CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214998Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology

Integrated Clinical Pharmacology Review

[Amendment]

NDA Number	214998
Link to EDR	\\CDSESUB1\evsprod\NDA214998\0001\
Submission Date	28-Jan-2021
Submission Type	505(b)(1) Application (Review Amendment)
Brand Name	Camzyos®
Generic Name	Mavacamten
Dosage Form (Strength)	Immediate-release Capsule (2.5, 5, 10, and 15 mg)
Proposed Indication	Treatment of symptomatic obstructive hypertrophic cardiomyopathy in adults to improve functional capacity, (b) (4) and symptoms.
Applicant	MyoKardia Inc.
Associated IND	IND-121904
OCP Review Team	Girish Bende, Ph.D., Nan Zheng, Ph.D., Ying-Hong Wang, Ph.D., Katarzyna Drozda, Pharm.D., M.S., Christian Grimstein, Ph.D., Xinyuan Zhang, Ph.D., Liang Li, Ph.D., and Doanh Tran, Ph.D.
OCP Final Signatory	Doanh Tran, Ph.D.

Table of Contents

List of Abbreviations

AUC	Area under the concentration-time curve
Cmax	Maximum (peak) drug concentration
ECHO	Echocardiography
EM	Extensive metabolizers
ESRD	End-stage renal disease
fm	Fraction metabolized
HCM	Hypertrophic cardiomyopathy
IM	Intermediate metabolizers
LVEF	Left ventricular ejection fraction (as %)
LVOT	Left ventricular outflow tract gradient (as mm Hg)
NM	Normal metabolizers
NYHA	New York Heart Association functional classification
PD	Pharmacodynamics
PK	Pharmacokinetics
PM	Poor metabolizers
RM	Rapid metabolizers
UM	Ultra-rapid metabolizers

1 Executive Summary

In this original New Drug Application (NDA), Myokardia Inc. is seeking approval of mavacamten capsule for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in adult patients to improve functional capacity, (b) (4) and symptoms. This review is an amendment to our previous Integrated Clinical Pharmacology Review in DARRTS (Dt: 10/18/2021; Reference ID: 4872643) and describes discussions following the last review and additional analyses which were performed to determine a dosing posology and monitoring plan that could offer acceptable safety and efficacy profile without CYP2C19 genotyping.

Mavacamten (MYK-461) is a first-in-class, new molecular entity (NME) and it is not marketed in the US for any indication. It is a reversible cardiac myosin inhibitor which exhibits negative inotropic and positive lusitropic effects and is developed for oral administration. Since mavacamten is a cardiac myosin inhibitor, its treatment is also associated with reduction in baseline systolic function resulting reduced cardiac contractility. Mavacamten exhibits a high pharmacokinetic variability and positive exposure-response relationships between average weekly exposure and decreases in both left ventricular outflow tract gradient (LVOT) gradient and left ventricular ejection fraction (LVEF). In addition, the Applicant proposed a dose titration algorithm based on ECHO (LVEF and LVOT) monitoring and eliminating pharmacokinetic monitoring which was implemented in the pivotal study. Significantly increased exposures of mavacamten were observed in the subjects who are poor metabolizers (PM) of CYP2C19 compared to normal metabolizers (NM) of CYP2C19. Patients who are PM of CYP2C19 have higher exposures of mavacamten compared to normal, rapid (RM), and ultrarapid (UM) metabolizers. Previously, the OCP recommended genotyping patients for CYP2C19 status before initiation of mavacamten treatment (Discipline Review Letter, 09/30/2021) highlighting that prospective CYP2C19 genotyping, and availability of a companion diagnostic is required for optimizing therapeutic use of mavacamten and minimizing safety risks for patients who are PM of CYP2C19. There were also concerns regarding the challenges in therapeutic management of mavacamten including an inherent risk from inadvertent drug interactions (e.g., over the counter use of CYP2C19 inhibitors) that are difficult to control in clinical use. However, there are no FDA approved CYP2C19 genotype diagnostics on the market for the purpose of ensuring the safe use of mavacamten. It was necessary that the Applicant develops a companion diagnostic for mavacamten prior to approval if prospective genotyping is required for safe use of the product. Considering that the regulatory requirements for a companion diagnostic would lead to a delay in availability of this treatment option for patients, alternate strategies such as increasing monitoring schedule and/or a slower up-titration to ensure safe dosing in all patients were explored.

In absence of approved diagnostic test for prospective genotyping of CYP2C19 status, the primary focus of this review amendment is to evaluate and identify 1.) if there are dose titration scheme and monitoring plan in absence of available genotyping data for CYP2C19 status that would be safe and effective and 2.) the need for dose adjustments for drug interactions management.

1.1 Recommendations

The Office of Clinical Pharmacology reviewed the information submitted under NDA-214998 and previously recommended approval of mavacamten capsule (starting dose of 5 mg; with the maximum dose of 15 mg once daily; with prospective genotyping) for the treatment of oHCM in adults. Since that time, a new dosing algorithm and safety monitoring schedule has been developed to allow safe and effective treatment irrespective of their CYP2C19 genotypes. Key review issues with specific recommendations and comments are summarized below in Table 1-1.

Table 1-1 Summary of Review Issues and OCP Recommendations

Review Issues	Recommendations and Comments
General dosing instructions:	The recommended dosing regimen includes: 1) starting dose of 5 mg once daily; 2) dose titration based on ECHO (LVEF and LVOT gradient) monitoring; 3) and maximum daily dose of 15 mg. (b) (4)
	Monitoring on Treatment: • We recommend a starting dose of 5 mg once daily in all patients irrespective of their CYP2C19 genotype and mandatory clinical assessment (ECHO) visits at Week 4, Week 8, Week 12, and every 12 weeks thereafter.
	• The proposed dosing algorithm allows down-titration at Week 4 and Week 8 if VLVOT gradient is less than 20 mmHg (indicating that higher than desirable efficacy has reached; potential exaggerated pharmacology).
	• A stepwise dose increase may be considered every 12 weeks (on Week 12, 24, etc.) if symptoms of obstructive HCM persist, i.e., LVOT gradient is (b) (4) 30 mmHg (indicating that desirable efficacy has not reached) and LVEF is (b) (4) (b) (4) 55% (indicating that it's safe to increase dose with available ejection fraction).
	• In addition, the dosing algorithm includes additional mandatory clinical assessment visit at week 4 following dose increase (i.e., due to up-titration or restart treatment after temporary discontinuation) ensuring safety at new dose level.

Review Issues	Recommendations and Comments
	• Temporary discontinuation (for at least 4 weeks) of mavacamten therapy is recommended if LVEF drops below 50% at any clinical visit during the treatment duration. Patient may resume mavacamten at one lower dose level (i.e., 15 to 10 mg; 10 to 5 mg; 5 to 2.5 mg; once daily) if LVEF returns to above 50% at an additional visit 4 weeks after the temporary discontinuation.
	• If up-titrated or re-started (after temporary discontinuation), schedule a clinical assessment visit at week 4 following a dose increase or re-start to evaluate if same dose level could be maintained (LVEF > 50%) or discontinue for 4 weeks if LVEF < 50% and resume at previous dose level if LVEF returns to >50%.
	• Permanent discontinuation is recommended if a patient experiences 2 incidences of LVEF falling below 50% at the lowest dose (i.e., at 2.5 mg once daily) at any clinical visit during the treatment duration.
Dosing in patient subgroups (intrinsic and extrinsic factors)	**Specific Populations:** **Hepatic Impairment** • Mavacamten undergoes extensive hepatic metabolism. Increased plasma concentrations of mavacamten were observed in subjects with mild to moderate hepatic impairment (Child-Pugh A and B). However, no additional dose adjustment is required in patients with mild to moderate hepatic impairment with the recommended dose titration algorithm and monitoring plan. Mavacamten has not been studied in patients with severe (Child-Pugh C) hepatic impairment.
	Extrinsic factors: **Drug Interactions:** *Impact of Other Drugs on Mavacamten* Mavacamten is extensively metabolized, primarily through CYP2C19 and to lesser extent by CYP3A4. This section describes dosing recommendations for mavacamten during concomitant administration with modulators of CYP2C19 and CYP3A4.
	CYP2C19 or CYP3A4 Inhibitors • Concomitant administration of mavacamten with a moderate to strong CYP2C19 or a strong CYP3A4 inhibitor increases mavacamten exposures. Increased exposures of mavacamten may increase the risk of heart failure due to systolic dysfunction. Concomitant use of mavacamten with a moderate to strong CYP2C19 inhibitor or a strong CYP3A4 inhibitor is contraindicated.
	• Concomitant administration of mavacamten with a weak CYP2C19 inhibitor or a moderate CYP3A4 inhibitor increases mavacamten exposures. Increased exposures of mavacamten may increase the risk of adverse drug reaction. o Considering the dose titration algorithm and monitoring plan, no additional dose adjustment is recommended during initiation of mavacamten therapy. It is recommended to initiate mavacamten at the recommended dosage in patients who are on stable therapy with a weak CYP2C19 inhibitor or a moderate CYP3A4 inhibitor.

