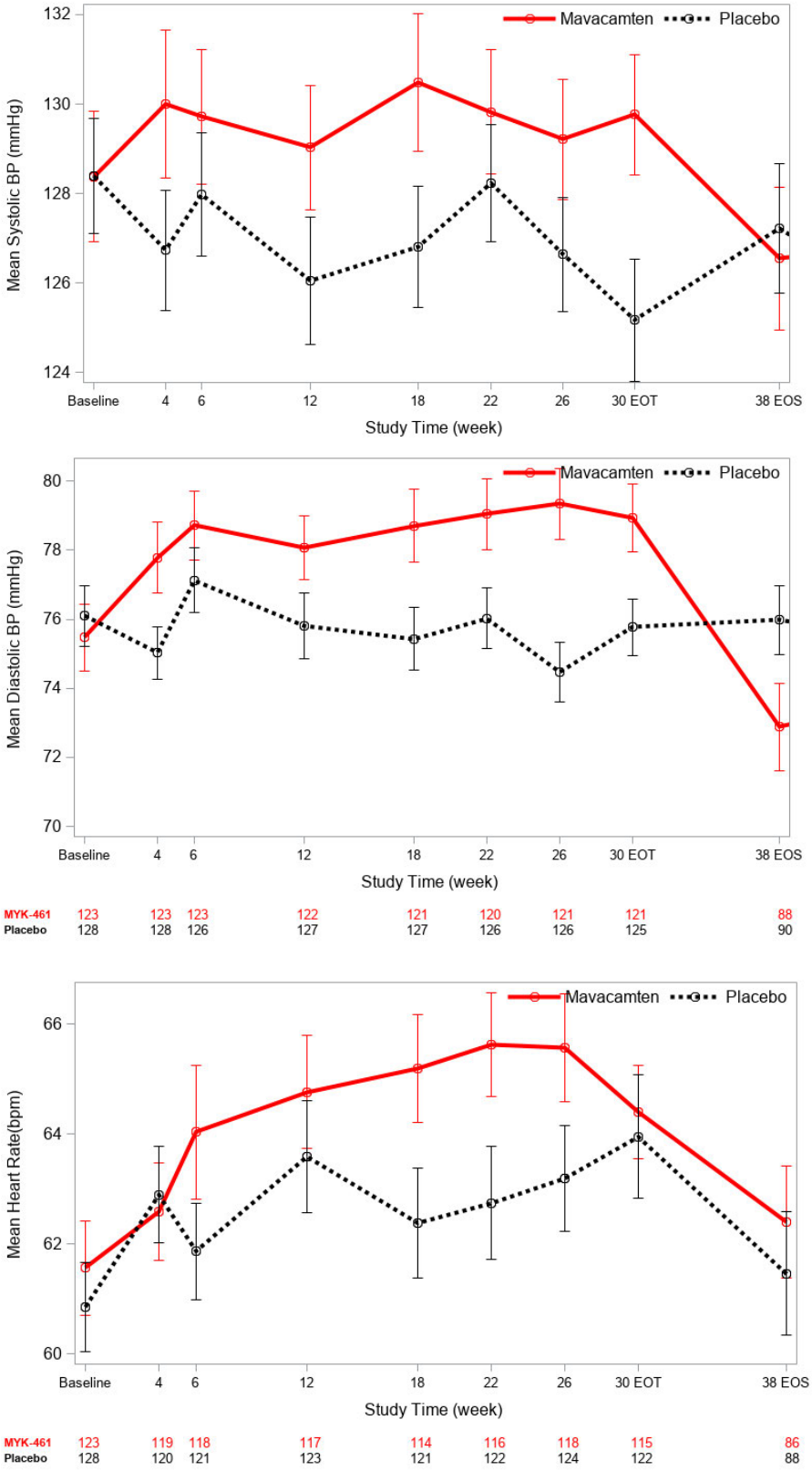
Table 36 Mean Blood Pressure and Heart Rate: Baseline, Last Visit and Change from Baseline, Safety Population, EXPLORER-HCM

	Mavacamten (N=123)	**Placebo (N=128)**	**Mavacamten vs. Placebo** Change from Baseline (ΔΔ) LS Mean (95% CI)
Systolic BP (mmHg)			
N	121	127	4.8 (1.4, 8.2)
Baseline, Mean (SD)	128.4 (16.3)	128.5 (14.6)	
Last Visit (LOCF[a]), Mean (SD)	129.7 (14.8)	124.9 (15.3)	
Change from Baseline LS Mean (SE)	1.3 (1.2)	-3.5 (1.2)	
Diastolic BP (mmHg)			
N	121	127	3.4 (1.2, 5.5)
Baseline, Mean (SD)	75.6 (10.7)	76.0 (9.9)	
Last Visit (LOCF[a]) Mean (SD)	78.9 (10.6)	75.7 (9.1)	
Change from Baseline LS Mean (SE)	3.1 (0.8)	-0.3 (0.8)	
Heart Rate (bpm)			
N	120	127	2.5 (0.1, 4.8)
Baseline, Mean (SD)	63.1 (10.1)	62.4 (10.6)	
Last Visit (LOCF[a]), Mean (SD)	67.0 (10.5)	64.1 (11.2)	
Change from Baseline LS Mean (SE)	4.0 (0.9)	1.6 (0.8)	

a. Last observation carried forward (LOCF)
Source: Reviewer's Table, data: EXPLORER adsl and adlb
Abbreviations: N, number of subjects with the measure; SD, standard deviation; LOCF, last observation carried forward, LS, least square; SE, standard error; CI confidence interval

It is noted that the differences in systolic BP between groups were largely driven by the reduction of systolic BP in the placebo group. Mavacamten-related BP increases are more apparent in diastolic BP. The time-course plots suggest that mean BP and HR returned to baseline at Week 38 after 8 weeks wash-out period. Evaluations of CDF curves for systolic BP, diastolic BP and HR did not reveal major safety concern with worrisome outliers (see Appendix III.11.5 Figure 25)

Figure 11 Mean Vital Signs Across time, EXPLORER-HCM, Safety Population



Source: Reviewer's Figure, data: EXPLORER adsl and advs

Reviewer's Comment: Although there were small increases in BP and HR in the mavacamten group compared to the placebo, no significant corresponding clinical findings were found in the EXPLORER-HCM. Low and similar percent of patients reported tachycardia and hypertension AEs in both treatment groups. Given the limitations of these office measurements in clinical trials and no major safety concerns on the observed small changes in BP and HR, the vital sign results will not be included in the label.

6.6.15. Safety Updates

The 120-day Safety Update (SU) was submitted on May 21, 2021, with the data cutoff date of October 30, 2020. The safety profile of mavacamten presented in this SU is in general consistent with that presented in the original NDA. The principal risk of mavacamten remains HF and/or systolic dysfunction due to excessive exposure. No new safety signals were identified during this period. In response to FDA's clinical IR dated 12 May 2021, the applicant further provided safety data through May 05, 2021 for the ongoing extension study MAVA-LTE and May 04, 2021 for the ongoing study PIONEER-OLE. The updated mavacamten exposure is listed in Table 37. This data cut point represents approximately 1-year of additional follow-up for ongoing extension studies since the data cutoff for the original NDA submission.

Table 37 Updated Duration of Exposure Through May 2021

	EXPLORER-HCM		MAVA-LTE[4] (EXPLORER Cohort)	ISS
Parameter	**Mavacamten N=123**	**Placebo N=128**	**Mavacamten N = 231**	**All Mavacamten N=314**
Duration of treatment (months)[1]				
Mean (SD)	6.9 (0.8)	6.9 (0.6)	12.8 (4.9)	16.8 (8.4)
Median (min, max)	7.0 (0.3, 9.3)	7.0 (1.4, 7.7)	12.8 (1.1, 24.6)	16.9 (0.3, 38.6)
Adjusted duration of treatment[2]				
Mean (SD)	6.8 (0.8)	6.8 (0.8)	12.7(4.8)	16.7 (8.4)
Median (min, max)	7.0 (0.3, 9.3)	7.0 (1.4, 7.7)	12.7 (1.1, 23.8)	16.7 (0.3, 38.6)
Patients treated, by duration[3], n (%)				
Any duration (at least 1 dose)	123 (100%)	128 (100%)	231 (100%)	314 (100%)
<1 month	1 (0.8%)	0 (0%)	0 (0%)	2 (0.6%)
≥1 month	122 (99.2%)	128 (100%)	231 (100%)	312 (99.4%)
≥3 months	121 (98.4%)	127 (99.2%)	225 (97.4%)	295 (94.0%)
≥6 months	120 (97.6%)	125 (97.7%)	213 (92.2%)	280 (89.2%)
≥12 months	0 (0%)	0 (0%)	120 (52.0%)	214 (68.2%)
≥18 months	0 (0%)	0 (0%)	37 (16.2%)	136 (43.3%)
≥24 months	0 (0%)	0 (0%)	1 (0.4%)	56 (17.8%)

1. Duration of treatment is defined as (last dose date - first dose date + 1 day) within a single study, regardless of intermittent discontinuation.
2. Adjusted duration of treatment excludes time off drug due to temporary interruptions
3. Cumulative duration of treatment
4. MAVA-LTE, an ongoing long-term extension trial with a data cutoff date of May 04, 2021 for safety update
Source: Reviewer's table, data: ISS Safety update adex
Abbreviations: N, number of subjects in group; n, number of subjects with given treatment duration; SD, standard deviation; ISS, integrated summary of safety

Cases with serious HF and/or LVEF ≤ 30%:

There were an additional 5 cases of SAEs of HF, systolic dysfunction and/or LVEF ≤30% that occurred in the MAVA-LTE study between NDA data cut and May 2021. A brief summary of these cases is listed below (clinical profile of each case is attached in Appendix III.11.1):

- Subject (b) (6) (cardiac failure SAE): This case is a 70-year-old man with oHCM. His CYP2C19 genotype is unknown. He received 5 mg mavacamten throughout the treatment period and completed the study in EXPLORER-HCM. He experienced non-serious AEs including dizziness, dyspnea and fatigue in EXPLORER-HCM. The subject was started on mavacamten 5 mg in the long-term extension study MAVA-LTE. Due to a data-entry error in the IXRS system, the subject was inappropriately kept on the same dose of 5 mg at Week 4 (dose reduction to 2.5 mg would have occurred without data error). At Week 60, the subject had multiple episodes of premature ventricular contractions (PVCs) and was hospitalized for severe HF with progressively worsening shortness of breath and chest pressure. Chest x-ray results showed the possibility of pneumonia. The subject's PVC was resolved after a successful ablation procedure. Throughout the study, LVEF was in the 50-69% range. No action was taken with study treatment throughout the hospitalization. The subject discontinued study treatment at Week 72 due to worsening fatigue.
- Subject (b) (6) (cardiac failure SAE, LVEF <30%): This case is a 73-year-old male with oHCM and intermediate metabolizer of CYP2C19. He received 5 mg mavacamten throughout the treatment period and completed the study in EXPLORER-HCM. The subject was started on mavacamten 5 mg in the long-term extension study MAVA-LTE. Due to a data-entry error in the IXRS system, the subject was incorrectly up-titrated twice to 15 mg. The subject was diagnosed with HF (LVEF 29%, SAE) at around Week 15. Study drug was interrupted on the same day and mavacamten plasma trough concentration was 1,570 ng/mL on the next day. The subject's LVEF recovered following the event. LVEF measures at subsequent visits were 50% (Week 16) and 65% (Week 24).
- Subject (b) (6) (cardiac failure SAE): This case is a 50-year-old male with oHCM and intermediate metabolizer of CYP2C19. He received 5 mg mavacamten throughout the treatment period and completed the study in EXPLORER-HCM. His on-treatment LVEF measures were > 50% (range 55% to 68%), with the exception of an LVEF of 49% at the last treatment visit at Week 30. He started mavacamten 5 mg in the MAVA-LTE study and reduced the dose to 2.5 mg at Week 4. He was on mavacamten 2.5 mg through Week 24 with stable Ctrough in the range of 150-250 ng/mL and LVEF >55-60%. He was hospitalized with right sided cardiac failure and fluid retention (increased leg edema up to the knees). His LVEF was 60% with no evidence of left HF. The subject was treated with furosemide and the event of cardiac failure was considered resolved 2 days later. There was no action taken with the study drug.
- Subject (b) (6) (SAE of systolic dysfunction, LVEF < 30%): This is a 75-year-old female with oHCM and normal metabolizer of CYP2C19. She received placebo and completed the study in EXPLORER-HCM. She started mavacamten 5 mg and experienced AF with RVR based on a site-read echocardiogram at Week 4. The subject was hospitalized the same day for the SAE of AF with RVR and discharged 3 days later. Her LVEF was 67%, Ctrough was <500 ng/mL and NT-proBNP was 1,620 ng/L (her baseline NT-proBNP was > 3,200 ng/L). Mavacamten was interrupted for one day due to this SAE. One week later, the subject was hospitalized due to a SAE of acute kidney

injury and an SAE of decreased LVEF (LVEF = 34%). The SAE of acute kidney injury was resolved the next day but the subject's LVEF continued to decrease with a LVEF of 17%. LVEF was in the range of 20-25% two days later and study drug was permanently discontinued. LVEF measures at subsequent visits were 45% (~1 month after) and 65% (~ 3 months after).

- Subject (b) (6) (SAE of ejection fraction decreased): This case is a 74-year-old male with oHCM and unknown CYP2C19 phenotype. He received placebo and completed the study in EXPLORER-HCM. The subject started 5 mg mavacamten and later was up-titrated to 10 mg at Week 8 in MAVA-LTE. His LVEF was around 50% and his Ctrough was at the high end of the target range (~ 800 ng/mL) at Week 24 and Week 36. The subject had new onset of atrial flutter at Week 48 and the site read LVEF was stable at 50%. His NT-proBNP was 1,904 ng/L, an increase from the Week 36 value of 380 ng/mL and higher than the baseline value of 421 ng/mL. There was no action taken with the study drug and the subject continued 10 mg. The subject experienced recurrent atrial flutter at Week 50 and had a LVEF of 35%. Mavacamten was temporarily discontinued per protocol. The NT-proBNP was further increased to 3,461 ng/mL. There was no evidence of any new potential DDIs. The subject's Ctrough was 826 ng/mL, which was stable from the previous visit. The subject did not restart mavacamten after the event and his LVEF returned to 50% about 20 days after the event. About one month after the event, ECG showed first degree atrioventricular block with HR of 62 bpm at an unscheduled visit. The subject subsequently decided to withdraw from the study.

Cases in VALOR-HCM

VALOR-HCM is a new and ongoing Phase 3 study conducted after NDA submission in adults with symptomatic obstructive HCM who are eligible for septal reduction therapy. Although VALOR-HCM is not part of the ISS, the safety data are relevant. There have been two reported cases of LVEF ≤30% in VALOR-HCM during review of this NDA.

- Subject (b) (6)
  This case is a 72-year-old man with relevant medical history of asymptomatic non-sustained ventricular tachycardia, aortic valve insufficiency, hypertension and mitral valve regurgitation. The patient had asymptomatic AF at Week 28 scheduled visit and underwent successful direct current cardioversion to normal sinus rhythm one month later (Day 226). Three days later, on Day 229, the subject began to experience increased shortness of breath, dyspnea on exertion, palpitations, fatigue and malaise. On Day 331, the subject experienced symptomatic persistent AF with rapid HR and decreased ejection fraction (<30%). Study treatment was permanently discontinued. On Day 332, the subject underwent direct current cardioversion but did not convert to normal sinus rhythm and was hospitalized the next day with HF. A causal relationship to mavacamten is biologically plausible based on the mechanism of action.

- Subject (b) (6)
  This case was an 82-year-old female, a CYP2C19 intermediate metabolizer phenotype with relevant medical history including oHCM (diagnosed in 2014), alcohol septal ablation (2017), mitral regurgitation, coronary artery disease and dizziness. The subject had no history of syncope, non-sustained ventricular tachycardia, or malignant

arrhythmias. She received placebo from Day 1 to Week 16 and began dosing with 5 mg mavacamten from Week 16 to Week 28. She was up-titrated per protocol to 10 mg at the Week 28 visit. At the Week 56 visit, the site-read LVEF was 30% (echocardiogram core lab read showed 51%) and LVOT rest and Valsalva gradients were 0 mmHg. Her LVEF was 69% at baseline and 60% at Week 44. Worsening mitral regurgitation (MR) was noted from screening (1+ MR) to Week 56 (3-4+MR). She was assessed as NYHA class III. ECG showed no evidence of prolonged QTcF. Mavacamten was permanently discontinued due to the event of site-read LVEF ≤ 30% (non-serious). The subject's Ctrough was 482 ng/mL. The subject continued her standard of care HCM therapy of disopyramide 150 mg three times daily and verapamil 180 mg twice daily. Two days after the Week 56 visit, the subject was evaluated by a pulmonologist for cough, dyspnea, and fatigue since finding mold in her home two weeks earlier. She was found to have mild forced expiratory wheeze, consistent with mild asthma, assessed to be possibly secondary to mold exposure. She also had bilateral lower extremity edema. The patient received inhaled steroid, and did not require hospitalization. She remained clinically stable; however, two days later (five days after the last dose of mavacamten), the subject died during her sleep. An autopsy was performed. The gross report noted cardiomegaly, LV 1.5 cm thick, dilated thoracic ascending aorta. There was no coronary artery disease, and no evidence of MI. Pneumonia was found, although it was grossly difficult to assess lobar versus diffuse pneumonia due to fibrosis. Due to the temporal relationship between reduced LVEF with severe MR and sudden death, the investigator assessed the presumptive cause of death to be sudden cardiac death likely due to ventricular fibrillation; related to mavacamten. Although the autopsy was remarkable for probable pneumonia, the patients had no fever, no elevated WBC and no symptoms of respiratory distress. Alternatively, the investigator agreed that pneumonia with a poorly functioning left ventricle could contribute to death.

Reviewer's Comment: Although the extent of decrease of LVEF is unclear in the fatal case in VALOR-HCM, the contributory role of mavacamten in the event of decreased LVEF and sudden cardiac death cannot be ruled out due to the temporal relationship. It should be noted that VALOR-HCM is studying severely symptomatic drug-refractory oHCM patients and the addition of mavacamten to all HCM standard of care medications (including beta-blockers, calcium channel blockers and disopyramide taken as monotherapy or in combination) and this case was complicated. This patient received mavacamten with verapamil and disopyramide concomitantly during the study and continued to receive these two negative inotropes at the time of LV dysfunction after discontinuation of mavacamten. We recommend avoiding concurrent use of mavacamten in patients on disopyramide, ranolazine, verapamil with beta blockers or diltiazem with beta blockers as these agents and combinations were excluded from the EXPLORER-HCM study.