Review Issues	Recommendations and Comments
	o However, dose adjustment is recommended in patients who are on stable mavacamten therapy during the concomitant use. It is recommended to reduce dose of mavacamten by one level (i.e., 15 to 10 mg; 10 to 5 mg; 5 to 2.5 mg; once daily) in patients who are on stable therapy and intend to initiate a weak CYP2C19 inhibitor or a moderate CYP3A4 inhibitor. In addition, a clinical assessment visit should be scheduled 4 weeks after inhibitor initiation; however, no potential up-titration should be performed until 12 weeks after inhibitor initiation.
	• Concomitant administration of mavacamten with a moderate to strong CYP2C19 or a moderate to strong CYP3A4 inducer decreases mavacamten exposures. Decreased exposure of mavacamten may reduce its efficacy. Concomitant use of mavacamten with a moderate to strong CYP2C19 inducer or a moderate to strong CYP3A4 inducer is contraindicated. Depending on medical need, mavacamten treatment may be initiated after discontinuing the use of moderate to strong CYP2C19 or moderate to strong CYP3A4 inducers.
	Impact of Mavacamten on Other Drugs • Mavacamten is an inducer of CYP3A4, CYP2C9, and CYP2C19. Concomitant administration of mavacamten with CYP3A4, CYP2C19, or CYP2C9 substrates may reduce plasma concentration of these drugs. It is recommended to closely monitor when mavacamten is used in combination with CYP3A4, CYP2C19, or CYP2C9 substrates where decreases in the plasma concentration of these drugs may reduce their activity. • Combined Oral Contraceptives: Progestin and ethinyl estradiol are CYP3A4 substrates. Concomitant administration of mavacamten may decrease exposures of ethinyl estradiol and progestin. Decreased exposures of hormonal contraceptives may lead to contraceptive failure and/or an increase in breakthrough bleeding. It is suggested to avoiding concomitant administration of mavacamten with combined oral contraceptives. If concomitant use is unavoidable, it is recommended to use an alternative contraceptive method that is not affected by enzyme inducers (e.g., intrauterine system) or additional nonhormonal contraception (such as condoms) during concomitant use and for 4 months after discontinuation of mavacamten.
Labeling	The product label requires changes to reflect the recommended dose/regimen optimizations based on intrinsic and extrinsic factors described above.

Based on these recommendations, the Division of Risk Management (DRM) included a REMS requiring periodic ECHO assessment of LVEF during the mavacamten therapy for early detection of mavacamten-induced depression of ventricular dysfunction and prevention of further deterioration through drug discontinuation or dose adjustment. In addition, the REMS included a pharmacy checklist of patients' prescription and mechanisms to decrease the probability of drug interactions including over the counter medications, etc.

1.2 Post-marketing Commitments and Requirements

None.

2 Summary of Clinical Pharmacology Assessment

2.1 Dosing and Therapeutic Individualization

2.1.1 General Dosing

For the acute treatment of oHCM, the recommended starting dose is 5 mg to be administered orally once daily and the maximum daily dose is 15 mg. Refer to Table 1-1 for recommended dose titration algorithm as well as monitoring plan using echocardiography.

2.1.2 Therapeutic Individualization

Therapeutic individualization is necessary for the following extrinsic/intrinsic factors:

Drug Interactions

Refer to Table 1-1 for dosing recommendations for mavacamten during its concomitant administration with modulators of CYP2C19 and CYP3A4.

Specific Populations

Hepatic Impairment

In a clinical study, higher exposures of mavacamten (AUC increased by ~3.2-fold and ~1.9-fold) were observed in subject with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment, respectively, compared to matched controls. However, no additional dose adjustment is required in patients with mild to moderate hepatic impairment with the recommended dose titration algorithm and monitoring plan.

Other Specific Populations:

No clinically significant differences in the pharmacokinetics of mavacamten were observed based on age (range: 18-82 years), sex, race, ethnicity or mild (eGFR: 60 to 89 mL/min/1.73 m^2) to moderate (eGFR: 30 to 59 mL/min/1.73 m^2) renal impairment. The effect of severe (eGFR: 15 to 30 mL/min/1.73 m^2) renal impairment and ESRD (eGFR: < 15 mL/min/1.73 m^2; including patients on dialysis) are unknown.

2.1.3 Outstanding Issues

None.

2.1.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology has the following labeling concepts to be included in the final package insert.

- The recommended starting dose is 5 mg once daily with the maximum daily dose of 15 mg. The recommended dose titration algorithm and ECHO monitoring plan is described in Table 1-1.

- Mavacamten is extensively metabolized and <3% (~2.6% of total radioactivity) is excreted unchanged in the urine. Dose adjustment is not required for mild and moderate renal impairment with the recommended dose titration algorithm and monitoring plan. Mavacamten has not been studied in patients with severe renal impairment and ESRD (with or without dialysis).
- Increased plasma concentrations of mavacamten were observed in subjects with mild to moderate hepatic impairment. However, no additional dose adjustment is required in patients with mild to moderate hepatic impairment with the recommended dose titration algorithm and monitoring plan. Mavacamten has not been studied in patients with severe hepatic impairment.
- Mavacamten is extensively metabolized, primarily through CYP2C19 and to lesser extent by CYP3A4. Concomitant use of mavacamten with a moderate to strong CYP2C19 inhibitor or a strong CYP3A4 inhibitor is contraindicated. Similarly, concomitant use of mavacamten with a moderate to strong CYP2C19 inducer or a moderate to strong CYP3A4 inducer is contraindicated. Although concomitant administration of mavacamten with a weak CYP2C19 inhibitor or a moderate CYP3A4 inhibitor also increases mavacamten exposures, given the magnitude of impact dose adjustment is recommended (in patients who are on stable mavacamten therapy during the treatment duration). Refer to Table 1-1 for impact of mavacamten on other drugs.

3 Comprehensive Clinical Pharmacology Review

3.1 Clinical Pharmacology Questions

3.1.1 Is there a dosing posology and monitoring plan that could provide acceptable safety and efficacy profile without the need for CYP2C19 genotyping?

Since mavacamten undergoes extensive CYP enzymes mediated metabolism with a major contribution from polymorphic CYP2C19 (fm: ~74%) enzyme, the OCP previously recommended prospective genotyping for CYP2C19 status before initiation of mavacamten treatment with different dosing regimens in patients with PM and non-PM of CYP2C19 genotype status, in order to maintain a low incidence (~2%) of LVEF <50% in all CYP2C19 genotype groups. Refer to the previous review (Reference ID: 4872643) for more information.

After the original clinical pharmacology review was archived, the clinical review team determined that an incidence of less than 5% of patient experiencing LVEF<50%, in any CYP2C19 genotypes, is considered acceptable from the safety perspective. The Applicant's original proposed dosing regimen resulted in remarkably higher proportion of patients with CYP2C19 PM genotype experiencing LVEF<50% during the course of treatment, especially from Week 8 and Week 24. (b) (4) Refer to Figure 4-10 in the previous review (Reference ID: 4872643) for details.

Table 3-1 Comparison of the Review Team's Proposed Dosing Regimen (USPI+) and the Applicant's Originally Proposed Dosing Regimen

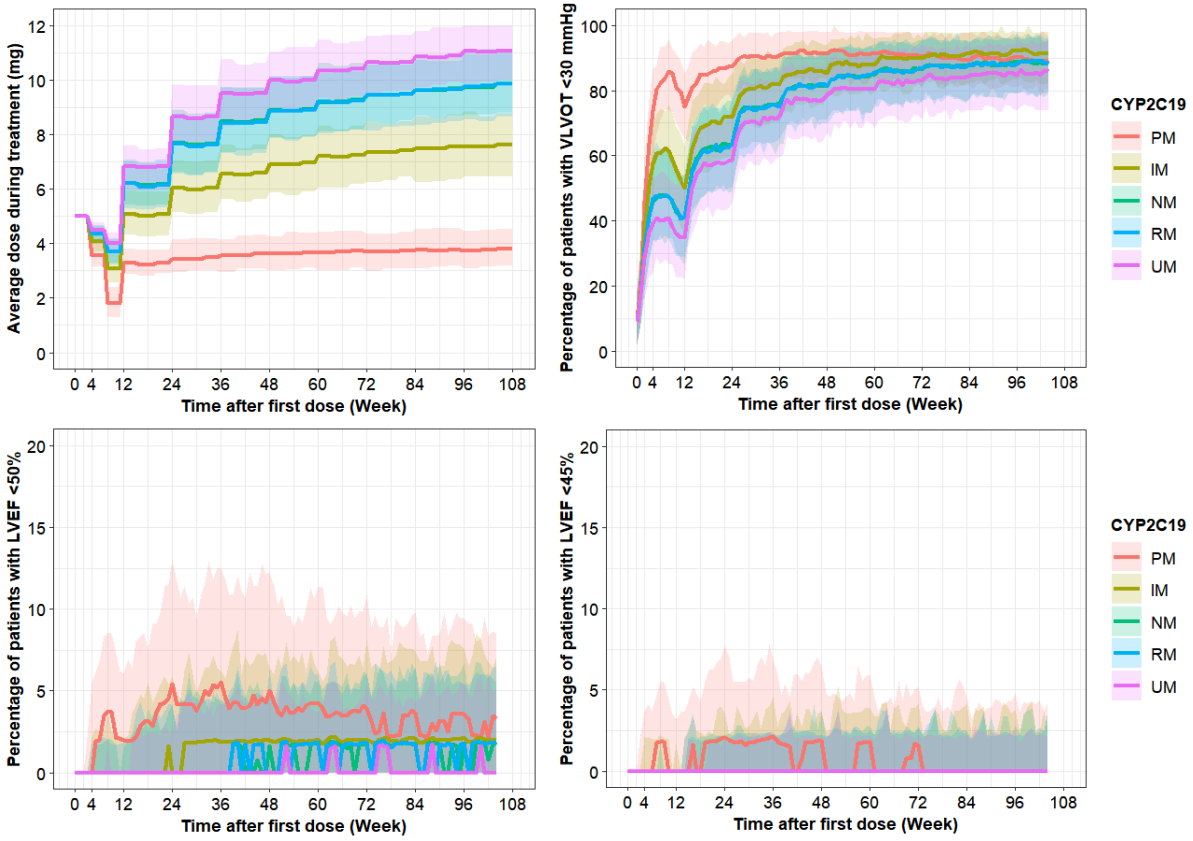
Scenario	Initial dose	Down-titration	Up-titration	Monitoring plan	Permanent discontinuation
USPI	5 mg QD	If VLVOT<20 mmHg at WK4, reduce dose from 5 mg QD to 2.5 mg QD	No dose up-titration until WK12. Dose up-titration if LVEF≥55% and VLVOT (b) (4) 30 mmHg. Up-titration no more frequently than Q12W.	(b) (4)	(b) (4)
USPI+	5 mg QD	If VLVOT<20 mmHg at WK4 or WK8, reduce dose from 5 mg QD to 2.5 mg QD. If VLVOT<20 mmHg at WK4 and WK8, reduce dose from 5 mg QD to 2.5 mg QD at WK4 and further interrupt treatment at WK8.		WK4, WK8, WK12, then Q12W. 4 weeks after dose increase	LVEF<50% for 2 times at 2.5 mg QD

Source: Reviewer's analysis.

Therefore, the review team proposed an additional clinical visit at Week 8 during the initiation of treatment (Week 0 to Week 12) and a monitoring plan of every 12 weeks during the first two years of therapy. Mavacamten dose should be decreased to 2.5 mg QD if VLVOT is < 20 mmHg at Week 4 and may further be interrupted (0 mg) if VLVOT is still <20 mmHg at Week 8. In addition, to reduce the risk of cardiac events, the review team proposed permanent discontinuation of mavacamten treatment if LVEF<50% is observed for 2 times in patients who are on the lowest dose of 2.5 mg QD. A comparison of the review team's proposed dosing regimen (USPI+) and the Applicant's originally proposed dosing regimen (USPI) is shown in Table 3-1.

Simulations were conducted in 200 virtual trials with each trial containing 500 patients equally distributed to 5 genotype groups to verify the review team's proposed dosing regimen. Simulation analysis was based on the Applicant's final popPK and E-R models. Refer to Section 4.1 of the previous review (Reference ID: 4872643) for more details regarding the Applicant's models.

Figure 3-1. Time Course of Average Daily Dose (Upper Left), Percent of Patients with VLVOT<30 mmHg (Upper Right), Percent of Patients with LVEF<50% (Lower Left), and Percent of Patients with LVEF<45% (Lower Right) with the Review Team's Proposed Dosing Regimen.



Source: Reviewer's analysis.

Figure 3-1 shows the time course of mavacamten average daily dose, percent of patients with VLVOT <30 mmHg, percent of patients with LVEF <50%, and percent of patients with LVEF <45% with the review team's proposed dosing regimen. As expected, patients with CYP2C19 PM genotype would have a slightly higher risk of experiencing LVEF<50% during the course of treatment. Overall, the review team's proposed dosing regimen is expected to achieve acceptable benefit-risk (based upon <5% incidence of LVEF <50%, low risk of LVEF <45%, and similar VLVOT <30 mmHg) in all CYP2C19 genotype groups.

In summary, the review team proposed the following dosing regimen for mavacamten for the treatment of symptomatic oHCM in adults to improve functional capacity, (b) (4) and symptoms.

In the proposed dosing regimen, the starting dose is 5 mg QD (Week 0) in all patients. Pre-planned clinical visits are at Week 4, Week 8, Week 12, and every 12 weeks in the first 2 years. A patient may get down-titration at Week 4 and Week 8 only, if VLVOT is less than 20 mmHg. A patient may get up-titration every 12 weeks (Week 12, 24, etc.), if VLVOT is (b) (4) 30 mmHg and LVEF is (b) (4) 55%. If a patient get dose increase at any visit (i.e. due to up-titration or restart treatment after temporary discontinuation), an additional visit will occur at 4 weeks after the dose increase.

At any clinical visit, a patient will be placed on temporary discontinuation (0 mg QD) if LVEF<50%. The patient will have an additional visit at 4 weeks after the temporary discontinuation. The patient can restart at the next lower dose level if LVEF returns to >50% at the additional visit. If a patient experiences LVEF<50% twice at 2.5 mg QD dose, the patient will permanently discontinue from study treatment. A diagram of the dosing regimen is shown below.

Figure 3-2. Revised Dosing Algorithm

3.1.2 Is dose adjustment needed for management of drug interactions with revised dosing posology and monitoring plan?

The main reason that led to the changes in CYP3A and CYP2C19 drug interaction management recommendation is the availability of CYP2C19 genotyping upon approval. The previous CYP3A and CYP2C19 DDI management recommendations in the previous review (Reference ID: 4872643) was based on CYP2C19 genotype or phenotype while the revised recommendation is regardless of CYP2C19 genotype or phenotype. The comparison of the recommendations is summarized in Table 3-2. Of note, at the time the previous review (Reference ID: 4872643) was finalized, there was no simulation for CYP2C19 IMs, or evaluation of the effects of a moderate CYP2C19 inhibitor.