6.7. Review Issues Relevant to the Evaluation of Risk

6.7.1. Proposed Dosing Strategies

Issue: EXPLORER-HCM implemented dosing strategies based on frequent monitoring of both PK and PD (every 4-6 weeks) to ensure safety by titrating to the lowest effective dose in each individual. However, the dosing strategies in the proposed USPI for mavacamten were based on PD alone (LVEF, VLVOT) and with a longer monitoring interval (every 12 weeks (b) (4) once an individualized maintenance dose is achieved. Whether or not the proposed monitoring intervals and dosing strategies without concurrent PK monitoring could ensure safe use of mavacamten is a review issue.

Background: Systolic dysfunction is the identified risk based on mavacamten's mechanism of action. Thus, dosing was carefully monitored according to the pre-specified PK and PD criteria to ensure safe use and clinical benefits for individual subjects in the phase 3 study EXPLORER-HCM. The sponsor has an ongoing long-term extension study (MAVA-LTE) that recruited patients who have completed EXPLORER-HCM, and the Phase 2 trial MAVERICK-HCM in the nHCM population. In this extension study, particularly among the cohort who previously completed the EXPLORER-HCM study, dosing adjustment was primarily based on PD, similar to what was proposed for mavacamten's USPI. It should be noted that Ctrough was measured in MAVA-LTE but was not used for dose adjustment. A summary of the key dose-titration guidelines used in EXPLORER-HCM, the long-term extension trial MAVA-LTE, and the proposed labeling (at the time of submission) is shown in the table below:

Table 38 Key Titration Regimen Criteria in EXPLORER, MAVA-LTE and the Proposed Product Labeling

	EXPLORER-HCM Phase 3 study	MAVA-LTE[1] Extension study	Proposed Label[2]
Starting dose	5 mg QD	5 mg QD	5 mg QD
Up-titration	As early as Week 8 if Ctrough <350 ng/mL and VLVOT ≥ 30 mmHg LVEF ≥ 50% Next up-titration could occur at Week 14	As early as Week 8 if VLVOT ≥ 30 mmHg LVEF ≥ 50% Next up-titration could occur at Week 12 and Week 24	As early as Week 12 if VLVOT gradient ≥ 30 mmHg LVEF ≥ 55% Minimum 12 weeks between up-titrations
Temporary discontinuation	LVEF < 50% QTcF prolongation Ctrough ≥ 1,000 ng/mL	LVEF < 50% QTcF prolongation Ctrough ≥ 1,000 ng/mL	LVEF < 50%
Early Down titration	700 < Ctrough <1000 ng/mL At any visit Dosing may be resumed at a lower doe after treatment interruptions due to PK/PD criteria	Week 4 if VLVOT gradient <**30** mmHg Dosing may be resumed at a lower doe after treatment interruptions due to PK/PD criteria	Week 4-(b) (4) if VLVOT gradient < **20** mmHg Dosing may be resumed at a lower dose after treatment interruptions due to PD criteria
Other dosing instructions	No up-titration was allowed after week 14 LVEF was monitored on day 1, week 4, week 6 and then every 4-6 weeks onward	Up-titration at week 24 was based on stress echocardiogram evaluation (post-exercise LVOT gradient ≥50 mmHg) Up-titration was allowed after week 24 if VLVOT ≥ 30 mmHg LVEF was monitored every 4 weeks up to Week 16 then every 12 weeks after Week 24	Assess LVEF 4 (b) (4) weeks after any dose increase, and return to monitoring every 12 weeks (b) (4)

1 This table shows the dose strategies for EXPLORE-LTE Cohort (oHCM patients) in the MAVA-LTE study

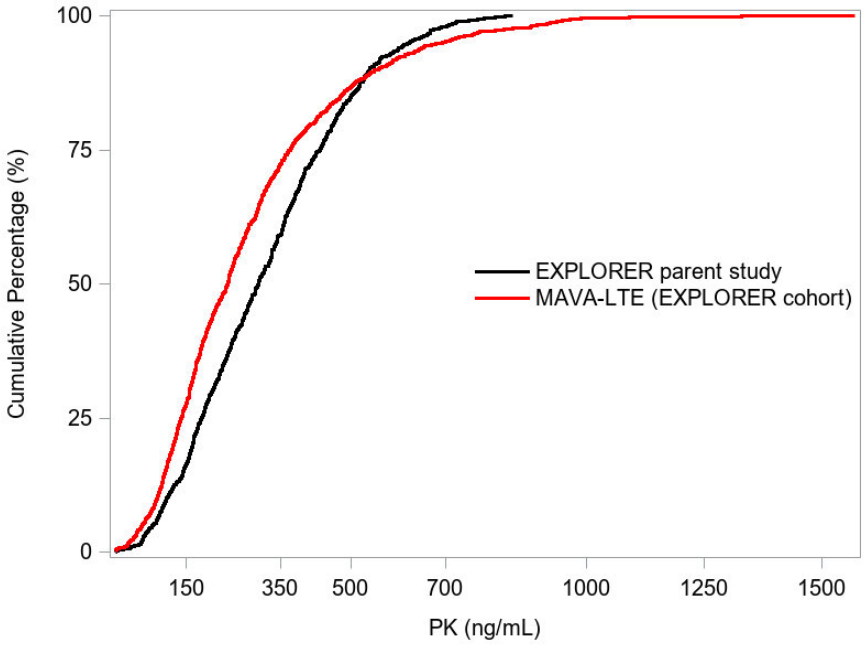
2 Based on the original submission on 1/28/2021

Assessment:

Distribution of mavacamten plasma concentration in EXPLORER-HCM vs. MAVA-LTE

Figure 12 shows that the distributions of mavacamten trough concentrations in EXPLORE-HCM and MAVA-LTE were largely similar, but it is noted that the distribution in MAVA-LTE shifted to the left slightly and with a longer tail. The higher proportion of subjects with plasma concentration < 350 ng/mL in MAVA-LTE could be attributed to the early-down titration strategy implemented in the study where subjects with an early response (VLVOT < 30 mmHg at Week 4) were down titrated from a dose of 5 mg to 2.5 mg in the study. On the contrary, there were no subjects in EXPLORER-HCM who had an early down titration from 5 mg to 2.5 mg based on Ctrough at Week 6. A higher percentage of subjects who had Ctrough above 700 ng/mL in MAVA-LTE vs. EXPLORER-HCM is due to lack of PK monitoring (700-1000 ng/mL) for down titration in MVAV-LTE.

Figure 12 Cumulative Distribution of Mavacamten Concentrations in EXPLORER and MAVA-LTE[1]



1.Using updated safety data through May 2021 (section 0)
Source: Reviewer's Figure, data: ISS seq0023: adsl and adpc
Abbreviations: PK, pharmacokinetics (trough plasma concentration)

Pre-specified criteria for temporary dose discontinuation and dose reduction

Table 39 shows the incidence and event rate of subjects who met the pre-specified criteria for dose discontinuation and reduction in EXPLORER-HCM and MAVA-LTE. Overall, the incidence of all these pre-specified criteria remained low and similar between the studies. It is noted that no subjects had Ctrough > 1,000 ng/mL in EXPLORER-HCM compared to 10 subjects (4%) in MAVA-LTE. This finding is attributed to the fact that Ctrough was not monitored for down titration in MAVA-LTE (no dose reduction based on Ctrough between 700 and 1000 ng/mL) so there was likelihood that Ctrough could continue to rise above 1,000 ng/mL. The majority of these patients with Ctrough > 1,000 ng/mL either did not have relevant concurrent AEs or had AEs associated with the expected PD effect of LVEF reduction. Eight of these 10 patients had concurrent LVEF ≤ 55% (3 with LVEF < 50%). In both studies, Ctrough

between 700 and 1,000 ng/mL did not seem to consistently precede LVEF < 50%. Less than 20% of subjects who had Ctrough between 700 and 1,000 ng/mL also experienced LVEF < 50% in both studies. A similar proportion of patients in both studies met the QTcF prolongation criteria (see section 6.6.11 for QT evaluation). There have been no cases of Torsade de pointes in either study.

Table 39 Incidence of Subjects Who Met the Pre-specified Criteria for Temporary Dose Discontinuation and Dose Reduction in EXPLORER and MAVA-LTE

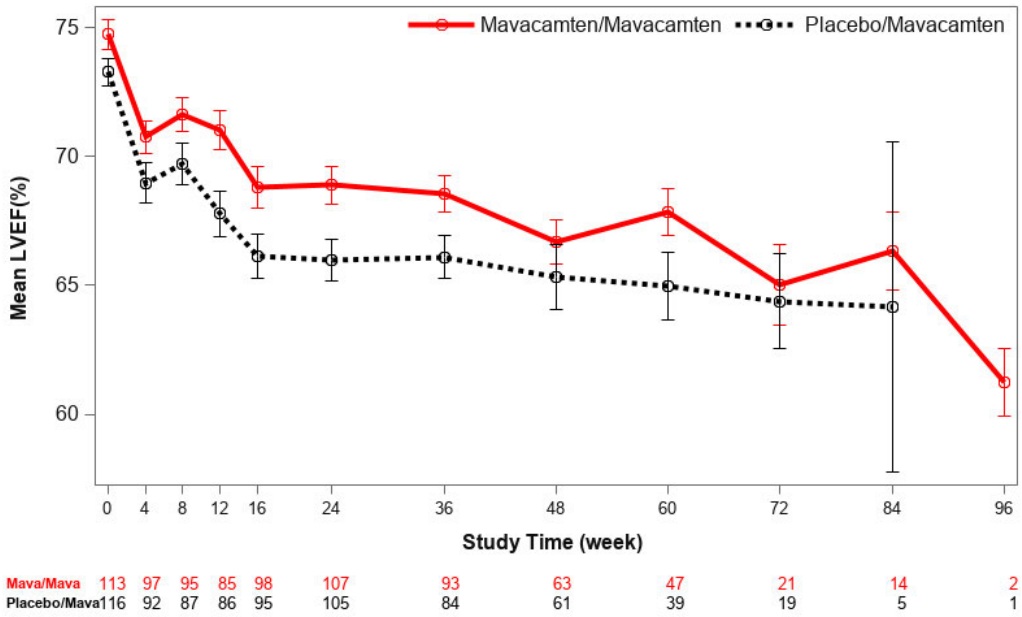
Protocol-Specified Criteria	EXPLORER-HCM (PK/PD Monitoring)				MAVA-LTE[1] (EXPLORER Cohort, PD Monitoring)	
	Mavacamten (N=123)		Placebo (N=128)		Mavacamten (N=231)	
	n (%)	ER (100 pt-yrs)	n (%)	ER (100 pt-yrs)	n (%)	ER (100 pt-yrs)
Temporary Treatment Discontinuation						
- Resting LVEF < 50%	7 (5.7)[2]	10.0	2 (1.6)	2.8	14 (6.1)	4.0
- QTcF prolongation	3 (2.4)	4.3	3 (2.3)	4.1	7 (3.0)[3]	2.3
- Ctrough ≥ 1,000 ng/mL	0 (0)	---	---	---	10 (4.3)	2.9
Dose Reduction due to Ctrough (700-<1,000 ng/mL)	17 (13.8)[4]	24.3	---	---	32 (13.9)[5]	9.2
- Resting LVEF < 50%	3 (2.4)	4.3	---	---	4 (1.7)[5]	1.2

Source: Reviewer's Table, the Applicant's response to the information request dated 02 and 04 March 2022
1.Using updated safety data with data cutoff date of October 29, 2021
2.Four of 7 subjects had LVEF < 50% at Week 30.
3. Excluding one subject who met the study criteria on Day 1 prior to dosing of mavacamten
4. Number of subjects who met the Ctrough criterion for dose reduction. A total of 13 subjects (10.6%) had actual dose reduction
5. Number of subjects who met the Ctrough criterion. No dose reduction based on Ctrough in MAVA-LTE
Abbreviations: N, number of subjects in group; n, number of subjects with given treatment duration; PK, pharmacokinetics; PD, pharmacodynamics; ER, event rate, LVEF, left ventricular ejection fraction; QTcF: Fridericia-corrected QT interval

LVEF Reduction

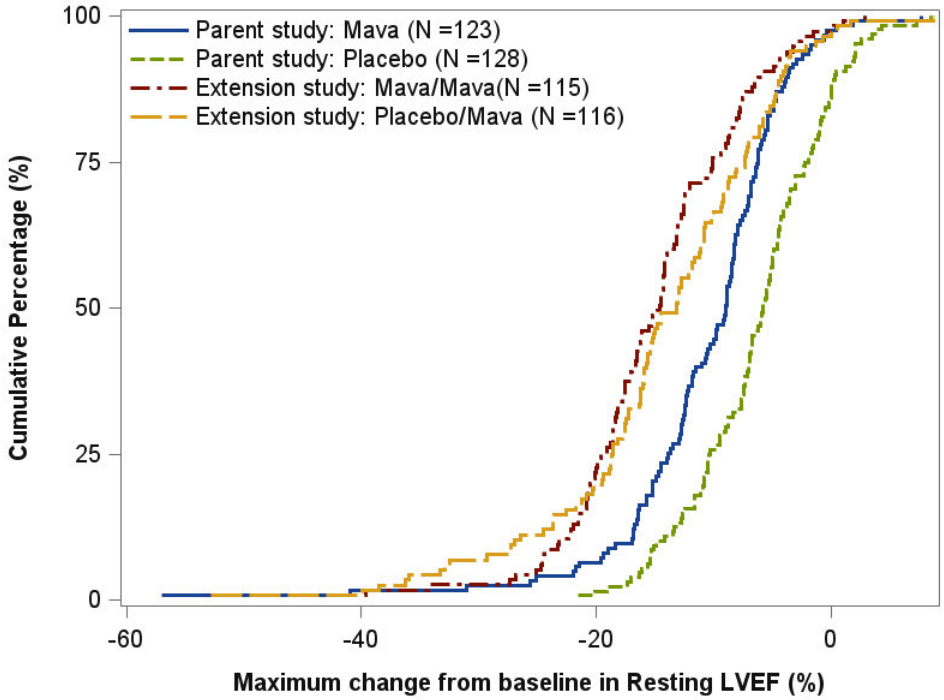
The average reduction of LVEF at the last visit (i.e., LOCF) from baseline in the mavacamten arm was about 7% in MAVA-LTE compared to 4% in EXPLORER-HCM (section 6.6.10). The cumulative distribution function of maximum change of LVEF (Figure 13) also indicates that a greater reduction in LVEF was observed in MAVA-LTE compared to EXPLORER-HCM.

Figure 13 Mean of LVEF Across Time in MAVA-LTE[1]



[1].Using updated safety data through May 2021 (section 0)
Source: Reviewer's Figure, ISS datasets seq0023: adsl and adcv
Abbreviations: LVEF, left ventricular ejection fraction

Figure 14 Cumulative Distribution of Maximum Decreases in Resting LVEF (%) in EXPLORER-HCM and MAVA-LTE[1]



[1].Using updated safety data through May 2021 (section 0)
Source: Reviewer's Figure, ISS datasets seq0023: adsl and adcv
Abbreviations: LVEF, left ventricular ejection fraction

Risk of cardiac failure/systolic dysfunction

To compare the risk of HF due to systolic dysfunction between studies, we identified subjects who had experienced serious cardiac failure defined as the occurrence of an SAE of cardiac failure (based on cardiac failure SMQ narrow), an SAE of systolic dysfunction (preferred term), or LVEF ≤ 30% (measured at study sites and/or external hospitals). In EXPLORER-HCM, only one patient had serious cardiac failure in each group resulting in an event rate of 1.1 per 100 pt-yrs in both groups. In MAVA-LTE, there were 5 patients with serious cardiac failure resulting in an event rate of 1.99 per 100 pt-yrs. In the ISS including all HCM patients, there were 8 patients with serious cardiac failure with an event rate of 1.7 per 100 pt-yrs.

Table 40 Incidence and Event Rate of Serious Cardiac Failure[1]

EXPLORER-HCM (PK/PD Monitoring)				MAVA-LTE[2] (EXPLORER Cohort, PD monitoring)		ISS[2] oHCM+nHCM		All RCT Placebo	
Mavacamten (N=123) n (%)		Placebo (N=128) n (%)		Mavacamten (N=231) n (%)		Mavacamten (N=314) n (%)		Placebo (N =147)	
n (%)	ER (per 100 pt-yrs)	n (%)	ER (per 100 pt-yrs)	n (%)	ER (per 100 pt-yrs)	n (%)	ER (per 100 pt-yrs)	n (%)	ER (per 100 pt-yrs)
1 (0.8)	1.14	1 (0.8)	1.09	5 (2.2)[3]	1.99	8 (2.5)	1.70	1 (0.7)	0.99

1. Serious cardiac failure was defined as the occurrence of an SAE of cardiac failure (SMQ, narrow), an SAE of systolic dysfunction (preferred term) or any LVEF ≤ 30% from hospital, local or central lab.
2.Using updated safety data through May 2021 (section 0)
3.Two cases were associated with data entry error resulting in incorrect up-titration of mavacamten
Source: Reviewer's Table, Response to FDA's IR dated 12 May 2021
Abbreviations: N, number of subjects in group; n, number of subjects with the event; PK, pharmacokinetics; PD, pharmacodynamics; ISS, integrated summary of safety; oHCM, obstructive hypertrophy cardiomyopathy; nHCM, non-obstructive hypertrophy cardiomyopathy, ER, event rate

Case review of the 8 patients with serious cardiac failure in the ISS revealed several important findings that are listed below:

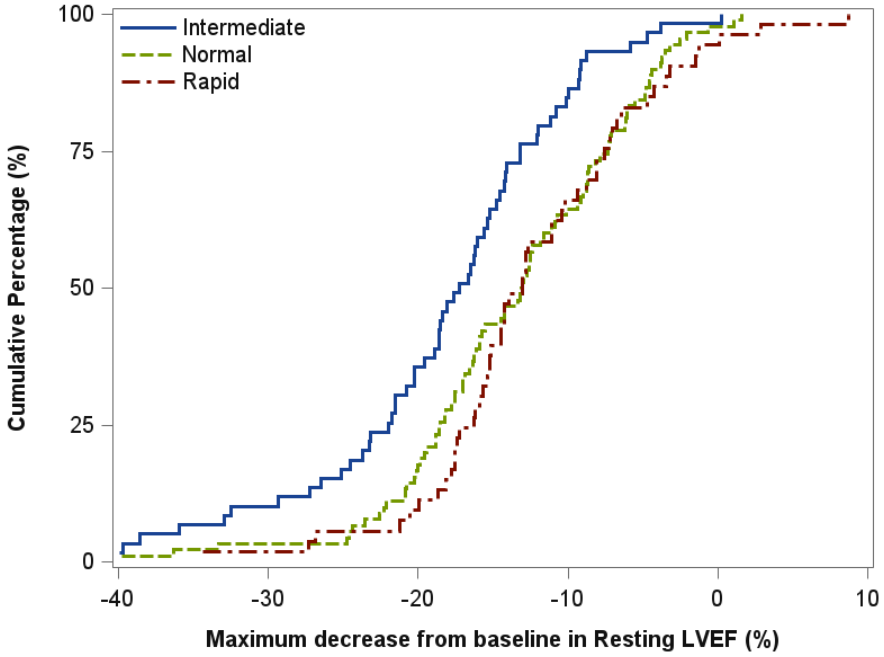
- Six of the 8 cases were associated with LVEF dysfunction: four with LVEF <30% and two with LVEF < 45% (The remaining two cases had LVEF > 50%)
  - Three of the 6 cases had LVEF decline after achieving a stable dose for more than 30 weeks.
  - LVEF decrease seemed reversible in all cases after discontinuation of mavacamten based on available subsequent LVEF assessments showing recovery or recovering.
- Six of the 8 cases had a new onset or worsening of arrhythmia prior to the serious cardiac failure
  - AF (n=3)
  - Atrial flutter (n = 2)
  - Ventricular extrasystoles (n = 1)
- Four of the 8 cases had significantly elevated NT-proBNP or worsening HF symptoms prior to the serious cardiac failure.