Table 3-2 Comparison of CYP3A and CYP2C19 Drug Interaction Management Recommendations

Concomitant medications		Previous recommendation*	Current recommendation
CYP2C19 inhibitors	Strong	Avoid in non-PMs	Avoid use regardless of CYP2C19 phenotypes
	Moderate	Avoid in non-PMs	
	Weak	Dose adjustment in non-PMs	Dose adjustment, refer to Figure 3-3
CYP3A inhibitors	Strong	Dose adjustment based on dose levels and CYP2C19 phenotypes	Avoid use regardless of CYP2C19 phenotypes
	Moderate		Dose adjustment, refer to Figure 3-3
CYP2C19 and CYP3A inducers	Strong	Avoid	Avoid use regardless of CYP2C19 phenotypes
	Moderate	Avoid or up titration based on dose levels	

** Refer to Clinical Pharmacology Review (Reference ID: 4872643) for details. Non-PM includes IM, NM, RM and UM of CYP2C19.*

In response to the FDA Discipline Review Letter (DRL) dated 09/30/3021, the sponsor submitted a PBPK Report Addendum II (Inhibition Simulations 14102021_full sims) to address the Agency's concern about lack of information to provide appropriate dosage recommendations for IM of CYP2C19 concomitantly administered with CYP2C19 and / or CYP3A inhibitors and for NM of CYP2C19 concomitantly administered with a moderate CYP2C19 inhibitor for CYP2C19 genotype-based drug interaction management.

After reviewing the report, the FDA requested the sponsor to provided verification that the IM and UM population models could predict the PK or drug interaction of other sensitive CYP2C19 substrates and PK of mavacamten in these populations (Clinical Pharmacology Information Request; Dt: 11/16/2021).

In general, the C_{max} and AUC of sensitive CYP2C19 substrates (e.g., omeprazole and lansoprazole) were underpredicted, especially for omeprazole, likely due to small sample size and different formulations (2021-11-16-fda-clin-pharm-q1-q2.pdf). Mavacamten pharmacokinetics, however, was reasonably predicted based on the limited data from phase I studies (Table 3-3).

Table 3-3 Comparison of Geometric Mean Exposure of Mavacamten in IMs and UMs Generated via PBPK and Observed in Phase 1 Studies.

PK Parameter	PBPK Geometric Mean for Intermediate Metabolizers	PBPK Geometric Mean for Ultra-Rapid Metabolizers	Phase 1 Observed Geometric Mean for Intermediate Metabolizers	Phase 1 Observed Geometric Mean for Ultra-Rapid Metabolizers
Dose Normalized AUC_{0-T} (ng.h/(mL.mg))	830.7	369.7	908.0	378.7
Dose Normalized AUC_{0-INF} (ng.h/(mL.mg))	875.8	376.0	694.6	266.3
Dose Normalized AUC_{ss} (ng.h/(mL.mg))	803.4	372.0	992.1	475.3
Dose Normalized C_{max} (ng/(mL.mg))	23.3	22.0	23.2	15.4
Dose Normalized $C_{max\ ss}$ (ng/(mL.mg))	53.3	35.8	54.8	36.9

Source: BMS-myo-1-b-model-app-TIC_AUC024_IM.xlsx; BMS-myo-1-b-model-app-TIC_AUC024_UM.xlsx; BMS-myo-1-b-model-app-TIC MULTI D120_AUCss_IM.xlsx; BMS-myo-1-b-model-app-TIC MULTI D120_AUCss_UM.xlsx

Source: Table 7 in 2021-11-16-fda-clin-pharm-q1-q2.pdf

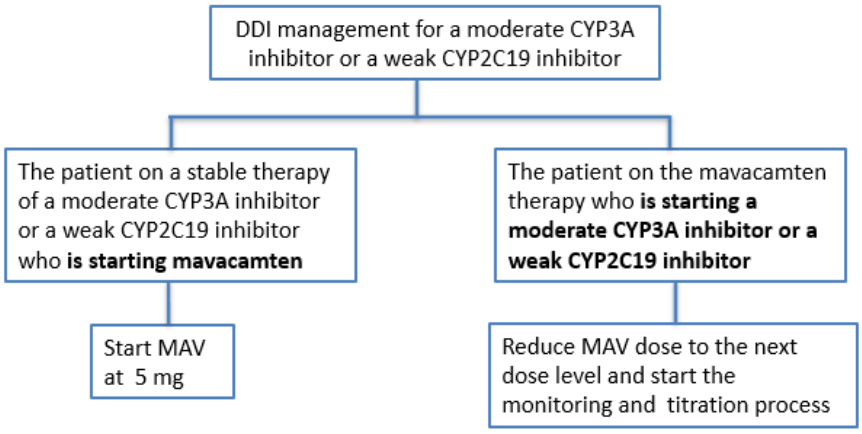
The predicted effects of CYP2C19 and CYP3A inhibitors on steady state mavacamten exposure in healthy subjects with various CYP2C19 phenotype are shown in Table 3-4. These results are, in general, consistent with the results from FDA's analyses described in the previous review (Reference ID: 4872643). Based on these results, it was recommended that strong and moderate CYP2C19 inhibitors, strong CYP3A inhibitors, and strong and moderate CYP2C19 and CYP3A inducers should not be co-administered with mavacamten in all circumstances. A drug interaction management strategy for a moderate CYP3A inhibitor or a weak CYP2C19 inhibitor is depicted in Figure 3-3.

Table 3-4 Predicted Effects of CYP2C19 and CYP3A Inhibitors on Mavacamten PK Following Concomitant Administration of Multiple Doses of Mavacamten in Healthy Subjects with Various CYP2C19 Phenotypes.

Inhibitor	Mavacamten	CYP2C19 PM	CYP2C19 IM	CYP2C19 NM	CYP2C19 UM
Strong CYP2C19 (ticlopidine)	Steady state	C_{max}: 1.00 AUC_{ss}: 1.00 C_{min}: 1.00	C_{max}: 1.36 AUC_{ss}: 1.68 C_{min}: 2.03	C_{max}: 1.59 AUC_{ss}: 1.98 C_{min}: 2.34	C_{max}: 1.57 AUC_{ss}: 2.26 C_{min}: 2.58
Moderate CYP2C19 (omeprazole, 20 mg BID)	Steady state	C_{max}: 1.00 AUC_{ss}: 1.00 C_{min}: 1.00	C_{max}: 1.23 AUC_{ss}: 1.44 C_{min}: 1.64	C_{max}: 1.39 AUC_{ss}: 1.63 C_{min}: 1.97	C_{max}: 1.20 AUC_{ss}: 1.41 C_{min}: 1.69
Weak CYP2C19 (omeprazole, 20 mg QD)	Steady state	C_{max}: 1.00 AUC_{ss}: 1.00 C_{min}: 1.00	C_{max}: 1.13 AUC_{ss}: 1.26 C_{min}: 1.36	C_{max}: 1.22 AUC_{ss}: 1.37 C_{min}: 1.57	C_{max}: 1.10 AUC_{ss}: 1.21 C_{min}: 1.36
Strong CYP3A (itraconazole)	Steady state	C_{max}: 1.54 AUC_{ss}: 1.76 C_{min}: 1.99	C_{max}: 1.17 AUC_{ss}: 1.31 C_{min}: 1.44	C_{max}: 1.17 AUC_{ss}: 1.29 C_{min}: 1.45	C_{max}: 1.11 AUC_{ss}: 1.18 C_{min}: 1.43
Moderate CYP3A (diltiazem)	Steady state	C_{max}: 1.42 AUC_{ss}: 1.55 C_{min}: 1.72	C_{max}: 1.11 AUC_{ss}: 1.19 C_{min}: 1.30	C_{max}: 1.12 AUC_{ss}: 1.19 C_{min}: 1.30	C_{max}: 1.08 AUC_{ss}: 1.13 C_{min}: 1.34
Weak CYP3A (cimetidine)	Steady state	C_{max}: 1.04 AUC_{ss}: 1.06 C_{min}: 1.06	C_{max}: 1.02 AUC_{ss}: 1.03 C_{min}: 1.04	C_{max}: 1.02 AUC_{ss}: 1.03 C_{min}: 1.03	C_{max}: 1.01 AUC_{ss}: 1.02 C_{min}: 1.03
Strong CYP2C19 + Strong CYP3A (ticlopidine + itraconazole)	Steady state	C_{max}: 1.54 AUC_{ss}: 1.76 C_{min}: 1.99	C_{max}: 1.90 AUC_{ss}: 2.72 C_{min}: 3.73	C_{max}: 2.18 AUC_{ss}: 3.05 C_{min}: 4.00	C_{max}: 2.15 AUC_{ss}: 3.47 C_{min}: 5.11
Strong CYP2C19 + Moderate CYP3A (fluvoxamine)	Steady state	C_{max}: 1.06 AUC_{ss}: 1.07 C_{min}: 1.10	C_{max}: 1.47 AUC_{ss}: 1.86 C_{min}: 2.27	C_{max}: 1.60 AUC_{ss}: 2.02 C_{min}: 2.35	C_{max}: 1.80 AUC_{ss}: 2.78 C_{min}: 3.05

Source: Table 9 in 2021-11-16-fda-clin-pharm-q1-q2.pdf

Figure 3-3. Mavacamten Drug Interaction Management Strategy for Concomitant Administration with a Moderate CYP3A Inhibitor or a Weak CYP2C19 Inhibitor.



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/

GIRISH K BENDE
02/24/2022 10:11:33 AM

NAN ZHENG
02/24/2022 10:27:19 AM

YING-HONG WANG
02/24/2022 12:14:55 PM

KATARZYNA DROZDA
02/24/2022 12:19:20 PM

CHRISTIAN GRIMSTEIN
02/24/2022 12:39:11 PM

XINYUAN ZHANG
02/24/2022 12:40:38 PM

LIANG LI
02/24/2022 12:43:37 PM

DOANH C TRAN
02/24/2022 01:33:31 PM

Office of Clinical Pharmacology

Integrated Clinical Pharmacology Review

NDA Number	214998
Link to EDR	\\CDSESUB1\evsprod\NDA214998\0001\
Submission Date	28-Jan-2021
Submission Type	505(b)(1) Application (Standard Review)
Brand Name	Camzyos®
Generic Name	Mavacamten
Dosage Form (Strength)	Immediate-release Capsule (2.5, 5, 10, and 15 mg)
Proposed Indication	Treatment of symptomatic obstructive hypertrophic cardiomyopathy in adults to improve functional capacity, (b) (4) and symptoms.
Applicant	MyoKardia Inc.
Associated IND	IND-121904
OCP Review Team	Girish Bende, Ph.D., Nan Zheng, Ph.D., Ying-Hong Wang, Ph.D., Katarzyna Drozda, Pharm.D., M.S. Christian Grimstein, Ph.D., Xinyuan Zhang, Ph.D., Liang Li, Ph.D., and Manoj Khurana, Ph.D.
OCP Final Signatory	Doanh Tran, Ph.D.

Table of Contents

List of Abbreviations

AE	Adverse event
AUC	Area under the concentration-time curve
AUClast	AUC from time 0 to last measurable concentration
BCRP	Breast cancer resistance protein
Cmax	Maximum (peak) drug concentration
CPET	Cardiopulmonary exercise testing
ECHO	Echocardiography
EM	Extensive metabolizers
ESRD	End-stage renal disease
fm	Fraction metabolized
HCM	Hypertrophic cardiomyopathy
IM	Intermediate metabolizers
LLOQ	Lower limit of quantification
LVEF	Left ventricular ejection fraction (as %)
LVOT	Left ventricular outflow tract gradient (as mm Hg)
NM	Normal metabolizers
NYHA	New York Heart Association functional classification
PD	Pharmacodynamics
P-gp	P-glycoprotein
PK	Pharmacokinetics
PM	Poor metabolizers
pVO2	Peak oxygen uptake measured by CPET
RM	Rapid metabolizers
SAE	Serious adverse event
SRT	Septal reduction therapy
Tmax	Time of maximum (peak) drug concentration
UM	Ultra-rapid metabolizers

1 Executive Summary

In this original New Drug Applications (NDA), Myokardia Inc. is seeking approval of mavacamten capsule for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in adult patients to improve functional capacity, (b) (4) and symptoms.

Mavacamten (MYK-461) is a first-in-class, new molecular entity (NME) and it is not marketed in the US for any indication. It is a reversible cardiac myosin inhibitor which exhibits negative inotropic and positive lusitropic effects and is developed for oral administration. Currently, there is no approved treatment for oHCM and the disease condition is managed by cardiovascular medications (including beta-blockers, verapamil, diltiazem, and disopyramide) to improve left ventricular outflow. In addition, septal reduction therapy is known to reduce obstruction and improve left ventricular outflow.

The proposed starting dose of mavacamten is 5 mg once daily which can be adjusted based on electrocardiography (ECHO) monitoring to maintain the left ventricular ejection fraction above 50% and left ventricular obstruction gradient between 20- and 30- mm Hg using four different strengths (i.e., 2.5, 5, 10, and 15 mg) of available immediate-release capsule formulation. The proposed maximum daily dose is 15 mg.

To demonstrate efficacy, the Applicant is relying on a randomized, double-blind, placebo-controlled, safety, and efficacy study in patients with oHCM (EXPLORER-HCM). The study included a dose titration algorithm based on mavacamten concentrations, ECHO monitoring (left ventricular ejection fraction, LVEF and left ventricular outflow tract gradient, LVOT) and the starting dose of 5 mg once daily. The study was designed to measure improvement in exercise capacity (measured by peak oxygen consumption; pVO2) and functional status (measured by New York Heart Association; NYHA functional classification) associated with mavacamten administration (over 30 weeks) compared to placebo.

Higher proportion of patients treated with mavacamten achieved the composite primary endpoint. In addition, mavacamten treatment was also associated with reduction in obstruction gradient (LVOT) and increased exercise capacity (pVO_2). Additionally, the Applicant used data from one Phase 2 open-label, proof-of-concept study (PIONEER-HCM), and two subsequent Phase 2 or 2/3 ongoing, long-term treatment studies (MAVA-LTE and PIONEER-OLE) to support the use of mavacamten for treatment of oHCM. In addition to these safety efficacy studies, the Applicant included 12 phase 1 studies in this submission.

Since mavacamten is a cardiac myosin inhibitor, its treatment is also associated with reduction in baseline systolic function resulting reduced cardiac contractility. Mavacamten exhibits a high pharmacokinetic variability and a steep exposure-response relationship for ejection fraction (LVEF). In addition, the Applicant proposed a dose titration algorithm based on ECHO (LVEF and LVOT) monitoring and eliminating PK monitoring which was implemented in the pivotal study. Thus, the primary focus of this review is to evaluate the suitability of proposed dose titration scheme, monitoring plan, and the need for dose adjustments based on intrinsic and extrinsic factors.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information submitted under NDA-214998 and we recommend approval of mavacamten capsule (starting dose of 5 mg; with the maximum dose of 15 mg once daily) for the treatment of oHCM in adults. Key review issues with specific recommendations and comments are summarized below in Table 1-1.