- None of the cases was clearly associated with excessive mavacamten exposure due to the impact of DDI (e.g., CYP2C19 inhibitor).
- CYP2C19 genotype: rapid (n = 1), normal (n = 2), intermediate (n = 2), poor (n = 1) and unknown (n = 2). CYP2C19 genotype for six patients with LVEF dysfunction:
  - LVEF < 30%: rapid (n = 1), normal (n=1), intermediate (n=1), poor (n=1)
  - 30% <LVEF < 45%: normal (n=1) and unknown (n = 1)

Event rates of other clinical events of interest (e.g., MACE, AF, or syncope) were similar or lower in MAVE-LTE compared to EXPLORER-HCM (Appendix III.11.3 Table 50).

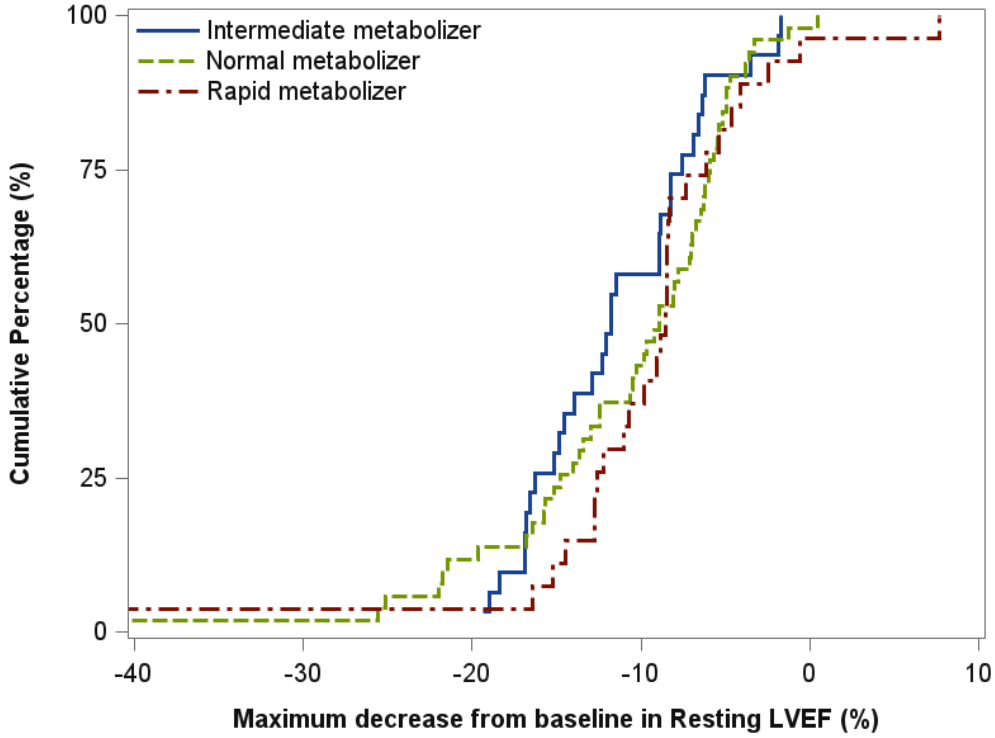
Uncertainties: Mavacamten is extensively metabolized, primarily through CYP2C19 (~74%) and CYP3A4 (~18%). The CYP2C19 metabolizing status impacts mavacamten clearance and PK variability. The clearance time is increased in poor metabolizers (~23 day) compared to that in normal metabolizers (~6-9 days). The clinical safety data on poor metabolizers are limited. Only 5 poor metabolizers have been exposed to mavacamten in the ISS with a median exposure of ~10 months. One out of 5 poor metabolizers experienced LVEF <50% at the end of treatment at Week 30 in EXPLORER-HCM and later developed a HF SAE and LVEF < 30% in a complex clinical scenario (see narrative for Subject 005-403-503). In MAVA-LTE using primarily PD monitoring, subjects with a slower metabolizing rate (i.e., intermediate CYP2C19 phenotype, n=59) had greater LVEF decreases compared to normal and rapid metabolizers (n = 143) (Figure 15). The differences in LVEF reduction by CYP2C19 genotype were less apparent in EXPLORER-HCM where PK was also monitored along with PD markers (Figure 16). Of note, 6 out of 10 patients who met the temporary discontinuation criterion for Ctrough >1,000 ng/mL were a CYP2C19 intermediate metabolizer. Review of these cases indicated that many patients had consecutive up-titrations at Week 8 and Week 12; this up-titration regimen did not allow sufficient time to achieve steady-state in light of the long half-life of mavacamten. The Applicant proposed delaying up-titration until Week 12 and a minimum of 12 weeks between up-titrations to enhance safety relative to the titration regimens used in the clinical studies based on their PK/PD simulations (Table 38). In order to further improve safety, LVEF ≥ 55%, a more conservative threshold than 50% used in clinical studies, is recommended in the proposed labeling when considering a dose increase. In addition, mavacamten has a complex PK profile in the setting of DDIs with inhibitors of CYP2C19 and CYP3A4 as well as inducers of CYP2C19 and CYP3A4, which poses additional challenges in therapeutic management of the drug (Clinical Pharmacology review dated 18 October 2021 and 24 February 2022).

Figure 15 Cumulative Distribution of Maximum Decreases in Resting LVEF (%) by CYP2C19 Genotype, MAVA-LTE[1], Safety Population



[1].Using updated safety data through May 2021 (section 0)
Source: Reviewer's Figure, data: ISS seq0023: adsl and adcv
Abbreviations: N, number of subjects in group; LVEF, left ventricular ejection fraction

Figure 16 Cumulative Distribution of Maximum Decreases in Resting LVEF (%) by CYP2C19 Genotype, EXPLORER, Safety Population



Source: Reviewer's Figure, data: EXPLORER adsl and adcv
Abbreviations: N, number of subjects in group; LVEF, left ventricular ejection fraction

Conclusion: The clinical data comparing the results in EXPLORER-HCM (PK/PD monitoring) to those in MAVA-LTE (PD monitoring) do not reveal significant differences in terms of mavacamten concentration distribution and the incidence of meeting prespecified safety criteria in the study. However, it is noted that MAVA-LTE had a higher number of subjects with plasma mavacamten concentration exceeding the safety threshold (> 1,000 ng/mL). In addition, LVEF decline was slightly greater in MAVA-LTE compared to that in EXPLORER-HCM; greater decreases were seen in patients with a slower metabolizing rate of CYP2C19. Despite these observed differences, there was no excessive risk of experiencing cardiac failure/systolic dysfunction SAEs in MAVA-LTE as compared to EXPLORER-HCM. The risk associated with exaggerated pharmacologic effects of mavacamten was generally contained and acceptable in MAVA-LTE using primarily PD-guided dosing strategies.

While the proposed dosing strategies based on PD monitoring seems reasonable for the majority of oHCM patients, we have concern that it may not be adequate for patients who have a slower metabolizing rate of CYP2C19 particularly those with a CYP2C19 poor metabolizer. This subset of patients will require a different initial dose and/or a more conservative dosing algorithm to ensure safe use of mavacamten. The Clinical Pharmacology review also concluded that the proposed posology is acceptable for the majority of oHCM patients except for those with a CYP2C19 poor metabolizer (refer to Clinical Pharmacology review dated 18 October 2021). The review team has discussed the potential need for prospective genotyping. However, given that the regulatory requirements for a companion diagnostic would lead to a significant delay for patients who have limited treatment options and considering the low prevalence of the poor

CYP2C19 metabolizer phenotype (1-5% of the US population), the review team sought other options that do not require prospective genotyping. Considering that the efficacy of mavacamten is not lifesaving, the review team decided on a conservative, universal dosing approach with an increased frequency of echocardiographic monitoring and slow up-titration to ensure safe dosing in all patients regardless of CYP2C19 metabolizing status (refer to Clinical Pharmacology review dated 24 February 2022). This conservative approach does not require a diagnostic test to assure safe and effective use of mavacamten. It should be noted that cardiologists would be the main prescribers of mavacamten, if approved, who have expertise and experience in clinical diagnosis and management of systolic dysfunction. Furthermore, the complex issues related to DDIs present challenges to safe use in postmarketing setting. Patients could easily access a variety of nonprescription drugs that could significantly change mavacamten exposure and alter the benefit-risk profile of mavacamten.

The risk of systolic dysfunction and drug interactions and need for periodic echocardiographic monitoring will be described in labeling in a box warning. The review team has determined that a REMS will be required to ensure the benefits of mavacamten outweigh the risks by mitigating the risk of heart failure through monitoring using periodic echocardiograms and attention to potential drug interactions. With regard to monitoring frequency of echocardiograms, we recommend requiring clinical monitoring at weeks 4, 8, 12 and then every 12 weeks for the duration of treatment given a SAE of HF or asymptomatic systolic dysfunction could occur after a long stable period of drug exposure (i.e., one subject developed SAE of reduced ejection fraction at Week 60). Clinical monitoring is to be sooner if the dose is up-titrated, treatment is interrupted due to LVEF < 50% or if the patient experiences heart failure symptoms or worsening clinical status. We also recommend interrupting therapy in patients with intercurrent illness (e.g., serious infection) or arrhythmia.

7. Therapeutic Individualization

Please refer to the Clinical Pharmacology review dated 18 October 2021 for detailed discussions on intrinsic factors and complex issues related to drug interactions. In brief, Mavacamten is extensively metabolized, primarily through CYP2C19 (~74%), CYP3A4 (~18%) and CYP2C9 (~8%). The CYP2C19 metabolizing status has been shown to impact mavacamten clearance and PK variability. The terminal half-life is 6 to 9 days in normal metabolizers of CYP2C19 and 23 days in poor metabolizers of CYP2C19. Increased mavacamten exposures were observed in poor metabolizers of CYP2C19 compared to normal metabolizers. Prospective genotyping for CYP2C19 and/or a modified dosing algorithm and safety monitoring are required to help in optimizing safe and effective use of mavacamten. Either contraindications or dose reduction is needed for mavacamten during its concomitant administration with modulators of CYP2C19 and CYP3A4. No dose adjustment is required based on age, renal impairment (mild and moderate) and hepatic impairment (mild and moderate).

The Applicant’s original proposed dosing regimen resulted in a remarkably higher proportion of patients with a CYP2C19 poor metabolizer genotype experiencing LVEF <50% during treatment, especially from Week 8 and Week 24. The Office of Clinical Pharmacology previously recommended prospective genotyping for CYP2C19 status before initiation of mavacamten treatment with different dosing regimens for patients with a CYP2C19 poor

metabolizer compared to others (e.g., a lower initial dose) (refer to the review dated 18 October 2021). Given that the benefits of mavacamten are associated with symptom relief and not a mortality benefit, the review team subsequently decided on a universal posology that implemented a more frequent monitoring schedule and a slow titration to ensure safe dosing in all patients irrespective of CYP2C19 genotype (refer to Clinical Pharmacology review dated 24 February 2022). LVEF < 50% at any time and Valsalva LVOT gradient < 30 mmHg from Week 12 onwards were selected as the threshold for the safety and efficacy biomarkers, respectively, to develop the optimal posology for all patients.

A starting dose of 5 mg once daily (i.e., the initial dose in EXPLORER-HCM) followed by clinical visits (including echocardiograms) scheduled at Week 4, Week 8, Week 12, and every 12 weeks thereafter is recommended for all patients. The posology includes an additional clinical visit at Week 8 during the initiation of treatment and allows for early opportunities to down-titrate at Week 4 and Week 8 if the Valsalva LVOT gradient is < 20 mmHg to minimize the risk for patients with a slow rate of mavacamten accumulation after exposure. Up-titration is allowed for eligible patients at Week 12 based on Valsalva LVOT (> 30 mmHg) and LVEF (≥ 55%). Thereafter the minimal interval between up-titrations is 12 weeks. In order to ensure safety at the new dose level, an additional clinical visit with echocardiogram assessment of Valsalva LVOT and LVEF is required 4 weeks following any dose increase. At any clinical visit, treatment will be temporarily interrupted if a patient has LVEF < 50%. The patient will have an additional visit at 4 weeks after temporary discontinuation and can restart at the next lower dose level if LVEF returns to > 50% at the follow-up visit. If a patient experiences LVEF < 50% twice on the 2.5 mg QD dose, the patient will permanently discontinue study treatment.

7.1. Pediatric Labeling / Plans for Pediatric Drug Development

Due to the PREA orphan exemption, the sponsor is not required to conduct a pediatric study. Thus, no Pediatric Study Plan has been submitted.

7.2. Pregnancy and Lactation

Please refer to the Division of Pediatrics and Maternal Health (DPMH) review dated 20 August 2021 and Non-Clinical review dated 22 September 2021 for detailed discussion. Non-clinical data suggest that mavacamten has a high probability of being a teratogen when administered during gestation as evidenced in animal developmental studies. There are no clinical data on pregnant women exposed to mavacamten. Based on these findings, DPMH recommends issuing a PMR for a descriptive pregnancy safety study (Appendix III.12). DPMH agrees with the Applicant's proposed labeling which does not include a pregnancy contraindication but does include a Warning and Precaution for Embryo-fetal Toxicity and recommends the use of contraception in females of reproductive potential during treatment and for 4 months after the final dose because of the concerns for teratogenicity.

There are no available data on the presence of mavacamten in human or animal milk, the effects on the breasted infant, or the effects on milk production. There are no available data to inform the risks related to the use of mavacamten during lactation. It is expected that exposure during

lactation is likely to be rare, DPMH does not recommend requiring a clinical study. Instead, DPMH recommends capturing infant outcomes related to exposure during lactation in the descriptive pregnancy safety study.

8. Human Subjects Protections/Clinical Site and Other GCP Inspections/Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators (Appendix III.13), and EXPLORER-HCM appears to have been conducted in compliance with U.S. regulations pertaining to Good Clinical Practice.

Based on this information, the lack of statistical influence of high enrolling sites or sites with a high treatment effect, and the lack of evidence for SAE under-reporting by high-enrolling sites, no site inspections were performed.

III. Appendices

9. Summary of Regulatory History

The original IND 121904 was submitted on November 16, 2014, and FDA granted Orphan designation and Breakthrough Therapy designation for treatment of symptomatic oHCM in adults to improve functional capacity, (b) (4) and symptoms on April 27, 2016 and July 22, 2020, respectively. The key regulatory history of the clinical development program of mavacamten is summarized in the table below:

Table 41 Summary of Ley Regulatory History

Source	Advice from Agency
June 04, 2014 Type B Pre-IND Meeting	The Division expressed concern that the risk of administering mavacamten in healthy subjects is unacceptably high given the narrow therapeutic margin observed in animals. The Division suggested to study HCM patients as first-in-human or in early phase trials such as DDI studies given their supra-normal ejection fraction. The Division requested the Applicant to characterize the safety and tolerability following a single ascending dose before designing a multiple ascending dose study. The Division requested more safety information and stated that their position would not be changed until more data are available. The Division commented that HCM patients that have progressed to dilation and reduced ejection fraction should not be studied. The Division also recommended evaluating the effect of mavacamten on indices of right ventricular (RV) performance. The Applicant acknowledged that RV performance effects have not been systematically assessed.
October 28, 2014 Type B IND Meeting	The Division agreed that the nonclinical development program was overall adequate but noted that mavacamten has a steep dose response and narrow therapeutic index, a factor of 3 between NOAEL and mortality in both rats and dogs. The Division stated that dosing in the initial study should at least be weight adjusted in an effort to minimize variability and continued questioning the adequacy of studying healthy volunteers. The Division recommended quantifying the relative contribution from each of P450 enzymes in the metabolism of mavacamten. The Division also suggested that the Applicant

	may want to genotype potential subjects in future multiple dose studies. The Division suggested that stopping criteria should be added in the study protocol in HCM patients such as HR, BP, and echocardiographic changes.
August 09, 2016 Type C Meeting	The Division did not think that (b) (4) is an appropriate primary endpoint given what little is known about myosin modulation as a therapeutic target and the cardiotoxicity that has been demonstrated in animal studies. The Division thought some sort of assessment of CV outcomes would seem more appropriate for an approval based on a single study. The Division also stated that improvements in symptoms would be an acceptable basis for approval, provided the drug's risks were adequately mitigated. For a single trial that does not assess CV outcomes as the primary endpoint, the sponsor should expect to see a substantial efficacy effect with a target p value of ≤ 0.01.
October 18, 2017 Type B End of Phase 2	The Division did not agree with the proposed Phase 3 study because a therapeutic range of mavacamten and safety monitoring have not been clearly identified and defined to ensure the safety. The Division recommended to measure NT-proBNP regularly in the phase 3 study and put in place additional safety measures regarding monitoring frequency and dosing instructions. The same recommendations should also be applied to the extension study. The Division agreed that the change in pVO_2 during exercise testing is an appropriate measure of exercise and functional capacity to serve as a primary endpoint in the Phase 3 study. The Division stated the proposed safety database at that time was insufficient and the Applicant should identify the lowest dose or exposure required for efficacy in order to minimize the risks of mavacamten. The Division further stated that the amount of safety information required will be roughly inversely proportional to the benefit demonstrated in the Phase 3.
April 04, 2018 Type C Meeting	The Division agreed that 5 mg is an acceptable starting dose in the Phase 3 study and thought the proposed dose titration seemed reasonable. The Division raised concern that there is no mechanism for an investigator to act on severe depression of LV function and QT data based on site-level data. The Division recommended to measure Ctrough at an additional

	visit at Week 8. The Division also recommended to utilize CYP2C19 genotype results to inform a dose reduction plan for CYP2C19 poor metabolizers. The Applicant subsequently submitted an amendment to the Phase 3 trial protocol to address these concerns.
October 17, 2019 Type C Meeting	The Division stated that the degree to which the pivotal trial (EXPLORER-HCM), together with other data from long-term extension studies and dose-ranging studies, support the proposed indication for mavacamten will depend on the benefit(s) demonstrated by the drug in the context of its risks. The Division mentioned that if the Agency determines that an FDA-cleared or approved device is necessary to assure safe and effective use of mavacamten, then lack of device approval would prevent drug approval. The Division recommended that the Applicant submit a pre-submission with CDRH to discuss their plans toward seeking clearance/approval of such a device.
July 17, 2020 Type B pre-NDA	The Division generally agreed with the format and content planned for NDA submission The Division stated that a REMS will be necessary to ensure that the benefits of the drug outweigh the risk of excessive reductions in cardiac contractility. The Division anticipated the need for a REMS to assure that scheduled echocardiograms are performed.

10. Clinical Efficacy Assessment Additional Information and Assessment

10.1. Key Efficacy Results in PIONEER-HCM

Table 42 Effect of Mavacamten on Exercise Capacity, PIONEER-HCM

	Part A			Part B		
	Baseline (N)	**Week 12 (N)**	**Mean Change (p-value)**	**Baseline (N)**	**Week 12 (N)**	**Mean Change (p-value)**
pVO_2 (mL/kg/min) ± SD	20.7 ± 7.4 (11)	24.6 ± 8.8 (10)	3.5 ± 3.3 (p = 0.004)	19.4 ± 4.6 (10)	21.1 ± 4.2 (10)	1.7 ± 2.3 (p = 0.121)
VE/VCO_2 ± SD	32.2 ± 5.4 (11)	30.3 ± 6.1 (10)	-2.2 ± 5.5 (p = 0.164)	32.3 ± 4.4 (10)	29.8 ± 4.9 (10)	-2.5 ± 2.5 (p = 0.014)
Circulatory Power (mmHg·mLO_2·kg −1·min−1) ± SD	3276 ± 1535 (11)	4400 ± 2040 (10)	1075.0 ± 931.9 (p = 0.010)	2944 ± 1422 (10)	3445 ± 1659 (10)	500.8 ± 680.4 (p = 0.065)
Ventilatory Power (mmHg) ± SD	5.0 ± 1.3 (11)	5.9 ± 1.5 (10)	1.0 ± 1.6 (p = 0.131)	4.7 ± 1.9 (10)	5.6 ± 2.5 (10)	0.9 ± 1.1 (p = 0.037)
Peak Workload (Watts) ± SD	7.5 ± 2.6 (11)	8.2 ± 2.5 (10)	0.5 ± 0.7 (p = 0.125)	6.8 ± 1.6 (10)	7.7 ± 2.3 (10)	0.9 ± 1.1 (p = 0.078)

Source: PIONEER-HCM CSR, Table 18

Table 43 New Yor Heart Association Class at Baseline and Week 12, PIONEER-HCM

	Part A			Part B		
	Baseline (N)	**Week 12 (N)**	**Mean Change (p-value)**	**Baseline (N)**	**Week 12 (N)**	**Mean Change (p-value)**
NYHA Class ± SD	2.4 ± 0.5 (11)	1.4± 0.7 (10)	-0.9 ± 0.7 (p = 0.016)	2.5 ± 0.5 (10)	1.5 ± 0.7 (10)	-1.0 ± 0.5 (p = 0.004)

Source: PIONEER-HCM CSR, Table 23

Table 44 KCCQ Overall Summary Score at Baseline and Week 12, PIONEER-HCM

	Part A			Part B		
	Baseline (N)	Week 12 (N)	Mean Change (p-value)	Baseline (N)	Week 12 (N)	Mean Change (p-value)
KCCQ OSS ± SD	64.9 ± 16.2 (11)	81.9 ± 16.9 (10)	14.4 ±9.9 (p = 0.002)	60.9 ± 26.3 (10)	76.8 ± 22.6 (10)	16.0 ± 21.9 (p = 0.021)

Source: PIONEER-HCM CSR, Table 25

Table 45 NT-proBNP Change from Baseline to Week 12, PIONEER-HCM

	Part A			Part B		
	Baseline (N)	Week 12 (N)	Mean Change (p-value)	Baseline (N)	Week 12 (N)	Mean Change (p-value)
NT-proBNP (pg/mL) ± SD	930 ± 647 (11)	454 ± 551 (10)	-459 ± 722 (p = 0.084)	1834 ± 3209 (9)	826 ± 1063 (10)	-1195 ± 2770 (p = 0.074)

Source: PIONEER-HCM CSR, Table 24

10.2. Additional Information in EXPLORER-HCM

Table 46 Criteria for Down-Titration of Mavacamten Dose, EXPLORER-HCM

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.

Source: Table 3 in EXPLORER-HCM CSR

Table 47 Criteria for Up-Titration or No Change in Mavacamten Dose at Week 8 and Week 14, EXPLORER-HCM

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.

Source: Table 4 in EXPLORER-HCM CSR

11. Clinical Safety Assessment Additional Information and Assessment

11.1. Narrative review for Death and SAEs of interest

Death	
(b) (6) Death (bacterial endocarditis)	This patient was a 64 y/o male, a CYP2C19 normal metabolizer with a BMI of 45.2. He was diagnosed with HCM in 2014 with relevant history of paroxysmal AF, congestive HF, non-sustained ventricular tachycardia, shortness of breath, Crohn's disease, stage 3 chronic kidney disease, gastrointestinal (GI) bleeding, morbid obesity and immunosuppression. The patient received placebo in EXPLORER-HCM and 5 mg in the MAVA-LTE long-term extension study. On SD 70, the subject was admitted to an ICU with the diagnosis of sepsis requiring intravenous antibiotics. A TTE showed mitral valve endocarditis. Mavacamten was withheld due to the event and was never re-introduced. His LVEF was 55% on SD 71 with normal right ventricular size and systolic function. His blood culture results showed MSSA on SD 72. LVEF was 60% on SD 75. A TTE showed a large mitral valve vegetation, and the subject underwent

	mitral valve replacement/a myectomy/a MAZE procedure on SD 78. The surgery was technically successful. The patient developed respiratory failure post-operatively and was intubated and under inotropic support of epinephrine. He also developed post-operative renal failure requiring dialysis. On SD 115, the patient died due to cardiac arrest secondary to multisystem organ failure induced by hemorrhagic shock due to acute GI bleeding. Relevant concomitant medications at the time of event included: adalimumab, metoprolol, rivaroxaban, torsemide, metronidazole.
(b) (6) Death (cardiac arrest)	This patient was a 68 y/o male, a CYP2C19 normal metabolizer with BMI 25.1. His relevant medical history included AF, left bundle branch block, dizziness, ICD, aortic stenosis, essential hypertension. He received mavacamten with a dose adjustment to 15 mg in EXPLORER-HCM. No SAE was reported in the study and his on treatment LVEF readings were >50% (ranged 66% to 75%) during the study. He was subsequently enrolled in the MAVA-LTE extension study. The patient had dose up-titration to 15 mg at Week 12 and maintained this dose through Week 72. His LVEF was in the range of 50-70% (74% at baseline) with the lowest reading of 54% at Week 72. The patient's AF was worsening between Week 64 and Week 73, and he experienced SAEs of "recurrence of paroxysmal AF" (week 64), "worsening arrhythmia" (Week 66) and "AF" (Week 73). Ctrough was 436 ng/mL at Week 60 and 754 ng/mL at Week 72. His NT-proBNP was significantly elevated at Week 72 (~2,800 pg/mL) from Week 60 (~200 pg/mL, his baseline was 1800 pg/mL). Amiodarone (IV bolus infusion followed by oral maintenance therapy) and oral metoprolol were started for the treatment of AF and worsening arrhythmia after Week 64. The subject underwent an atrial ablation procedure for treatment of the recurrent AF and the event resolved at Week 72. Six days after the procedure, the subject experienced a fatal cardiac arrest. Four ICD shocks occurred prior to the fatal cardiac arrest, and on 2 occasions the shocks converted the subject back to sinus rhythm but then the subject reverted back to ventricular fibrillation. The cause of death per the death certificate was congestive HF as a consequence of AF and coronary artery disease.
(b) (6) Death (acute myocardial infarction)	This patient was a 61 y/o male, a CYP2C19 normal metabolizer with BMI of 31. Relevant medical history included palpitations and shortness of breath. The patient received placebo in EXPLORER-HCM and did not report any AE. He subsequently enrolled in MAVA-LTE with a starting dose of 5 mg and underwent a dose increase to 10 mg at Week 24 and maintained the dose to Week 48. His LVEF was in the range of 55-70% during the study with a value of 70% at the Week 48 visit. His

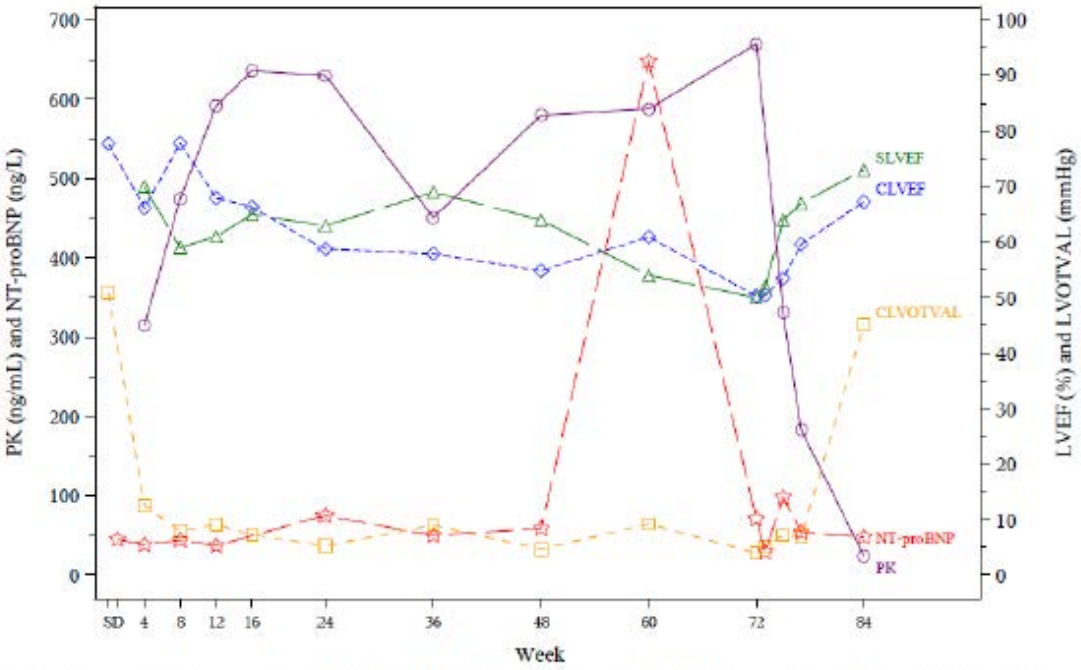
	LVOT was 50 mmHg at Week 48. His mavacamten Ctrough was < 300 ng/mL during the study. The subject felt well and asymptomatic up to the Week 48 visit. Two months after the Week 48 visit, the subject collapsed with no antecedent symptoms while in the garden outside his house. The subject's wife commenced CPR on the subject but unsuccessful. External defibrillation revealed the underlying rhythm (asystole). No autopsy. The subject underwent clinical Holter assessment beginning a week before his sudden death. The Holter was worn on the date of his death until late morning and the subject died later in the afternoon. Nothing in the recording was suggestive of the cause of death. The subject had been offered the option to have a primary prevention ICD implanted in the past, which he declined. The death certificate lists presumed acute MI and the cause of death was attributed to cardiac arrhythmia which was thought to be related to the underlying disease.
SAE of Syncope	
(b) (6) SAE of Syncope Study drug discontinuation Adjudicated CV hospitalization - syncope	The patient is a 64 y/o female, a CYP2C19 intermediate metabolizer, with BMI 33.3. She was diagnosed with HCM in (b) (6) with no family history of HCM or sudden cardiac death. Her HCM history included shortness of breath, chest pain and palpitations. She was on metoprolol (50 mg QD) at baseline. On SD 68, she experienced a syncope SAE that led to temporary discontinuation of study drug. She had low HR (40s bpm) with no arrythmia on telemetry. No significant change on ECG was found. Mavacamten was restarted on SD 70 and metoprolol was lowered to 37.5 mg QD on SD 71. On SD 89, the patient experienced a second SAE of syncope. Cardiac workup was unremarkable, and no arrhythmia was reported from cardiac monitor. The study drug was permanently discontinued due to the event and the subject underwent a myectomy with no complications on SD 95. Metoprolol was restarted at a lower dose of 12.5 mg BID on SD 96. Mavacamten trough concentrations were < 200 ng/mL during the time when the two syncope SAEs occurred (SD 60 174 ng/mL, SD 83 176 ng/mL, SD 91, 122 ng/mL). The investigator attributed both events to metoprolol and to underlying disease of oHCM.
(b) (6) SAE of Syncope Adjudicated TYPE II NSTEMI	This patient is a 49 y/o man, a CYP2C19 normal metabolizer with BMI 22.4. He was diagnosed with HCM in (b) (6) with no family history of HCM or sudden cardiac history death. His relevant HCM history included paroxysmal AF, shortness of breath, chest pain, palpitations, syncope, and collapse. Relevant concomitant medications include propranolol and finasteride. On SD 8 of taking mavacamten, he experienced a SAE of syncope.

	The patient reported lessened symptoms after study start and increased exercise tolerance and had gone hiking prior to the SAE. However, the patient reported over the past week, he had experienced a new symptom of slight chest pain and felt the syncope episode was distinct with chest pressure, different from his prior syncopal events. Evaluation in the ER was negative for orthostatic hypotension or acute findings; ECG showed sinus bradycardia with anterior fascicular block. Troponin I was 0.04 ng/mL (peak troponin was 0.17 ng/mL; reference range < 0.04 ng/mL. LVOT at rest increased to 75 mmHg from baseline (50 mmHg). The syncope event was considered resolved and the study dose was not changed due to the event. However, the patient decided to discontinue study treatment on SD 11. The investigator attributed the event to underlying worsening of oHCM and hypovolemia in the setting of a recent hike. This event was later adjudicated as a TYPE II NSTEMI.
(b) (6) SAE of Syncope	This patient is a 66 y/o male, a CYP2C19 intermittent metabolizer with BMI 30.5. He was diagnosed with HCM in (b) (6) with no family history of HCM or sudden cardiac death. His relevant history included shortness of breath, neurally mediated syncope and hypertension. Relevant concomitant medications included enalapril, propranolol, and edoxaban. On SD 90, the patient experienced a non-serious Grade 1 AE of AF that remined ongoing through study completion. On SD 239 (during the washout period), 25 days after receiving the last dose of mavacamten, the subject experienced dizziness and syncope SAE. He was admitted to the hospital on SD 240 with head trauma. The CT scan showed a cortical hyperdense area mainly in the right temporal region. The 24-hour Holter monitor showed AF with sporadic isolated ventricular extrasystoles. On SD 249, head CT scan revealed almost complete reabsorption of the hemorrhagic hyperdensity in the right temporal region. No action was taken with study treatment as the event occurred during the follow-up period. Mavacamten plasma trough concentrations were 445 ng/mL on SD 215 and 129 ng/mL on SD 260.
SAE of Stress Cardiomyopathy	
(b) (6) SAE of stress cardiomyopathy Adjudicated TYPE II NSTEMI Adjudicated HF	The patient is an 80 y/o female, a CYP2C19 non-poor metabolizer with BMI 23.5. She was diagnosed with HCM in (b) (6) with no family history of HCM or sudden cardiac death. Her HCM history included shortness of breath and palpitations. On SD 137, she stopped mavacamten treatment (10 mg) due to meeting the study criterion for prolonged QTcF (Ctrough <450 ng/mL on SD 127). Her symptoms including dyspnea and chest discomfort intensified since stopping the study drug. On SD 146, the patient was admitted to hospital with exertional chest

	pain/dyspnea and reduced LVEF of 40% and was diagnosed with Takotsubo/Apical ballooning syndrome. She was found to have elevated high-sensitivity troponins and was initially treated with IV heparin due to concern for NSTEMI. However, no evidence of obstructive coronary artery disease was found when she underwent cardiac catheterization on the same day. The patient had a cardiac MRI which confirmed the diagnosis of stress-induced cardiomyopathy superimposed on underlying oHCM, with no evidence of myocarditis or infarct. She resumed mavacamten at 5 mg on SD 176 and completed the study without any further cardiac AEs. She is enrolled in the ongoing long-term extension study with additional 60 weeks of treatment as of (b) (6) No additional SAE was reported.
(b) (6) SAE of stress cardiomyopathy Adjudicated TYPE II NSTEMI	This patient is a 66 y/o female, a CYP2C19 normal metabolizer with BMI of 27.1. She was diagnosed with HCM in (b) (6) with no family history of HCM or sudden cardiac death. Her HCM history included shortness of breath, chest pain, fatigue, and palpitations. Other relevant medical history included anxiety. On SD 57 at the Week 6 visit of taking mavacamten, her ECG showed sinus tachycardia with possible left atrial enlargement, non-specific T-wave abnormality, and abnormal rhythm. Her LVEF was 35% (baseline LVEF of 92%). Mavacamten plasma trough concentration was 176 ng/mL. On the same day, the patient was hospitalized for additional tests after experiencing retrosternal pressure and mild dyspnea. She was diagnosed with moderate intensity Takotsubo's syndrome. Coronary angiogram showed left dominance and coronary arteries without angiographically significant lesions. Her Troponin T was 226 ng/L (reference range < 14 ng/L) and C-Reactive protein (0.36 mg/dL, reference range < 0.2 mg/dL) were elevated. Five days after the event, the patient was discharged after her symptoms improved and the SAE was resolved. Treatment was not interrupted until SD 66 due to the previously recorded low LVEF at Week 6. The patient resumed mavacamten at the same dose on SD 127 and completed the study without any reported AE. She is enrolled in the ongoing long-term extension study with additional 60 weeks of treatment as of (b) (6) No additional SAE was reported.