Table 1-1 Summary of Review Issues and OCP Recommendations

Review Issues	Recommendations and Comments
Evidence of effectiveness:	The evidence of effectiveness of mavacamten for the treatment of oHCM is from a randomized, double-blind, placebo-controlled, safety, and efficacy study (EXPLORER-HCM). Additionally, two Phase 2, 2/3 long-term studies (MAVA-LTE and PIONEER-OLE) were submitted to support the use of mavacamten for treatment of oHCM.
General dosing instructions:	The recommended dosing regimen includes: 1) starting dose of 5 mg once daily; 2) dose titration based on ECHO (LVEF and LVOT) monitoring; 3) and maximum daily dose of 15 mg. We also recommend to genotype patients for CYP2C19 status before initiation of mavacamten treatment. Recommended dosing in poor metabolizers (PM) of CYP2C19 includes initial 5 mg once daily doses for 4 weeks followed by a three-time-per-week dosing regimen.
Dosing in patient subgroups (intrinsic and extrinsic factors)	**Specific Populations:** **Hepatic Impairment** • Mavacamten has not been studied in patients with severe (Child-Pugh C) hepatic impairment. Mavacamten undergoes extensive hepatic metabolism and thus, significantly increased plasma concentrations of mavacamten are expected in subjects with severe hepatic impairment (Child-Pugh C). Avoid use of mavacamten in patients with severe hepatic impairment. • Increased plasma concentrations of mavacamten were observed in subjects with mild to moderate hepatic impairment (Child-Pugh A and B). It is recommended to use lower starting dose of 2.5 mg once daily with maximum daily dose of 10 mg once daily in patients with mild to moderate hepatic impairment. **Renal Impairment** • Mavacamten has not been studied in patients with severe (eGFR: 15 to 30 mL/min/1.73 m^2) renal impairment or ESRD (eGFR: < 15 mL/min/1.73 m^2; including patients on dialysis). It is recommended to avoid use of mavacamten in patients with severe renal impairment or ESRD (including patients on dialysis). No dosage adjustment of mavacamten is required in patients with mild (eGFR: 60 to 89 mL/min/1.73 m^2) and moderate (eGFR: 30 to 59 mL/min/1.73 m^2) renal impairment.

Review Issues	Recommendations and Comments

Extrinsic factors:

Modulators of CYP2C19 & CYP3A4

The following table describes dosing recommendations for mavacamten during concomitant administration with modulators of CYP2C19 and CYP3A4.

Table 1-2 Dose Adjustment of Mavacamten during its Concomitant Administration with CYP Modulators

Perpetrators		CYP2C19 Phenotype	Current Mavacamten Dose (mg)			
			2.5	5	10	15
CYP2C19 Inhibitors	Strong	Non-PM†	Avoid			
	Moderate*	Non-PM†	Avoid			
	Weak	Non-PM†	Avoid	Reduce (to 2.5 mg)	Reduce (to 7.5 mg)	Reduce (to 10 mg)
CYP3A Inhibitors	Strong	NM, RM, UM	Avoid	Reduce (to 2.5 mg)	Reduce (to 7.5 mg)	Reduce (to 10 mg)
		PM, IM	Avoid	Reduce (to 2.5 mg)	Reduce (to 5 mg)	Reduce (to 7.5 mg)
	Moderate	NM, RM, UM	No Dose Adjustment			Reduce (to 12.5 mg)
		PM, IM	Avoid	Reduce (to 2.5 mg)	Reduce (to 5 mg)	Reduce (to 7.5 mg)
CYP3A & CYP2C19 Inducers	Strong	All	Avoid			
	Moderate	All	Up titration+	Up titration+	Avoid	Avoid

*+Up titration not to exceed 15 mg daily dose; †Non-PM includes IM, NM, RM and UM of CYP2C19. *No information is available on the effects of moderate inhibitors of CYP2C19.*

Labeling	The product label requires changes to reflect the recommended dose/regimen optimizations based on intrinsic and extrinsic factors described above.
Bridge between the "to-be-marketed" and clinical trial formulations	The Phase-3 safety and efficacy studies utilized 2 immediate-release capsule (strengths: 2.5, 5, 10, 15 mg) formulations of mavacamten (Capsule 1 and Capsule 2, intended for commercialization). Since the pivotal safety efficacy study (# 005) mostly utilized intended commercialization formulation (Capsule 2), PK bridging study was not required. However, the Applicant demonstrated bioequivalence between Capsule 1 and Capsule 2 in a relative bioavailability study (Section 3.3.5).

1.2 Post-marketing Commitments and Requirements

None.

2 Summary of Clinical Pharmacology Assessment

2.1 Pharmacology and Clinical Pharmacokinetics

Mechanism of Action:

Mavacamten (MYK-461; MW: ~273.3 g/mol; pyrimidinedione derivative) is a reversible inhibitor of cardiac myosin and exhibits negative inotropic and positive lusitropic effects. Hypertrophic cardiomyopathy is associated with hypercontractility, impaired relaxation, and dynamic outflow tract obstruction. It's believed that mavacamten treatment is associated with modulation of the number of myosin heads that can enter "on actin" states reducing force-producing (systolic) and residual (diastolic) cross-bridge formation resulting in reduced LVOT obstruction and ventricular filling pressures, improved symptoms, and increased exercise capacity.

Absorption:

The mean absolute bioavailability of mavacamten following oral administration is ~85%. The results of relative bioavailability study in healthy subjects demonstrated that the bioavailability of mavacamten from developmental capsule formulation is comparable to that with the intended to-be marketed capsule formulation. The median Tmax of mavacamten capsule are 1 and 4 h, under fasting and fed conditions, respectively.

Food effect:

Following administration of capsule formulation under fed condition with high fat meal, the rate and extent of absorption of mavacamten were decreased compared to that observed under fasting condition. The time to maximum plasma concentration was delayed by 3-hour, peak concentration was reduced by ~56% and total exposure was reduced by ~12%. However, the pivotal efficacy/safety studies were performed without regard to food. No information on fasted/fed state during efficacy assessments were collected in these studies.

Distribution:

The mean apparent volume of distribution of mavacamten is approximately 270 L in oHCM patients. Relatively lower volume of distribution was observed in healthy subjects (i.e., 114 to 206 L). Mavacamten is approximately 97 to 98% bound to human plasma proteins.

Metabolism:

Mavacamten is extensively metabolized forming multiple metabolites with no major metabolites (i.e., metabolites that represented >10% of drug-related material) detected in plasma. Mavacamten is primarily excreted as metabolites with unchanged drug being the most abundant (~70% of total radioactivity) moiety in plasma. The hydroxy metabolite (M2; MYK-1078; with total plasma radioactivity <4%; followed by M27: <2%; traces of M32, M36 to M46) was the most abundant metabolite in plasma. In addition to hydrolysis and oxidative N-dealkylation, oxidation of mavacamten is the predominant biotransformation pathway. The other minor biotransformation pathways include dehydrogenation, dehydration, methylation, glucuronidation, and glycine

conjugation. Studies indicate that the metabolism is mainly mediated by CYP2C19 (fm: ~74%), followed by CYP3A (fm: ~18%), and to lesser extent by CYP2C9 (fm: ~7.6%).

Excretion:

Following single oral dose administration of 25 mg [^{14}C]-mavacamten to healthy male subjects, mavacamten was primarily excreted as metabolites in urine (~85% of total radioactivity) with biliary excretion as a minor excretion pathway (~7% of total radioactivity). Only, 2.6% was recovered as unchanged mavacamten in urine with estimated renal clearance of 30 to 40 mL/h. Elimination half-life of mavacamten depends on CYP2C19 genotype (8 days in NM vs 23 days in PM).

Drug Interactions

Refer to Table 1-2 for dosing recommendations for mavacamten during concomitant administration with modulators of CYP2C19 and CYP3A4.

Specific Populations:

Renal Impairment

No dedicated clinical study was conducted to evaluate the effect of renal function on the pharmacokinetics of mavacamten. Considering that the renal elimination is a minor excretion pathway, population pharmacokinetic analysis was utilized. Population pharmacokinetic analysis did not reveal clinically meaningful differences in the pharmacokinetics of mavacamten in patients with mild and moderate renal impairment compared to patients with normal renal function (Sections 3.3.3.3 and 4.1). However, mavacamten has not been studied in patients with severe renal impairment, ESRD (eGFR: < 15 mL/min/1.73 m^2), and in patients on dialysis.

Hepatic Impairment

In a clinical study comparing pharmacokinetics of mavacamten in subjects with mild and moderate hepatic impairment (Child-Pugh Class A and B) to matched controls, higher exposures of mavacamten (AUC increased by ~3.4-fold) were observed in subject with mild hepatic impairment (Child-Pugh A). Although the observed exposures of mavacamten in subject with moderate hepatic impairment (Child-Pugh B) were relatively lower than those observed in subject with mild hepatic impairment, the correction between exposure and hepatic function could not be identified due to a limited sample size and high pharmacokinetic variability. Mavacamten is extensively metabolized by liver enzymes, significantly higher exposures of mavacamten are expected in subject with severe hepatic impairment (Child-Pugh C).