11.2. Clinical Profile for subjects with heart failure SAE

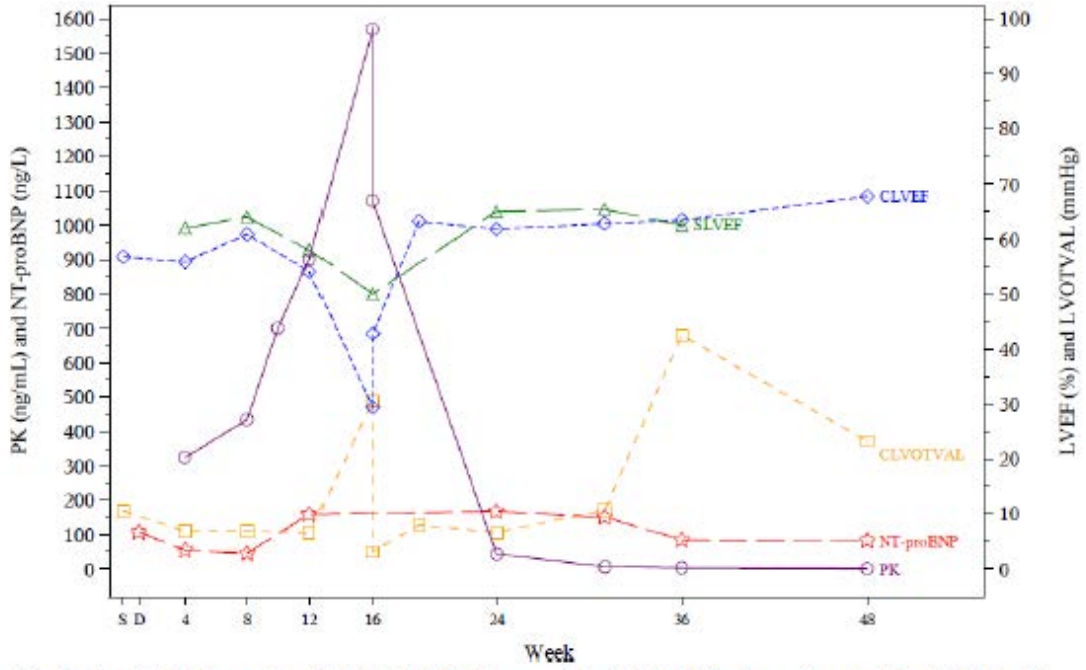
Figure 17 Clinical Profile for Subject (b) (6) MAVA-LTE



Abbreviations: CLVEF = central-read LVEF; CLVOTVAL = central-read LVOT Valsalva gradient; D = Day 1; LVEF = left ventricular ejection fraction; LVOTVAL = LVOT Valsalva gradient; NT-proBNP = N-terminal pro B-type natriuretic peptide; PK = mavacamten plasma concentration; S = Screening; SLVEF = site-read LVEF

Source: Sponsor's response to clinical IR dated May 28, 2021, Figure 7

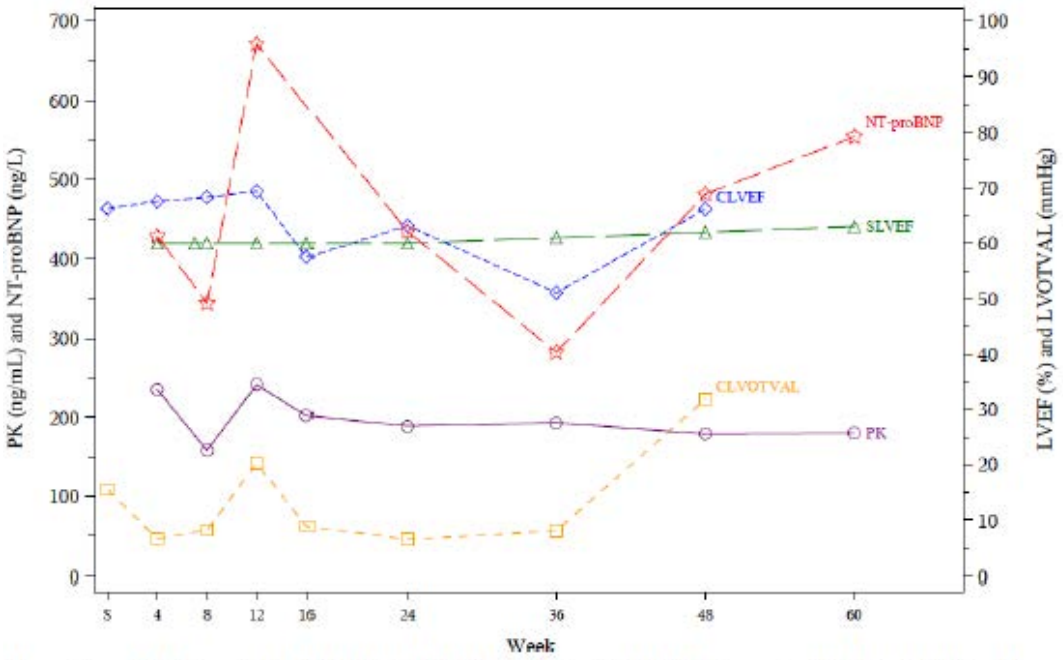
Figure 18 Clinical Profile for Subject (b) (6) MAVA-LTE



Abbreviations: CLVEF = central-read LVEF; CLVOTVAL = central-read LVOT Valsalva gradient; D = Day 1; LVEF = left ventricular ejection fraction; LVOTVAL = LVOT Valsalva gradient; NT-proBNP = N-terminal pro B-type natriuretic peptide; PK = mavacamten plasma concentration; S = Screening; SLVEF = site-read LVEF

Source: Sponsor's response to clinical IR dated May 28, 2021, Figure 9

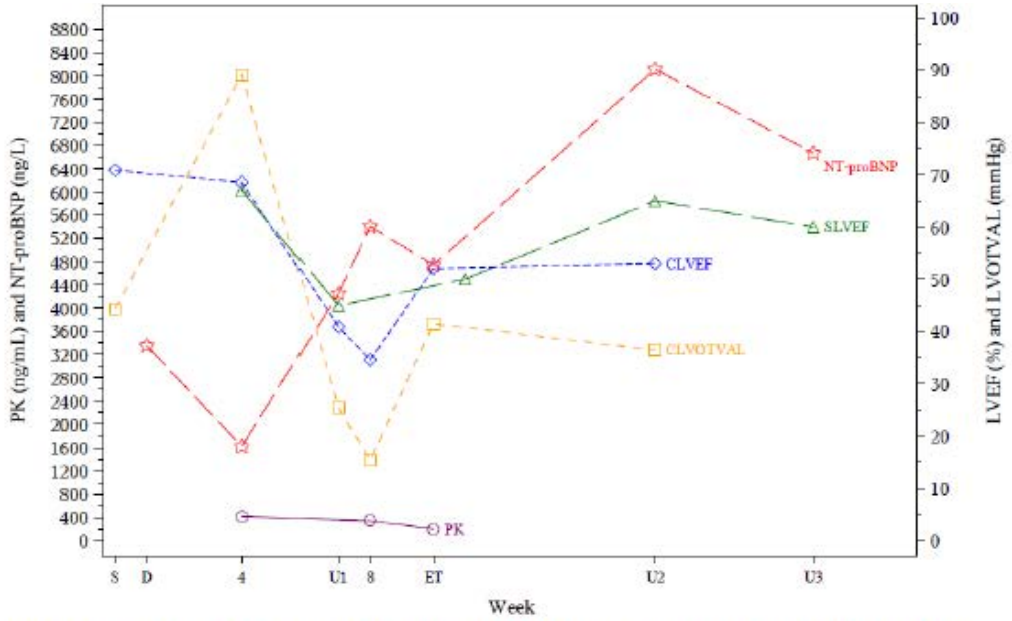
Figure 19 Clinical Profile for Subject (b) (6) MAVA-LTE



Abbreviations: CLVEF = central-read LVEF; CLVOTVAL = central-read LVOT Valsalva gradient; D = Day 1; LVEF = left ventricular ejection fraction; LVOTVAL = LVOT Valsalva gradient; NT-proBNP = N-terminal pro B-type natriuretic peptide; PK = mavacamten plasma concentration; S = Screening; SLVEF = site-read LVEF

Source: Sponsor's response to clinical IR dated May 28, 2021, Figure 9

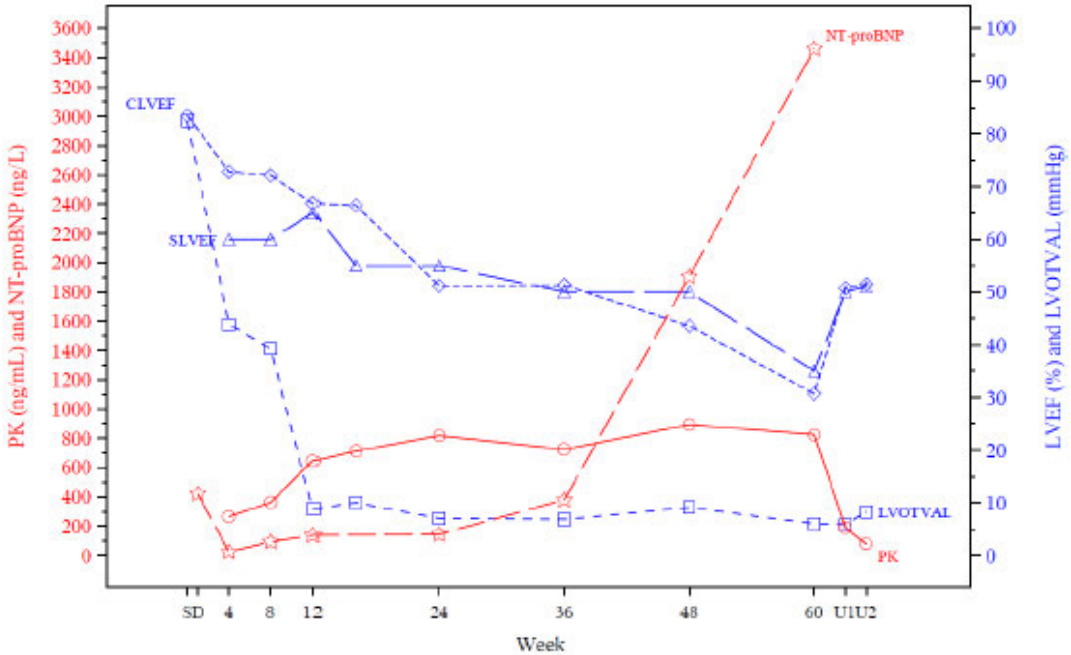
Figure 20 Clinical Profile for Subject (b) (6) MAVA-LTE



Abbreviations: CLVEF = central-read LVEF; CLVOTVAL = central-read LVOT Valsalva gradient; D = Day 1; ET = early termination visit; LVEF = left ventricular ejection fraction; LVOTVAL = LVOT Valsalva gradient; NT-proBNP = N-terminal pro B-type natriuretic peptide; PK = mavacamten plasma concentration; S = Screening; SLVEF = site-read LVEF; U1 = unscheduled visit #1 on 23NOV2020; U2 = unscheduled visit #2 on 02FEB2021; unscheduled visit #3 on 09MAY2021

Source: Sponsor's response to clinical IR dated May 28, 2021, Figure 8

Figure 21 Clinical Profile for Subject (b) (6) MAVA-LTE



Abbreviations: CLVEF = central-read LVEF; D = Day 1; LVEF = left ventricular ejection fraction; LVOTVAL = central-read LVOT Valsalva gradient; NT-proBNP = N-terminal pro B-type natriuretic peptide; PK = mavacamten plasma concentration; S = Screening; SLVEF = site-read LVEF; U1 = Unscheduled Visit #1 on 23 November 2020 (21 days after Week 60); U2 = Unscheduled Visit #2 on 09 December 2020 (37 days after Week 60)

Source: Sponsor's response to clinical IR dated May 28, 2021, Figure 6

11.3. Additional Safety Tables and Figures

Table 48 Clinical Studies that Contributed Integrated Safety Data

Study ID	Number of Centers Location(s)	Study Dates Enrollment planned / actual	Design	Study Objectives (non-exploratory)	Study Drug Starting Dose, Route, Regimen	Sex M/F Median Age (Range)	Diagnosis
Parent Studies							
MYK-461-005 EXPLORER	68 sites US (29), EU (31), UK (2), Israel (6)	30 May 18 to 06 May 20 220 / 251	Phase 3, randomized, double-blind, placebo-controlled	Efficacy, safety, PK, PRO	Mavacamten vs. placebo 5 mg po QD	149 M / 102 F 58.5 yrs (18, 82)	oHCM
MYK-461-004 PIONEER	7 sites US	07 October 16 to 17 November 17 20 / 21	Phase 2, open-label	Efficacy, safety, PK, PD, post-treatment reversibility	Mavacamten Part A: 10 or 15 mg po QD Part B: 2 mg po QD	Part A: 7 M/5 F 65 yrs (22-70) Part B: 5 M/5 F 62.5 yrs (26, 67)	oHCM
MYK-461-006 MAVERICK	26 sites US	07 March 2018 to 07 January 2020 60 / 59	Phase 2, randomized, double-blind, placebo-controlled	Safety and tolerability	Mavacamten vs. placebo 5 mg po QD	25 M/34 F 56 (45-66)	nHCM
Extension Studies							
MYK-461-007 MAVA-LTE (interim)	65 sites US (30), EMEA[a] (35)	05 October 18 to 27 May 20 oHCM: 220 / 137 nHCM: 60 / 43	Phase 2/3, long-term extension	Long-term safety, efficacy	Mavacamten EXPL-LTE Cohort: 5 mg po QD[b] MVR-LTE Cohort: last dose in parent study or 5 mg if not on active treatment in parent study[c]	oHCM: 86 M/51 F 62 (19-83) nHCM: 15 M/28 F 57 (19-78)	oHCM nHCM
MYK-461-008 PIONEER-OLE (interim)	4 sites US	09 May 18 to 29 January 20 Up to 20 / 13	Phase 2, open-label extension	Long-term safety, efficacy, PK	Mavacamten 5 mg po QD	9 M/ 4 F 62 yrs (27, 72)	oHCM

Abbreviations: EMEA = Europe, Middle East, and Africa; EOT = end of treatment; EU = Europe; F = female; LTE = long-term extension; M = male; MAVA = mavacamten; nHCM = non-obstructive hypertrophic cardiomyopathy; oHCM = obstructive hypertrophic cardiomyopathy; OLE = open-label extension; PD = pharmacodynamics; PK=pharmacokinetics; po = per oral; PRO = patient reported outcomes; QD = once daily; UK = United Kingdom; US = United States

[a] Includes Spain, Poland, Italy, Israel, France, Portugal, Czech Republic, Belgium, Netherlands, Germany, Denmark, and United Kingdom.

[b] For EXPLORER-LTE Cohort subjects with a parent study (EXPLORER-HCM) EOT visit dose of 5 mg *and* a mavacamten plasma trough concentration >700 ng/mL the starting dose was 2.5 mg QD in the MAVA-LTE study.

[c] For MAVERICK-LTE Cohort subjects with a parent study (MAVERICK-HCM) EOT visit mavacamten plasma trough concentration >1000 ng/mL the starting dose was either 5 mg QD (if EOT dose was 10 mg or 15 mg QD) or 2.5 mg (if EOT dose was 5 mg QD).

Source: Sponsor's Table 1 in SCS

Table 49 Protocol-Specified Criteria in the Integrated Studies for Actions Taken with Study Treatment Other than Due to AE

Study	Threshold	Guidance
Criteria for elevated mavacamten plasma concentration		
MYK-461-005 EXPLORER	C_{trough} of 700 to < 1000 ng/mL (requires LVEF ≥ 50%)	• Dose reduction • Permanent discontinuation (i.e. to placebo) if already on 2.5 mg daily dose
	C_{trough} of ≥ 1000 ng/mL	• Temporary discontinuation, resume at lower dose if resolves at follow-up visit; may result in permanent discontinuation if criteria are not resolved at follow-up visit • Permanent discontinuation (i.e. to placebo) if already on 2.5 mg daily dose
MYK-461-006 MAVERICK	C_{trough} of ≥ 1000 ng/mL	• Permanent discontinuation
MYK-461-007 MAVA-LTE	C_{trough} of > 450 ng/mL at week 4 (MAVERICK cohort treated with placebo in parent study only)	• Dose reduction from 5 mg to 2.5 mg
	C_{trough} of ≥ 1000 ng/mL	• Temporary discontinuation, resume at lower dose if resolves at follow-up visit; may result in permanent discontinuation if criteria are not resolved at follow-up visit • Permanent discontinuation if already on 2.5 mg daily dose
MYK-461-008 PIONEER-OLE	C_{trough} of ≥ 1000 ng/mL	• Temporary discontinuation, resume at lower dose (or same dose for 5 mg only) if resolves at follow-up visit; may result in permanent discontinuation if criteria are not resolved at follow-up visit

Table 26 Protocol-Specified Criteria in the Integrated Studies for Actions Taken with Study Treatment Other than Due to AE (Continued)

Study	Threshold	Guidance
Criteria for Valsalva gradient reductions		
MYK-461-007 MAVA-LTE	Valsalva gradient ≤ 30 mm Hg at week 4 (EXPLORER cohort only)	• Dose reduction from 5 mg to 2.5 mg
Criteria for LVEF reductions or systolic dysfunction		
MYK-461-005 EXPLORER	LVEF < 50% (central read)	• Temporary discontinuation, resume at lower dose if resolves at follow-up visit; may result in permanent discontinuation if criteria are not resolved at follow-up visit • Permanent discontinuation (i.e. to placebo) if already on 2.5 mg daily dose
	LVEF ≤ 30% (local site)	• Permanent discontinuation
	New or worsening heart failure associated with systolic dysfunction	
MYK-461-006 MAVERICK	LVEF ≤ 45%	• Permanent discontinuation
	LVEF ≤ 30% (local site)	
	New or worsening heart failure associated with systolic dysfunction	
MYK-461-007 MAVA-LTE	LVEF < 50%[a]	• Temporary discontinuation, resume at lower dose if resolves at follow-up visit; may result in permanent discontinuation if criteria are not resolved at follow-up visit • Permanent discontinuation if already on 2.5 mg daily dose
	LVEF ≤30% (local site)	• Permanent discontinuation
	New or worsening heart failure associated with systolic dysfunction	
MYK-461-008 PIONEER-OLE	LVEF < 45%	• Temporary discontinuation, resume at same (5 mg only) or lower dose if resolves at follow-up visit; may result in permanent discontinuation if criteria are not resolved at follow-up visit
	New or worsening heart failure associated with systolic dysfunction	• Permanent discontinuation
	Undergoing septal reduction therapy	
Criteria for prolonged QTc interval		
MYK-461-005 EXPLORER	Smaller of: - QTcF 15% increase from baseline - QTcF ≥ 520 ms (narrow QRS) - QTcF ≥ 550 ms (wide QRS)	• Temporary discontinuation, resume at lower dose if resolves at follow-up visit; may result in permanent discontinuation if criteria are not resolved at follow-up visit • Permanent discontinuation (i.e. to placebo) if already on 2.5 mg daily dose
MYK-461-006 MAVERICK	QTcF ≥ 500 ms	• Permanent discontinuation

Table 26 Protocol-Specified Criteria in the Integrated Studies for Actions Taken with Study Treatment Other than Due to AE (Continued)

Study	Threshold	Guidance
MYK-461-007 MAVA-LTE	Smaller of: - QTcF 15% increase from baseline - QTcF ≥ 520 ms (narrow QRS) - QTcF ≥ 550 ms (wide QRS)	• Temporary discontinuation, resume at lower dose if resolves at follow-up visit; may result in permanent discontinuation if criteria are not resolved at follow-up visit • Permanent discontinuation if already on 2.5 mg daily dose
MYK-461-008 PIONEER-OLE	Smaller of: - QTcF 15% increase from baseline - QTcF ≥ 520 ms (narrow QRS) - QTcF ≥ 550 ms (wide QRS)	• Temporary discontinuation, resume at same (5 mg only) or lower dose if resolves at follow-up visit; may result in permanent discontinuation if criteria are not resolved at follow-up visit
Criteria for hepatotoxicity		
MYK-461-005 EXPLORER MYK-461-004 PIONEER MYK-461-006 MAVERICK MYK-461-007 MAVA-LTE MYK-461-008 PIONEER-OLE	All criteria met for: - TBL > 2x ULN or INR > 1.5 - increased AST or ALT to > 3x ULN if baseline was < ULN - no other cause for the combination of laboratory abnormalities	• Permanent discontinuation • If alternative cause for hepatotoxicity is identified, temporary interruption may be determined appropriate by the investigator
	Any criteria met for: - increased AST or ALT to > 8x ULN - increased AST or ALT to > 5x ULN and < 8x ULN for ≥ 2 weeks, or unable to adhere to enhanced monitoring - increased AST or ALT to > 3x ULN with clinical signs or symptoms of hepatitis - increased TBL to > 3x ULN - increased ALP to > 8x ULN	• Temporary discontinuation pending evaluation for drug-induced liver injury; rechallenge may be considered if alternative cause is discovered and laboratory abnormalities resolve to normal or baseline
	Recurrent signs or symptoms of hepatotoxicity upon rechallenge of study treatment	• Permanent discontinuation

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; C_{trough} = mavacamten plasma trough concentration; INR = international normalized ratio; LTE = long-term extension; LVEF = left ventricular ejection fraction; MAVA = mavacamten; OLE = open-label extension; QTc = corrected QT interval; QTcF = Fridericia-corrected QT interval; TBL = total bilirubin; ULN = upper limit of normal

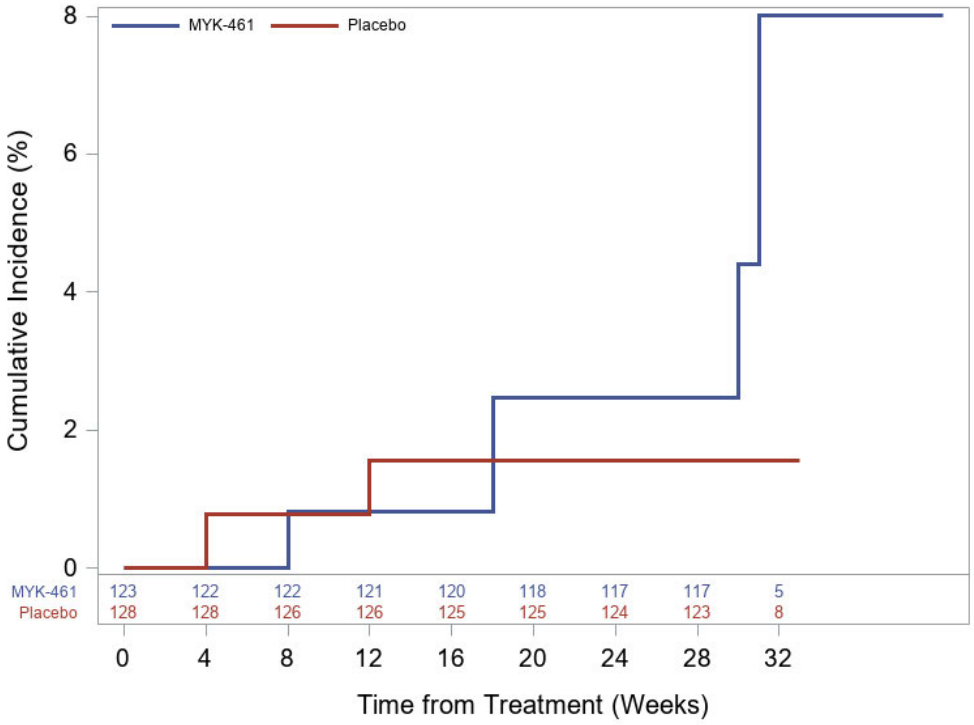
Note: Criteria in this table reflect current protocol versions at study completion or at the time of data cutoff for this SCS. Please refer to individual study protocols for additional details.

Note: Other protocol-specified criteria for actions taken with study treatment (e.g. pregnancy, subject withdrawal of consent, study termination, etc.) are not included in this table, but can be found in individual study protocols.

[a] LVEF reduction criteria for temporary discontinuation in Study MYK-461-007 were based on site-read LVEF values for the EXPLORER cohort and on central-read LVEF values for the MAVERICK cohort.

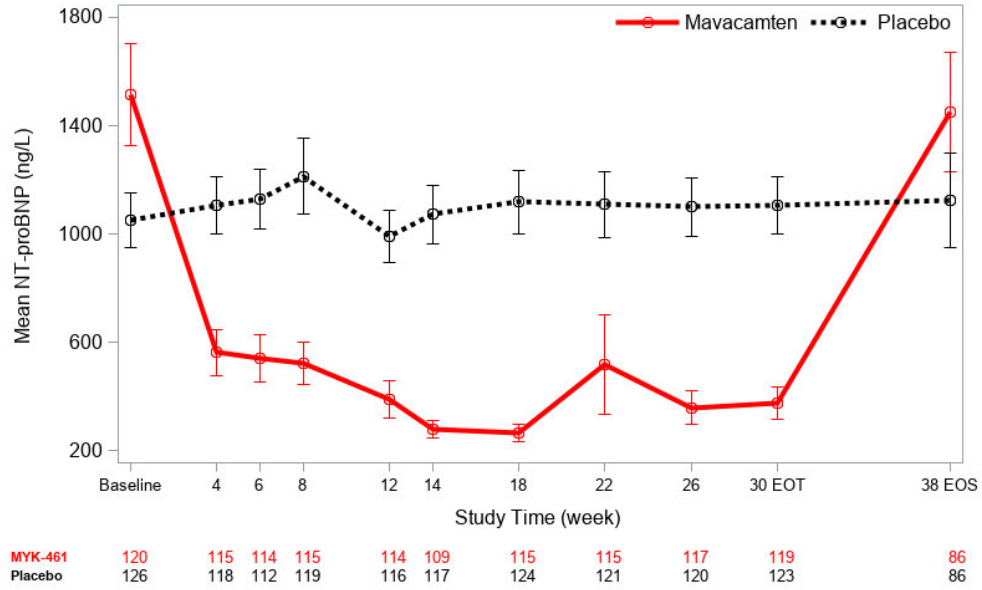
Source: Table 2 in SCS

Figure 22 The Kaplan-Meier Plot for LVEF < 50%, Safety Population, EXPLORER



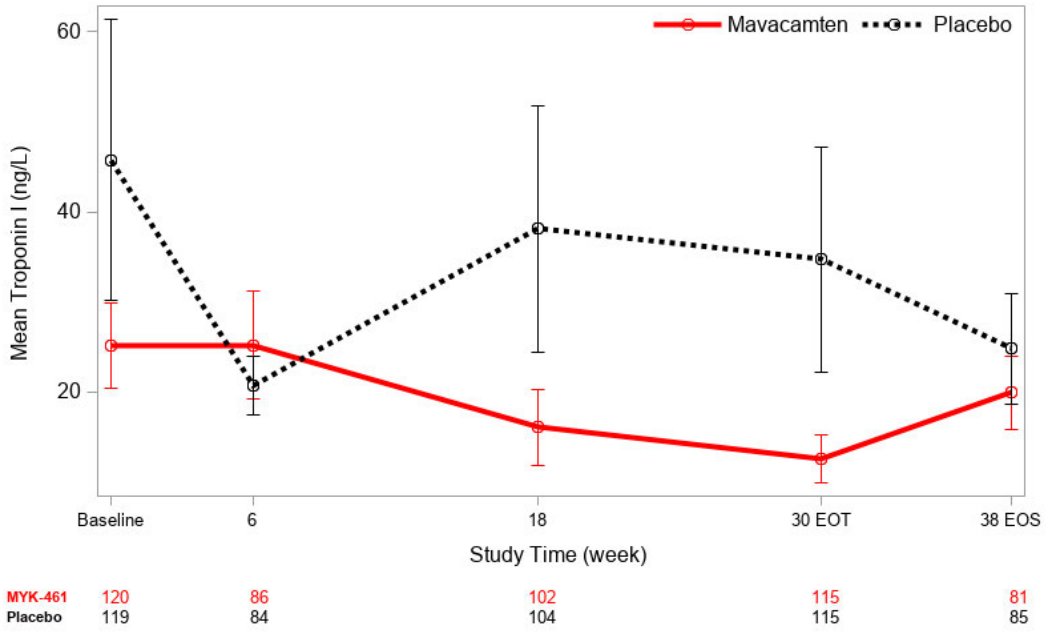
Source: Reviewer's Figure, data: EXPLORER adsl and adcv

Figure 23 Mean NT-proBNP Over Time, Safety Population, EXPLORER-HCM



Source: Reviewer's Figure, data: EXPLORER adlb.

Figure 24 Mean Troponin I over time, Safety Population, EXPLORER-HCM



Source: Reviewer's Figure, data: EXPLORER adlb.

Table 50 Event Rate of Clinical Events of Interest in EXPLORER-HCM and MAVA-LTE, Safety Population

	EXPLORER-HCM (PK/PD Monitoring)		MAVA-LTE[3] (EXPLORER Cohort, PD monitoring)
	Mavacamten N=123 ER (100 pt-yrs)	Placebo N=128 ER (100 pt-yrs)	Mavacamten N=231 ER (100 pt-yrs)
MACE SMQ[1]	2.3	3.3	0.8
Arrythmia (FMQ)	20.8	18.8	18.4
-Atrial Fibrillation/Atrial Flutter	11.9	11.3	8.8
-Ventricular arrhythmias	3.5	3.3	2.0
Syncope/Presyncope	9.2	7.9	2.4
- Syncope	8.1	2.2	1.9
QTc prolongation	0	1.1	0.4
Hypotension[2]	2.3	3.3	0.4
Hepatic events (SMQ)	4.6	4.4	0.8
Dizziness (FMQ)	43.6	28.5	19.4
Dyspnea (FMQ)	22.8	18.7	11.8

1. SMQ “myocardial infarction”, SMQ “hemorrhagic central nervous system vascular conditions” and SMQ “ischemic central nervous system vascular conditions”
2. Any AE with PT “hypotension”, “blood pressure orthostatic decreased” or “orthostatic hypotension”
3. Using updated safety data through May 2021

Source: Reviewer’s Table, data: ISS seq0023: adsl and adae
Abbreviations: N, number of subjects in group; PK, pharmacokinetic; PD, pharmacodynamic; ER, event rate; MACE, major adverse cardiovascular event; SMQ, Standardized MedDRA Query; FMQ, FDA Medical Queries; QTc, corrected QT interval

11.4. Liver Lab Analysis

Table 51 ALT Shift Table from Baseline, EXPLORER-HCM, Safety Population

		ALT (Maximum)			
Grouping Variable	**ALT (Baseline)**	**ULN<=1**	**1<ULN<=3**	**3<ULN<=5**	**5<ULN**
MYK-461 (N = 123)	ULN<=1	89 (72.4%)	20 (16.3%)	2 (1.6%)	0 (0%)
	1<ULN<=3	2 (1.6%)	8 (6.5%)	1 (0.8%)	0 (0%)
	3<ULN<=5	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)
	5<ULN	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Placebo (N = 128)	ULN<=1	100 (78.1%)	17 (13.3%)	1 (0.8%)	0 (0%)
	1<ULN<=3	1 (0.8%)	5 (3.9%)	2 (1.6%)	0 (0%)
	3<ULN<=5	0 (0%)	0 (0%)	2 (1.6%)	0 (0%)
	5<ULN	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Source: OCS Analysis Studio, Shift Table Tool.
X Cutoffs: ULN<=1; 1<ULN<=3; 3<ULN<=5; 5<ULN.
Y Cutoffs: ULN<=1; 1<ULN<=3; 3<ULN<=5; 5<ULN.

Table 52 AST Shift Table from Baseline, EXPLORER-HCM, Safety Population

		AST (Maximum)			
Grouping Variable	**AST (Baseline)**	**ULN<=1**	**1<ULN<=3**	**3<ULN<=5**	**5<ULN**
MYK-461 (N = 123)	ULN<=1	106 (86.2%)	12 (9.8%)	1 (0.8%)	0 (0%)
	1<ULN<=3	1 (0.8%)	2 (1.6%)	0 (0%)	0 (0%)
	3<ULN<=5	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	5<ULN	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)
Placebo (N = 128)	ULN<=1	111 (86.7%)	10 (7.8%)	0 (0%)	0 (0%)
	1<ULN<=3	2 (1.6%)	4 (3.1%)	0 (0%)	0 (0%)
	3<ULN<=5	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)
	5<ULN	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Source: OCS Analysis Studio, Shift Table Tool.
X Cutoffs: ULN<=1; 1<ULN<=3; 3<ULN<=5; 5<ULN.
Y Cutoffs: ULN<=1; 1<ULN<=3; 3<ULN<=5; 5<ULN.

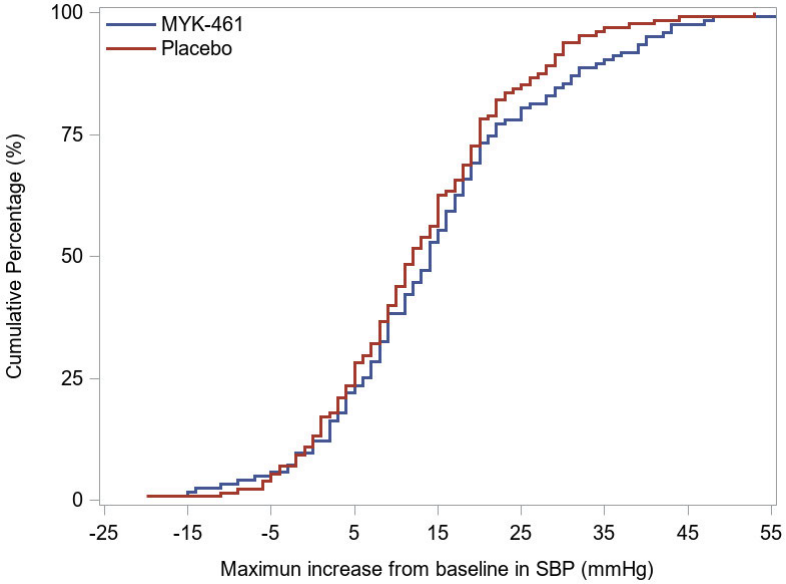
Table 53 Bilirubin (BILI) Shift Table from Baseline, EXPLORER-HCM, Safety Population

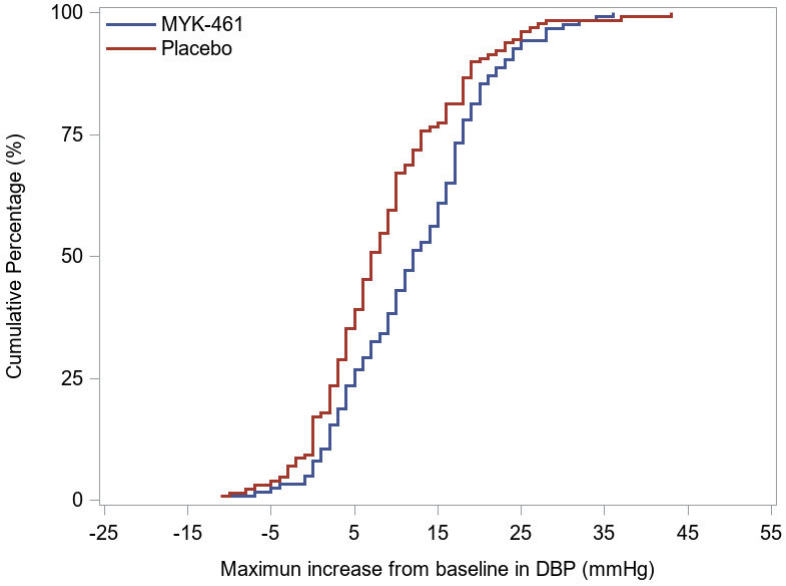
		BILI (Maximum)			
Grouping Variable	**BILI (Baseline)**	**ULN<=1**	**1<ULN<=3**	**3<ULN<=5**	**5<ULN**
MYK-461 (N = 122)	ULN<=1	109 (89.3%)	4 (3.3%)	0 (0%)	0 (0%)
	1<ULN<=3	3 (2.5%)	4 (3.3%)	0 (0%)	0 (0%)
	3<ULN<=5	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)
	5<ULN	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)
Placebo (N = 127)	ULN<=1	115 (90.6%)	5 (3.9%)	0 (0%)	0 (0%)
	1<ULN<=3	1 (0.8%)	2 (1.6%)	2 (1.6%)	0 (0%)
	3<ULN<=5	0 (0%)	2 (1.6%)	0 (0%)	0 (0%)
	5<ULN	0 (0%)	0 (0%)	0 (0%)	0 (0%)

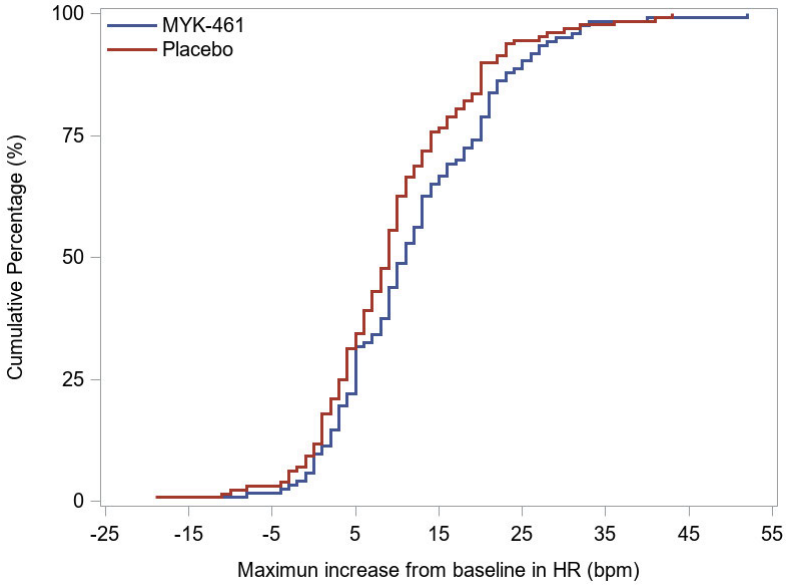
Source: OCS Analysis Studio, Shift Table Tool.
X Cutoffs: ULN<=1; 1<ULN<=3; 3<ULN<=5; 5<ULN.
Y Cutoffs: ULN<=1; 1<ULN<=3; 3<ULN<=5; 5<ULN.