Effects of Body Weight, Gender, Race, Age, and disease state

Body weight, sex, race, and age did not have a clinically relevant effect on the exposure (AUC and Cmax) of mavacamten (Section 3.3.3.4).

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

For the acute treatment of oHCM, the recommended starting dose is 5 mg to be administered orally once daily and the maximum daily dose is 15 mg.

2.2.2 Therapeutic individualization

Therapeutic individualization is necessary for following extrinsic/intrinsic factors:

CYP2C19 Poor Metabolizers

Significantly increased exposures of mavacamten were observed in the subjects who are PM of CYP2C19 compared to normal metabolizers (NM) of CYP2C19. Before initiation of mavacamten treatment, we recommended genotyping patients for CYP2C19 status. Patients who are PM of CYP2C19 have slower elimination and longer half-life compared to NM of CYP2C19 requiring less-frequent dosing than the proposed once daily regimen (Section 3.3.3.1). Recommended dosing in PM of CYP2C19 includes initial 5 mg once daily doses for 4 weeks followed by a three-time-per-week dosing regimen (Section 3.3.2).

Drug Interactions

Refer to Table 1-2 for dosing recommendations for mavacamten during its concomitant administration with modulators of CYP2C19 and CYP3A4 (Section 3.3.4).

Specific Populations

Renal Impairment

Population pharmacokinetic analysis did not reveal clinically meaningful differences in the pharmacokinetics of mavacamten in patients with mild and moderate renal impairment compared to patients with normal renal function (Section 4.1). No dose or dosing frequency adjustment is required in patients with mild to moderate renal impairment (Section 3.3.3.3).

However, mavacamten has not been studied in patients with severe renal impairment, ESRD (eGFR: < 15 mL/min/1.73 m^2), and in patients on dialysis. No dosing recommendations can be made for patients with severe renal impairment and ESRD. Therefore, use of mavacamten should be avoided in patient with severe renal impairment or ESRD.

Hepatic Impairment

In a clinical study, higher exposures of mavacamten (AUC increased by ~3.2-fold and ~1.9-fold) were observed in subject with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment, respectively, compared to matched controls. The correction factor between exposure and hepatic function could not be identified due to a limited sample size and high pharmacokinetic variability. It is recommended to use lower starting dose of 2.5 mg once daily with maximum daily dose of 10 mg once daily in patients with mild to moderate hepatic impairment (Section 3.3.3.2). Significantly higher exposures of mavacamten are expected in subject with severe hepatic

impairment (Child-Pugh C). Therefore, the use of mavacamten should be avoided in patients with severe hepatic impairment (Section 3.3.3.2).

Other Specific Populations:

No clinically significant differences in the pharmacokinetics of mavacamten were observed based on age, sex, race/ethnicity, body weight (Section 3.3.3.4).

2.2.3 Outstanding Issues

None.

2.2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology has the following labeling concepts to be included in the final package insert.

- The recommended starting dose is 5 mg once daily in general population with the maximum daily dose of 15 mg.
- It is recommended to genotype patients for CYP2C19 status before initiation of mavacamten treatment. Recommended dosing in PM of CYP2C19 includes initial 5 mg once daily doses for 4 weeks followed by a three-time-per-week dosing regimen.
- Dose adjustment is not required for mild and moderate renal impairment. Mavacamten has not been studied in patients with severe renal impairment and ESRD (with or without dialysis). It is recommended to avoid use of mavacamten in patients with severe renal impairment or ESRD.
- Increased plasma concentrations of mavacamten were observed in subjects with mild to moderate hepatic impairment. It is recommended to use lower starting dose of 2.5 mg once daily with maximum daily dose of 10 mg once daily in patients with mild to moderate hepatic impairment. Mavacamten has not been studied in patients with severe (Child-Pugh C) hepatic impairment. Avoid use of mavacamten in patients with severe hepatic impairment.
- The dosage adjustment of mavacamten when it is concomitantly administered with a CYP2C19 or CYP3A modulator is dependent upon the CYP2C19 phenotype of the patient (Table 1-2).
- Dose adjustment is not required based on demographic factors such as age, sex, race, and body weight.

3 Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

Mavacamten is a cardiac myosin inhibitor, and it is formulated as an immediate-release capsule formulation. The product is intended for oral administration and contains 2.5, 5, 10, and 15 mg of mavacamten. The clinical development program to demonstrate the safety/efficacy for mavacamten consisted of one placebo-controlled Phase 3 study in patients with oHCM (Study # 005). Additionally, the Applicant used data from 2 phase-2 dose finding studies (Study 004 in oHCM and Study # 006 in nHCM) in patients with HCM and 2 Phase 2/3, long-term safety studies (Study # 007; MAVA-LTE and Study # 008; PIONEER-OLE) to support the use of mavacamten for treatment of oHCM. The phase-3 studies were conducted with dose titration based on ECHO (LVOT and LVEF) monitoring. In addition, pivotal study (Study # 005) also included PK based dose adjustment. The application also included 12 phase 1 clinical studies.

3.2 General Pharmacological and Pharmacokinetic Characteristics

The pharmacokinetic properties of mavacamten have been characterized in the phase-1 and 2 studies (Table 3-1).

Table 3-1 Summary of Pharmacological and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Mavacamten is a cardiac myosin inhibitor.
Active Moieties	Mavacamten
QT Prolongation	The effect of mavacamten on the QTc interval was evaluated in multiple clinical studied conducted in healthy subjects and HCM patients. A concentration-dependent QT prolongation was detected with multiple dosing (over a dose range of 2 to 25 mg) in healthy subjects (Study # 003). However, no significant QTc prolongation of mavacamten was detected with target population (oHCM and nHCM; Studies # 004, 005, and 006) over the therapeutic concentration range. The mechanism for QTc prolongation is unknown (refer to the IRT review dated 07/19/2021).
General Information	
Bioanalysis	The concentrations of mavacamten human plasma were determined using a validated LC-MS/MS method (Section 5.1).
Healthy Subjects vs. Patients	Higher exposures of mavacamten (~2.7-fold) were observed in patients compared to healthy subjects at the same dose level (Section 4.1).

Dose Proportionality	Mavacamten exhibits dose proportionate pharmacokinetics in dose range of 6 and 48 mg (Study # 002).
Accumulation	Significant accumulation of mavacamten (AUC: ~7-fold; Cmax: 2-fold) was observed with once daily dosing. The accumulation is dependent on the metabolism status for CYP2C19 (Section 3.3.3.1).
Pharmacokinetic Variability	Mavacamten exhibits PK variability and coefficient of variation for Cmax and AUCinf were between ~30 to ~50% (Section 4.1).
Absorption	
Bioavailability	The mean absolute bioavailability of mavacamten following oral administration is ~85% (Study # 013).
Tmax	Approximately 1 h under fasting condition Approximately 4 h under fed condition
Food Effect	Mavacamten exhibits a negative food effect with decreased exposures under fed condition (with high-fat meal) compared to fasting condition (Section 3.3.4.3.1). • AUCinf decreased by ~12% • Cmax decreased by ~56% • Tmax was delayed by ~3 hour
Distribution	
Apparent Volume of Distribution	~270 L in oHCM patients (Section 4.1); Relatively lower volume of distribution was observed in healthy subjects (i.e., 114 to 206 L).
Protein Binding	97 to 98%
Transports	In vitro human transporter studies indicated that mavacamten is a substrate of P-gp and BCRP (Section 3.3.4.2). It was not found to be a substrate of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K. Moreover, mavacamten exhibits a low renal clearance. Mavacamten was not found to be a potent inhibitor of P-gp, BSEP, BCRP, OAT1, OAT3, OCT1, OCT2, and MATE2k. It is a weak to moderate inhibitor of MATE1 (Section 3.3.4.2).
Elimination	
Mean Terminal Elimination Half-life	Elimination half-life considerably depends on CYP2C19 genotype (8 days in NM vs 23 days in PM; Section 3.3.3.1).