11.5. Additional analyses on vital sign data

Figure 25 Cumulative Distribution Function Plot for Maximum Increase in Vital Signs, Safety Population, EXPLORER-HCM







Source: Reviewer's table, data: EXPLORER ad b

12. Postmarketing Requirements and Commitments

We will issue a PMR aligned with DPMH's recommendations to require the Applicant to conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to mavacamten during pregnancy and/or lactation to assess risk of pregnancy, maternal complications, and adverse effects on the developing fetus, neonate and infant. Infant outcomes will be assessed through at least the first year of life.

13. Financial Disclosure

Table 54. Covered Clinical Studies: [EXPLORER-HCM]

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 316		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

14. References

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10. Nielen JTH, Frank de Vries et al. The Association Between b-Blocker Use and Cardiorespiratory Fitness: The Maastricht Study. Journal of Cardiovascular Pharmacology and Therapeutics. 2019; 24:37-45.

15. Review Team Acknowledgements

Table 55. Reviewers of Interdisciplinary Assessment

Role	Name(s)
Regulatory Project Manager	Alexis Childers
Nonclinical Reviewer	Gowra Jagadeesh
Nonclinical Team Leader	Xuan Chi
Office of Clinical Pharmacology Reviewer(s)	Girish Bende/Nan Zheng/Ying-Hong Wang/Katarzyna Drozda
Office of Clinical Pharmacology Team Leader(s)	Doanh Tran/ Liang Li /Christian Grimstein/ Xinyuan Zhang
Clinical Reviewer	Preston Dunnmon/Rosalyn Adigun/Tzu-Yun McDowell
Clinical Team Leader	Fortunato Senatore
Statistical Reviewer	Ququan Liu
Statistical Team Leader	Jialu Zhang
Cross-Disciplinary Team Leader	Fortunato Senatore
Division Director (OB)	Mark D Rothmann
Division Director (DCN)	Norman Stockbridge
Office Director (signatory)	Hylton Joffe

Table 56. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Daniel Jansen, Rao Kambhampati, Joan Zhao, Lixia Cai, ted Carver
OSI	N/A
OSE/DEPI	Margie Goulding
OSE/DMEPA	Mariette Aidoo
OSE/DRM	Courtney Cunningham
DCOA	Susan Pretko

OPQ=Office of Pharmaceutical Quality; OSI=Office of Scientific Investigations; OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology; DMEPA=Division of Medication Error Prevention and Analysis; DRM=Division of Risk Management

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TZU-YUN C MCDOWELL
04/26/2022 04:38:44 PM

ROSALYN O ADIGUN
04/27/2022 03:29:36 AM

QUQUAN LIU
04/27/2022 09:25:25 AM

JIALU ZHANG
04/27/2022 10:15:41 AM

MARK D ROTHMANN
04/27/2022 10:29:03 AM
concur

FORTUNATO F SENATORE
04/27/2022 11:52:42 AM

NORMAN L STOCKBRIDGE
04/27/2022 11:54:48 AM

HYLTON V JOFFE
04/28/2022 04:22:15 PM
This serves as the decisional memorandum on this application.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CARCINOGENICITY STUDIES

NDA/BLA #:	NDA214998
Drug Name:	Mavacamten (MYK-461) Immediate Release Capsule
Indication(s):	The treatment of symptomatic obstructive hypertrophic cardiomyopathy
Applicant:	MyoKardia, Inc. 1000 Sierra Point Parkway, Brisbane, CA 94005, USA (b) (4)
Date(s):	Consultation Received on 4/27/2021
Documents Reviewed:	Mouse study 8383637 and the electronic tumor.xpt file and SEND datasets were submitted on 1/28/2021 (via NDA214998/S-0001)
Review Priority:	Regular Review
Biometrics Division:	Division of Biometrics VI
Statistical Reviewer:	Feng Zhou, MS
Concurring Reviewers:	Karl Lin, Ph. D., Team Leader
Medical Division:	CDER/OCHEN/DCN
Nonclinical Team:	Xuan Chi, Ph.D; Gowra G. Jagadeesh, Ph.D
Project Manager:	Alexis Childers
Keywords:	Carcinogenicity, Dose response

Table of Contents

1 Summary

This review evaluates statistically the data of the 6-month carcinogenicity study of Mavacamten (MYK-461) in RasH2 transgenic mice by oral gavage for at least 26 weeks. The review analyzes the dose-response relationship of tumor incidences and mortality (including tumor-related mortality). From the statistical point of view, the review concludes that MYK-461 did not show evidence of a carcinogenic potential.

Mouse Study: Mice (25/sex/group) were dosed by oral gavage with MYK-461 once daily for up to 26 weeks. The respective MYK-461 doses in the vehicle control (VC), low (LD), mid (MD), and high-dose (HD) groups were 0, 0.5, 1, and 2 mg/kg/day for the males and 0, 0.5, 1, and 3 mg/kg/day for the females. Twenty mice (ten per sex) in the positive control group were treated with single dose of NMU at 75 mg/kg by intraperitoneal injection on Day 1. All mice were terminated at Week 27.

Excluding the positive control group, the survival analyses didn't show any statistically significant dose response relationship in mortality for both male and female mice. The respective survival rates in the VC, LD, MD, HD, and PC groups at the time they were terminated were 100%, 96%, 92%, 100%, and 10% for male mice and 92%, 96%, 96%, 96%, and 20% for female mice. The mortality was statistically significantly higher in PC group compared with VC group ($p<0.0001$).

Excluding the positive control group, the tumor analysis showed that there was no statistically significant positive dose response among the individual MYK-461treated groups and vehicle control group for both male and female mice. There were also no statistically significant increases in incidence rate in test article treated groups when compared with the vehicle control group. However, the incidence rates of the following tumor types were statistically significant higher in positive control group compared to vehicle control group: malignant lymphoma in hemolympho-reticular system, carcinoma squamous cell and papilloma squamous cell in stomach nonglandular and in skin/subcutis.

2 Background

The Sponsor, MyoKardia, submitted an original new drug application NDA 214998 for mavacamten (MYK-461) immediate release capsule for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in adults to improve functional capacity, (b) (4) and symptoms. The sponsor stated:" Mavacamten was additionally evaluated in a 26-week mouse carcinogenicity study and is currently being evaluated in a 104-week rat carcinogenicity study. No evidence of carcinogenic potential has been identified in the mouse study, and results from the rat study are pending." The agency agreed the 2-year rat study was the part of the post-approval submission. The sponsor submitted the report and electronic dataset of the 6-Month Oral Gavage Mouse Carcinogenicity Study in RasH2 Transgenic Mice on 1/28/2021 via NDA214998/S-0001.

The phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases. Results of this review have been discussed with the nonclinical team.

3 Mouse Study- 8383637

Study Report: 8383637-nc18-0002.pdf (statistical report on page 1596)
SAS data: tumor.xpt and SEND data files

The objective of this study was to assess the carcinogenic potential of MYK-461, an allosteric, selective, and reversible inhibitor of cardiac myosin, when administered to RasH2 transgenic mice by oral gavage for at least 26 weeks. The respective MYK-461 doses in the vehicle control (VC), low (LD), mid (MD), high-dose (HD), and positive control (PC) groups were displayed in following table:

		No. of Animals		Dose Level (mg/kg/day)		Dose Concentration (mg/mL)[a]	
Group	Subgroup	Male	Female	Male	Female	Male	Female
1 (Vehicle Control)[b]	1 (Carcinogenicity)	25	25	0	0	0	0
	2 (Toxicokinetic)	6	6	0	0	0	0
2 (Low)	1 (Carcinogenicity)	25	25	0.5	0.5	0.05	0.05
	2 (Toxicokinetic)	18	18	0.5	0.5	0.05	0.05
3 (Mid)	1 (Carcinogenicity)	25	25	1	1	0.1	0.1
	2 (Toxicokinetic)	18	18	1	1	0.1	0.1
4 (High)	1 (Carcinogenicity)	25	25	2	3	0.2	0.3
	2 (Toxicokinetic)	18	18	2	3	0.2	0.3
5 (Positive Control)[c]	1 (Carcinogenicity)	10	10	75	75	7.5	7.5

a Concentrations (Groups 2 through 4 only) were based on test article as supplied. A correction factor was not used.
b Group 1 was administered vehicle control article only.
c Group 5 was dosed with one intraperitoneal dose of N-methyl-N-nitrosourea (MNU) on Day 1 of the dosing phase. These animals were included as positive controls to ensure animals supplied appropriately express oncogenes and respond to carcinogenic insult.

Assessment of toxicity was based on dose analysis, morbidity, mortality, injury, body weight, food consumption, clinical observations and masses, ophthalmology, clinical pathology, toxicokinetics, macroscopic observations, and microscopic evaluations.

3.1 Sponsor's Analyses

3.1.1 Survival Analysis

Tests to compare survival were performed, with a two-sided risk for increasing and decreasing deaths with dose. Tests were performed for dose response and for each test-article treated group against the vehicle control using Kaplan-Meier product-limit estimation curves, along with log-rank and Wilcoxon tests. These were performed using the LIFETEST procedure in SAS. The time to death or sacrifice (in weeks) was the dependent variable. The treatment group was included as the stratum. Animals with a death or sacrifice status recorded as a planned terminal sacrifice or an accidental death were censored in the analysis.

Sponsor's concluded results: For both males and females, there were no statistically significant differences in survival.

3.1.2 Tumor Data Analysis

Only tumors from tissues listed in the protocol to be examined for all animals were analyzed. For each given tumor type, statistical analysis was performed if the incidence in at least one test-article treated group was increased by at least two occurrences over the control group.

Tests to compare tumor incidence were performed, with a one-sided risk for increasing incidence with dose. Tests were performed for dose response and for each test-article treated group against the vehicle control.

For tumors occurring in animals dying spontaneously or sacrificed in a moribund condition, the Pathologist classified the context of observation as one of the following:

1. Fatal: The tumor was a factor in the demise of the animal.
2. Non-fatal: The tumor was not a factor in the demise of the animal.
3. Uncertain

Occult or non-palpable tumors were analyzed by the International Agency for Research on Cancer (IARC) asymptotic fixed interval-based prevalence test (Peto et al., 1980). The cut off points for the interval-based test were Weeks 1 to 13, 14 to 26, and the terminal sacrifice. Fatal and non-fatal tumors were analyzed together, with a separate stratum for each. No tumors of uncertain context were noted. The test was implemented using PROC MULTTEST in the SAS system. In the case of sparse tables (10 or less total in a stratum), the exact form of the test was used for that stratum. Otherwise, the asymptotic version of the test was used.

Animals were assigned to the terminal sacrifice stratum based on the death or sacrifice status recorded in the data and were not assigned based on their week of necropsy. No observable or palpable (superficial as in mammary or skin) tumors were analyzed using the Peto on-set rate method.

Unadjusted P-values were reported for types of tumors. As there were no statistically significant findings, indication of a possible treatment effect did not need to be assessed on the basis of rare or common tumor type, in line with the current FDA guidelines (Food and Drug Administration Draft Guidance for Industry, 2001).

Sponsor's findings: For both males and females, there were no statistically significant dose-response in tumor incidence rates among the vehicle group and the test-article treated groups, and pairwise increases in test article treated groups compared with the vehicle control group.

3.2 Reviewer's Analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this review analyzed the SAS data sets of this study received on 1/28/2021 (via NDA214998/S-0001) The vehicle control group was compared to each of treated group and water control group for the survival analyses and the tumor analyses.

3.2.1 Data Quality

The sponsor submitted both tumor.xpt file and SEND datasets on 1/28/2021 via NDA214998/S-0001. The sponsor stated: "(b) (4) does not perform any mapping from the SEND dataset to the tumor.xpt file. They are both independently populated directly from the data capture system." There were many discrepancies between two datasets due to the tumor, organ names, and tumor coding, and organ coding were different from two datasets. Following are some examples of the discrepancies. The survival and tumor analyses results based on the two datasets were similar, and conclusions were the same. This report presents the analyses results based on the tumor.xpt file.

1. There was one extra animal in the SEND dataset. Animal (M0407) was replaced due to the moribund. It had no tumor information and was deleted in the tumor.xpt file.

2. The sponsor recoded the tumor codes and combined some organs for some tumors. In the tumor.xpt file, the following organs were combined into Marrow Sternum since the tumor incidence of malignant hemangiosarcoma was in only one mouse (M0024) and the tumor incidence of malignant lymphoma was in only one mouse (M0125). The tumor name of hemolymphoreticular tumor malignant was recoded as malignant lymphoma

   Tumor.xpt:

Organ name	Tumor name	0 mg/kg/day Control P - Trend	0.5 mg/kg/day Low (L) P - C vs. L	1 mg/kg/day Mid (M) P - C vs. M	2 mg/kg/day High (H) P - C vs. H	75 mg/kg/day Positive (PC) P - C vs. PC
Hemolympho-Reticular System	M-Malignant Lymphoma	0/25 (25) 0.7500	1/25 (25) 0.5000	0/25 (25) NS	0/25 (25) NS	9/10 (9) 0.0000 **
Marrow, Sternum	M-Hemangiosarcoma	1/25 (25) 1.0000	0/25 (24) 1.0000	0/25 (25) 1.0000	0/24 (24) 1.0000	0/10 (4) 1.0000

Send dataset:

Organ name	Tumor name	0 mg/kg/day Control P - Trend	0.5 mg/kg/day Low (L) P - C vs. L	1 mg/kg/day Mid (M) P - C vs. M	2 mg/kg/day High (H) P - C vs. H	75 mg/kg/day Positive (PC) P - C vs. PC
Bone, sternum	Hemangiosarcoma, malignant	1/25 (25)	0/25 (24)	0/25 (25)	0/24 (24)	0/10 (4)
		1.0000	1.0000	1.0000	1.0000	1.0000
Bonemarrow, femur	Hemolymphoreticulartumor, malignant	0/25 (25)	1/25 (25)	0/25 (25)	0/24 (24)	0/10 (4)
		0.7475	0.5000	NC	NC	NC
Bonemarrow, sternum	Hemangiosarcoma, malignant	1/25 (25)	0/25 (24)	0/25 (25)	0/24 (24)	0/10 (4)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Hemolymphoreticulartumor, malignant	0/25 (25)	1/25 (25)	0/25 (25)	0/24 (24)	0/10 (4)
		0.7475	0.5000	NC	NC	NC

3.2.2 Survival Analysis

The survival distributions of rates in all treatment groups were estimated using the Kaplan-Meier product limit method. For vehicle control, low, medium, and high dose groups, the dose response relationship was tested using the likelihood ratio test and the homogeneity of survival distributions were tested using the log-rank test. The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 1A and 1B in the appendix for male and female mice. The intercurrent mortality data of all treatment groups are given in Tables 1A and 1B in the appendix for male and female mice. Results of the tests for dose response relationship and homogeneity of survivals for control, low, medium, and high dose groups are given in Tables 2A and 2B in the appendix for male and female mice, respectively.

Reviewer's findings: All mice were killed in week 27. This reviewer's analysis showed the numbers (percent) of death that occurred prior to termination of the group were 0, 1 (4%), 2 (8%), 0 and 9 (90%) for male mice and 2 (8%), 1 (4%), 1 (4%), 1 (4%) and 8 (80%) for female mice in the VC, LD, MD, HD, and PC groups, respectively. The survival analyses didn't show any statistically significant dose response relationship in mortality in males when data of the positive control group were excluded. The mortality was statistically significantly higher in PC group compared with VC group ($p<0.0001$).

3.2.3 Tumor Data Analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of control group with each of the treated groups. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-k method described in the papers of Bailer and Portier [2] and Bieler and Williams [3]. In this method an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of $s_h = 1$. An animal that dies at week w_h without developing the tumor before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}}\right)^k < 1$. The adjusted group size is defined as Σs_h. As an interpretation, an animal with score $s_h = 1$ can be considered as a whole animal while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size

Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor of the tumor type being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104-week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used.

The adjusted levels of significance for testing a positive dose response in the 6-month mice study are 0.05 and 0.05 for a common tumor and a rare tumor, respectively. The adjusted levels of significance for the pairwise comparison in the 6-month mice study are 0.05 and 0.05 for a common tumor and a rare tumor, respectively. A rare tumor is defined as one in which the tumor rate is less than 1% in the vehicle control group. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for male and female mice, respectively.

Reviewer's findings: Based on the criteria of adjustment for multiple testing discussed above, there were no statistically significant positive dose response relationships among the MYK-461 treated groups and vehicle control group for male and female mice when data of the positive control group were excluded. There were also no statistically significant increases in incidence rate in test article treated group when compared with the vehicle control group. However, the incidence rates of tumor types listed in following table were statistically significantly higher for positive control group compared to vehicle control group.

Tumor Types with Statistically Significant (at 0.05 significant level) Dose Response Relationships or Pairwise Comparisons of Treated Groups and Controls in Mice

Sex	Organ name	Tumor name	0 mg/kg/day Vehicle Control (VC)	75 mg/kg/day Positive (PC) P - VC vs. PC
Male	Hemolympho- Reticular System	M-Malignant Lymphoma	0/25 (25)	9/10 (9) 0.0000 **
	Skin/Subcutis	B-Papilloma, Squamous Cell	0/25 (25)	3/10 (6) 0.0044 **
		M-Carcinoma, Squamous Cell	0/25 (25)	4/10 (6) 0.0005 **
	Stomach, Nonglandular	B-Papilloma, Squamous Cell	0/25 (25)	3/10 (5) 0.0025 **
Female	Hemolympho- Reticular System	M-Malignant Lymphoma	1/25 (24)	10/10 (10) 0.0000 **
	Skin/Subcutis	M-Carcinoma, Squamous Cell	0/25 (24)	4/10 (5) 0.0002 **
	Stomach, Nonglandular	B-Papilloma, Squamous Cell	0/25 (24)	5/10 (7) 0.0001 **
		M-Carcinoma, Squamous Cell	0/25 (24)	2/10 (5) 0.0246 **

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NS = Not significant. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.05 for both a common tumor and a rare tumor.

4 Conclusion

This review evaluates statistically the data of the 6-Month Carcinogenicity Study of Mavacamten (MYK-461) in RasH2 Transgenic Mice by oral gavage for at least 26 weeks. The review analyzes the dose-response relationship of tumor incidences and mortality (including tumor-related mortality). From the statistical point of view, the review concludes that MYK-461 did not show evidence of a carcinogenic potential.

Mouse Study: Mice (25/sex/group) were dosed by oral gavage with MYK-461 once daily for up to 26 weeks. The respective MYK-461 doses in the vehicle control (VC), low (LD), mid (MD), and high-dose (HD) groups were 0, 0.5, 1, and 2 mg/kg/day for the males and 0, 0.5, 1, and 3 mg/kg/day for the females. Twenty mice (ten per sex) in the positive control group were treated with single dose of NMU at 75 mg/kg by intraperitoneal injection on Day 1. All mice were terminated at Week 27.

Excluding the positive control group, the survival analyses didn't show any statistically significant dose response relationship in mortality for both male and female mice. The respective survival rates in the VC, LD, MD, HD, and PC groups at the time they were terminated were 100%, 96%, 92%, 100%, and 10% for male mice and 92%, 96%, 96%, 96%, and 20% for female mice. The mortality was statistically significantly higher in PC group compared with VC group ($p<0.0001$).

Excluding the positive control group, the tumor analysis showed that there was no statistically significant positive dose response among the individual MYK-461treated groups and vehicle control group for both male and female mice. There were also no statistically significant increases in incidence rate in test article treated groups when compared with the vehicle control group. However, the incidence rates of the following tumor types were statistically significant higher in positive control group compared to vehicle control group: malignant lymphoma in hemolympho-reticular system, carcinoma squamous cell and papilloma squamous cell in stomach nonglandular and in skin/subcutis.

Feng Zhou
Mathematical Statistician

Concurring Reviewer: Karl Lin, Ph.D., Team Leader, Biometrics-6
cc:
Dr. Xuan Chi
Dr. Gowra G. Jagadeesh
Dr. Yi Tsong
Dr. Karl Lin

5 Appendix

Table 1A: Intercurrent Mortality Rate in Male Mice

	Vehicle Control		Low Dose		Mid Dose		High Dose		Positive C	
Week / Type of Death	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**
0 - 13	.	.	.	.	.	.	.	.	4	40.00
14 - 26	.	.	1	4.00	2	8.00	.	.	5	90.00
Terminal sacrifice	25	100.00	24	96.00	23	92.00	25	100.00	1	10.00
Total	25	.	25	.	25	.	25	.	10	.

Table 1B: Intercurrent Mortality Rate in Female Mice

	Vehicle Control		Low Dose		Mid Dose		High Dose		Positive C	
Week / Type of Death	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**	**No. of Death**	**Cum %**
0 - 13	.	.	.	.	1	4.00	1	4.00	3	30.00
14 - 26	2	8.00	1	4.00	.	.	.	.	5	80.00
Terminal sacrifice	23	92.00	24	96.00	24	96.00	24	96.00	2	20.00
Total	25	.	25	.	25	.	25	.	10	.

Table 2A: Intercurrent Mortality Comparison in Male Mice

Test	**All Dose Groups**	**VC vs. Low**	**VC vs. Mid**	**VC vs. High**	**VC vs. PC**
Dose-Response (Likelihood Ratio)	0.9183	0.2390	0.0935	.	<.0001
Homogeneity (Log-Rank)	0.2947	0.3173	0.1531	.	<.0001

Table 2B: Intercurrent Mortality Comparison in Female Mice

Test	**All Dose Groups**	**VC vs. Low**	**VC vs. Mid**	**VC vs. High**	**VC vs. PC**
Dose-Response (Likelihood Ratio)	0.6636	0.5599	0.5678	0.5678	<.0001
Homogeneity (Log-Rank)	0.9013	0.5610	0.5717	0.5717	<.0001

Table 3A: Tumor Rates and P-Values for Trend and Pairwise Comparisons with Vehicle Control in Male Mice

Organ name	**Tumor name**	**0 mg/kg/day Control P - Trend**	**0.5 mg/kg/day Low (L) P - C vs. L**	**1 mg/kg/day Mid (M) P - C vs. M**	**2 mg/kg/day High (H) P - C vs. H**	**75 mg/kg/day Positive (PC) P - C vs. PC**
Harderian Gland	B-Adenoma	0/25 (25)	1/25 (24)	0/25 (25)	0/24 (24)	0/10 (4)
		0.7449	0.4898	NS	NS	NS
	M-Adenocarcinoma	0/25 (25)	1/25 (24)	0/25 (25)	0/24 (24)	0/10 (4)
		0.7449	0.4898	NS	NS	NS
	C_Adenoma+	0/25 (25)	2/25 (24)	0/25 (25)	0/24 (24)	0/10 (4)
	Adenocarcinoma	0.6211	0.2347	NC	NC	NC

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Organ name	Tumor name	0 mg/kg/day Control P - Trend	0.5 mg/kg/day Low (L) P - C vs. L	1 mg/kg/day Mid (M) P - C vs. M	2 mg/kg/day High (H) P - C vs. H	75 mg/kg/day Positive (PC) P - C vs. PC
Hemolympho-	M-Malignant	0/25 (25)	1/25 (25)	0/25 (25)	0/25 (25)	9/10 (9)
Reticular System	Lymphoma	0.7500	0.5000	NS	NS	0.0000 **
Lung	B-Adenoma,	4/25 (25)	2/25 (24)	2/25 (25)	4/25 (25)	0/10 (4)
	Bronchiolo-Alveo*	0.4602	0.8961	0.9053	0.6490	1.0000
	M-Carcinoma,	0/25 (25)	0/25 (24)	2/25 (25)	0/25 (25)	0/10 (4)
	Bronchiolo-Alveo*	0.5051	NS	0.2449	NS	NS
	C-Bronchiolo-Alveo*	4/25 (25)	2/25 (24)	4/25 (25)	4/25 (25)	0/10 (4)
	B+M	0.4265	0.8961	0.6490	0.6490	1.0000
Marrow, Sternum	M-Hemangiosarcoma	1/25 (25)	0/25 (24)	0/25 (25)	0/24 (24)	0/10 (4)
		1.0000	1.0000	1.0000	1.0000	1.0000
Prostate	M-Sarcoma, Nos	0/25 (25)	0/25 (24)	1/25 (25)	0/25 (25)	0/10 (4)
		0.5051	NS	0.5000	NS	NS
Rectum	M-Hemangiosarcoma	0/25 (25)	0/25 (24)	0/23 (23)	1/24 (24)	0/10 (4)
		0.2500	NS	NS	0.4898	NS
Skin/Subcutis	B-Papilloma,	0/25 (25)	0/25 (24)	0/25 (25)	0/25 (25)	3/10 (6)
	Squamous Cell	NS	NS	NS	NS	0.0044 **
	M-Carcinoma,	0/25 (25)	0/25 (24)	0/25 (25)	0/25 (25)	4/10 (6)
	Squamous Cell	NS	NS	NS	NS	0.0005 **
Spleen	M-Hemangiosarcoma	1/25 (25)	1/25 (24)	3/25 (25)	1/25 (25)	0/10 (4)
		0.4944	0.7449	0.3046	0.7551	1.0000
Stomach,	B-Papilloma,	0/25 (25)	0/25 (24)	0/25 (25)	1/25 (25)	3/10 (5)
Nonglandular	Squamous Cell	0.2525	NS	NS	0 5000	0.0025 **
	M-Carcinoma,	0/25 (25)	0/25 (24)	0/25 (25)	0/25 (25)	1/10 (5)
	Squamous Cell	NS	NS	NS	NS	0.1667
	M-Hemangiosarcoma	0/25 (25)	0/25 (24)	1/25 (25)	0/25 (25)	0/10 (4)
		0.5051	NS	0.5000	NS	NS
Testis	M-Hemangiosarcoma	1/25 (25)	0/25 (24)	0/25 (25)	0/25 (25)	0/10 (4)
		1.0000	1.0000	1.0000	1.0000	1.0000
Thymus	M-Malignant	0/25 (25)	1/25 (24)	0/25 (25)	0/25 (25)	0/10 (4)
	Thymoma	0.7475	0.4898	NS	NS	NS
Whole body	Hemangiosarcoma	3/25 (25)	1/25 (24)	4/25 (25)	2/25 (25)	0/10 (4)
		0.4991	0.9403	0.5000	0.8257	1.0000

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NS = Not significant.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.05 for both common tumor and rare tumor. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.05 for both common tumor and a rare tumor.

Table 3B: Tumor Rates and P-Values for Trend and Pairwise Comparisons with Vehicle Control in Female Mice

Organ name	Tumor name	0 mg/kg/day Control P - Trend	0.5 mg/kg/day Low (L) P - C vs. L	1 mg/kg/day Mid (M) P - C vs. M	3 mg/kg/day High (H) P - C vs. H	75 mg/kg/day Positive (PC) P - C vs. PC
Eye	B-Melanoma, Uveal, Benign	0/24 (24) 0.4948	0/25 (25) NS	1/24 (24) 0 5000	0/25 (24) NS	0/10 (4) NS
Harderian Gland	B-Adenoma	0/25 (24) 0.7526	1/25 (25) 0.5102	0/24 (24) NS	0/25 (24) NS	0/10 (4) NS
	M-Adenocarcinoma	0/25 (24) 0.7526	1/25 (25) 0.5102	0/24 (24) NS	0/25 (24) NS	0/10 (4) NS
	C_Adenocarcinoma +Adenoma	0/25 (24) 0.6237	2/25 (25) 0.2551	0/24 (24) NC	0/25 (24) NC	0/10 (4) NC
Hemolympho-Reticular System	M-Malignant Lymphoma	1/25 (24) 0.9407	1/25 (25) 0.7653	0/25 (24) 1.0000	0/25 (24) 1.0000	10/10 (10) 0.0000 **
Lung	B-Adenoma, Bronchiolo-Alveo*	0/25 (24) 0.1830	0/25 (25) NS	1/25 (24) 0 5000	1/25 (24) 0.5000	0/10 (4) NS
	M-Carcinoma, Bronchiolo-Alveo*	0/25 (24) 0.6263	1/25 (25) 0.5102	1/25 (25) 0 5102	0/25 (24) NS	0/10 (4) NS
	C-Bronchiolo-Alveo* B+M	0/25 (24) 0.3159	1/25 (25) 0.5102	2/25 (25) 0 2551	1/25 (24) 0.5000	0/10 (4) NC
Oral Mucosa	B-Papilloma, Squamous Cell	0/25 (24) NS	0/25 (25) NS	0/25 (24) NS	0/25 (24) NS	1/10 (4) 0.1429
Ovary	M-Choriocarcinoma	0/25 (24) NS	0/24 (24) NS	0/24 (24) NS	0/25 (24) NS	1/10 (5) 0.1724
Rectum	M-Hemangiosarcoma	0/25 (24) 0.4896	0/25 (25) NS	1/23 (23) 0.4894	0/25 (24) NS	0/10 (4) NS
Skin/Subcutis	B-Papilloma, Squamous Cell	0/25 (24) NS	0/25 (25) NS	0/25 (24) NS	0/25 (24) NS	1/10 (5) 0.1724
	M-Carcinoma, Squamous Cell	0/25 (24) NS	0/25 (25) NS	0/25 (24) NS	0/25 (24) NS	4/10 (5) 0.0002 **
	M-Hemangiosarcoma	1/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (24) 1.0000	0/25 (24) 1.0000	0/10 (4) 1.0000
Spleen	B-Hemangioma	0/25 (24) 0.2474	0/25 (25) NS	0/25 (24) NS	1/25 (24) 0.5000	0/10 (4) NS
	M-Hemangiosarcoma	1/25 (24) 0.3647	2/25 (25) 0.5156	1/25 (24) 0.7553	2/25 (25) 0.5156	0/10 (4) 1.0000
Stomach, Nonglandular	B-Papilloma, Squamous Cell	0/25 (24) NS	0/25 (25) NS	0/25 (24) NS	0/25 (24) NS	5/10 (7) 0.0001 **
	M-Carcinoma, Squamous Cell	0/25 (24) NS	0/25 (25) NS	0/25 (24) NS	0/25 (24) NS	2/10 (5) 0.0246 **
Thymus	B-Thymoma	3/25 (24) 0.8051	1/25 (25) 0.9498	1/24 (24) 0 9454	1/24 (23) 0.9404	0/10 (4) 1.0000
	M-Hemangiosarcoma	0/25 (24) 0.7500	1/25 (25) 0.5102	0/24 (24) NS	0/24 (23) NS	0/10 (4) NS
	M-Malignant Thymoma	0/25 (24) 0.7500	1/25 (25) 0.5102	0/24 (24) NS	0/24 (23) NS	0/10 (4) NS

Organ name	Tumor name	0 mg/kg/day Control P - Trend	0.5 mg/kg/day Low (L) P - C vs. L	1 mg/kg/day Mid (M) P - C vs. M	3 mg/kg/day High (H) P - C vs. H	75 mg/kg/day Positive (PC) P - C vs. PC
Uterus	B-Polyp, Endometrial	0/25 (24)	1/25 (25)	1/25 (24)	0/25 (24)	0/10 (4)
	Stromal	0.6237	0.5102	0 5000	NS	NS
	M-Hemangiosarcoma	3/25 (24)	3/25 (25)	1/25 (24)	2/25 (24)	0/10 (4)
		0.6995	0.6864	0 9454	0.8262	1.0000
Vagina	M-Hemangiosarcoma	0/25 (24)	1/25 (25)	0/24 (24)	0/25 (24)	0/10 (4)
		0.7526	0.5102	NS	NS	NS
Whole body	Hemangioma	0/25 (24)	0/25 (25)	0/25 (24)	1/25 (24)	0/10 (4)
		0.2474	NS	NS	0.5000	NS
	Hemangiosarcoma	5/25 (25)	7/25 (25)	3/25 (24)	4/25 (25)	0/10 (4)
		0.7149	0.3708	0.8636	0.7683	1.0000
	C_Hemangiocoma	5/25 (25)	7/25 (25)	3/25 (24)	5/25 (25)	0/10 (4)
	/Hemangiosarcoma	0.5586	0.3708	0.8636	0.6374	1.0000

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NS = Not significant.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.05 for both common tumor and rare tumor. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.05 for both common tumor and a rare tumor.

Figure 1A: Kaplan-Meier Survival Functions for Male Mice

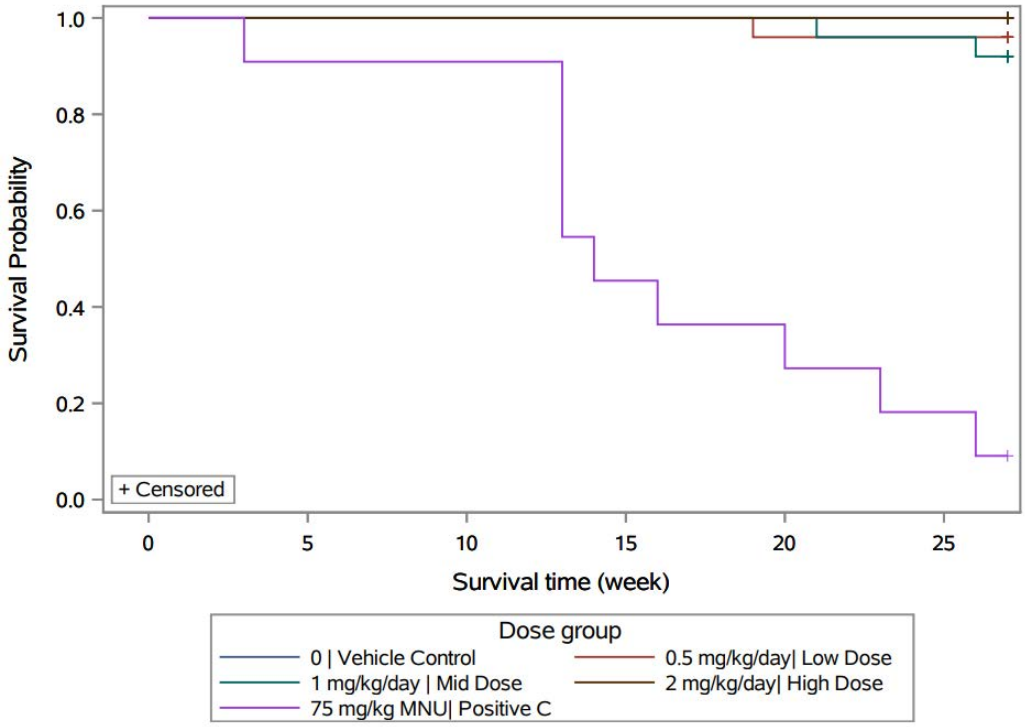
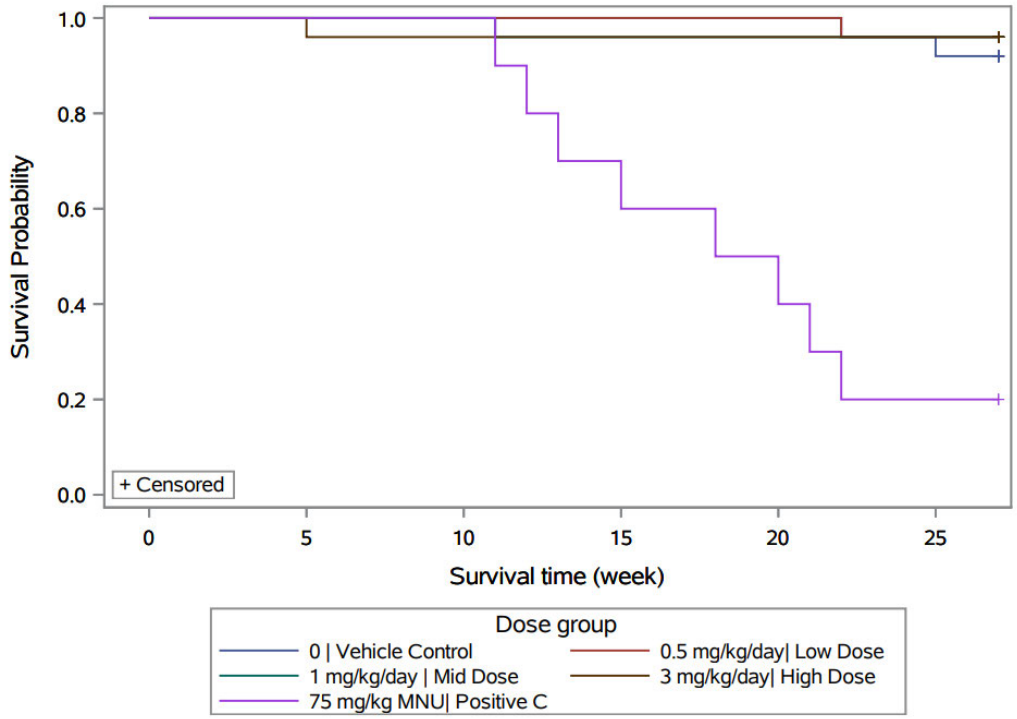


Figure 1B: Kaplan-Meier Survival Functions for Female Mice



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