Metabolism	
Metabolic Pathway	Mavacamten is extensively metabolized primarily by oxidation with major contribution from CYP2C19 (fm: ~74%), followed by CYP3A (fm: ~18%), and to lesser extent by CYP2C9 (fm: ~7.6%). The hydroxy metabolite (M2; MYK-1078; with total plasma radioactivity <4%; followed by M27: <2%; traces of M32, M36 to M46) was the most abundant metabolite in plasma. In addition to hydrolysis and oxidative N-dealkylation, oxidation of mavacamten is the predominant biotransformation pathway. The other minor biotransformation pathways include dehydrogenation, dehydration, methylation, glucuronidation, and glycine conjugation.
Inhibitor / Inducer	In-vitro studies using human liver microsomes indicated that mavacamten is not an inhibitor of CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4/5 up to 10 µM (Study # NC-17-0020). In-vitro studies using human liver microsomes also indicated that mavacamten is not a time-dependent inhibitor of CYP2C9, 2D6, or 3A4/5 up to 100 µM (Study # NC-17-0021). In-vitro studies using primary human hepatocyte culture indicated that mavacamten is an inducer of CYP2B6, 2C8, 2C9, 2C19 and 3A4 with no induction effect on CYP1A2 (Study # NC-17-0006 & # NC-17-0012).
Excretion	
Excretion Pathway	Mavacamten is predominately eliminated by metabolism and metabolites are primarily excreted in urine (~85% of total radioactivity) with biliary excretion as a minor excretion pathway (~7% of total radioactivity). Approximately, 2.6% of the dose was recovered as unchanged mavacamten in urine (~92% of total recovery over 47 days post-dose; Study # 013; administered as a single oral administration of 25 mg of ^{14}C mavacamten under the fasting condition in healthy subjects and NM of CYP2C19).

3.3 Clinical Pharmacology Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The evidence of effectiveness of mavacamten for the treatment of acute oHCM is from a pivotal clinical study (Study # 005; EXPLORER-HCM). In addition, the Applicant used data from one preceding Phase 2 open-label, proof-of-concept study (Study # 004; PIONEER-HCM, Table 3-2), and two subsequent Phase 2 or 2/3 ongoing, long-term treatment studies (Study # 007; MAVA-LTE and Study # 008; PIONEER-OLE) to support the use of mavacamten for treatment of oHCM (Table 3-3).

To inform the dosing in pivotal studies, the Applicant conducted an open-label, placebo-controlled, dose-ranging study in patients with symptomatic oHCM (Study # 004; PIONEER-HCM). In this 2-part study, the Applicant utilized higher starting doses (i.e., 10 mg once daily for BW ≤ 60 kg and 15 mg once daily for BW > 60 kg) in part-A of the study with dose titration at Week 4 (up to 20 mg) based on percent decrease from baseline in LVEF. Part-B utilized, lower starting dose (i.e., 2 mg once daily) with dose titration at Week 4 (to 5 mg) was based on percent change from baseline in LVOT gradient.

Table 3-2 Summary of Left Ventricular Outflow Tract Gradient (Top) and Left Ventricular Ejection Fraction (Bottom) [Study # 004]

	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)

	Part A			Part B		
	Baseline (N)	Week 12 (N)	Mean Change (p-value)	Baseline (N)	Week 12 (N)	Mean Change (p-value)
Resting LVEF (%) ± SD	70 ± 7 (11)	55 ±10 (10)	-15 ± 12 (p = 0.004)	75 ± 5 (10)	69 ± 6 (10)	-6 ± 6 (p = 0.002)
Post-exercise LVEF (%) ± SD	76 ± 8 (11)	60 ± 22 (4)	-17 ± 22 (p = 0.375)	76 ± 8 (9)	72 ± 3 (9)	-4 ± 7 (p = 0.098)

**LVOT: Left Ventricular Outflow Tract Gradient.*

Source: Applicant's Analysis; Study # 004 CSR

The study explored PK/PD relationship and identified concentrations of mavacamten (Ctrough) associated LVOT gradient and LVEF. Considering steep PK/PD relationship for ejection fraction, the protocol pre-specified temporary discontinuation based on 1) mavacamten trough concentration ≥ 1000 ng/mL, 2) LVEF < 50%, or 3) increased QT interval (with ΔQTcF ≥ 15% as change from baseline). The PK/PD modeling was also used to inform the starting dose (i.e., 5 mg once daily) for subsequent Phase-3 studies. Phase-3 studies were designed to target a mavacamten plasma trough concentration <700 ng/mL to maintaining normal ejection fraction (i.e., LVEF > 50%) while attaining and maintaining relevant decrease in gradient (i.e., LVOT < 30 mm Hg and > 20 mm Hg).

Table 3-3 Summary of Clinical Safety and Efficacy Studies

Clinical Studies	Study # 005 (EXPLORER-HCM)	Study # 008 (PIONEER-OLE)	Study # 007 (MAVA-LTE)
Objective	Superiority to Placebo	Long-term Safety	Long-term Safety
Treatment	Starting dose: 5 mg once daily; maximum daily dose: 15 mg once daily		
PK Guided	PK	PK	-
PD Guided	PD*	PD*	PD*
Dosing Duration	30-Weeks	104-Week	104-Week
Design	Double-blinded	Open-label Extension	Open-label Extension
Placebo	Placebo-controlled	-	-
Formulation	Capsule	Capsule	Capsule
Patients	oHCM	oHCM	nHCM and oHCM
Continuation of Previous Studies	-	Study # 004	Studies # 005 & # 006

Dose titration based on mavacamten concentrations, LVEF and LVOT measurements using ECHO.

Study # 005 was the pivotal phase-3, randomized, double-blind, placebo-controlled study evaluating safety and efficacy of mavacamten in patients with oHCM (resting or provoked gradient ≥ 50 mm Hg and LVEF >55%). Patients (n=251) received titration-based mavacamten dose (starting dose of 5 mg and maximum daily dose of 15 mg once daily) or placebo for 30 weeks. The study utilized a dosing algorithm based on measurements of mavacamten plasma concentrations and echocardiography (measurements of LVOT gradient and LVEF) assessed by a central laboratory.

The primary objective of the study was to evaluate improvement in functional capacity and symptom burden with mavacamten treatment compared to placebo using 2 indicators: 1) peak oxygen uptake (pVO2) by cardiopulmonary exercise testing (CPET) and 2) NYHA functional classification. Study results indicated that a greater proportion of subjects treated with mavacamten achieved the primary composite functional endpoint that included both objective (pVO2) and subjective (NYHA class) assessments of functional capacity and symptoms compared with placebo (36.6% *vs*. 17.2%; between-group difference 19.4%, 95% CI: 8.7 to 30.1; p = 0.0005).

Furthermore, the proportion of subjects who achieved the most stringent components of the composite functional endpoint (≥ 3.0 mL/kg/min increase in pVO2 AND ≥ 1 NYHA class improvement) was 20.3% for mavacamten-treated subjects compared with 7.8% for placebo subjects. Mavacamten treatment was associated with post-exercise LVOT gradient to below the standard threshold for invasive septal reduction therapy (i.e., < 50 mm Hg) in 74% of subjects who had post exercise gradient ≥ 50 mm Hg at baseline compared with 21% of subjects in the placebo group (Study # 005), and 65% of mavacamten-treated subjects improved by ≥ 1 NYHA class from baseline to Week 30 compared with 31% of subjects in the placebo group (Study # 005).

Although the magnitude of the changes from baseline in the pVO2, KCCQ, and HCMSQ were statistically significant, considerable within-subject variabilities were observed for these parameters. The clinically relevance of these endpoints and the benefit-risk profile of mavacamten is discussed in the clinical review (by Dr. Tzu-Yun McDowell and Dr. Preston Dunnmon). The available safety data from completed and on-going studies is also available in a separate clinical review (by Dr. Tzu-Yun McDowell and Dr. Preston Dunnmon, MD).

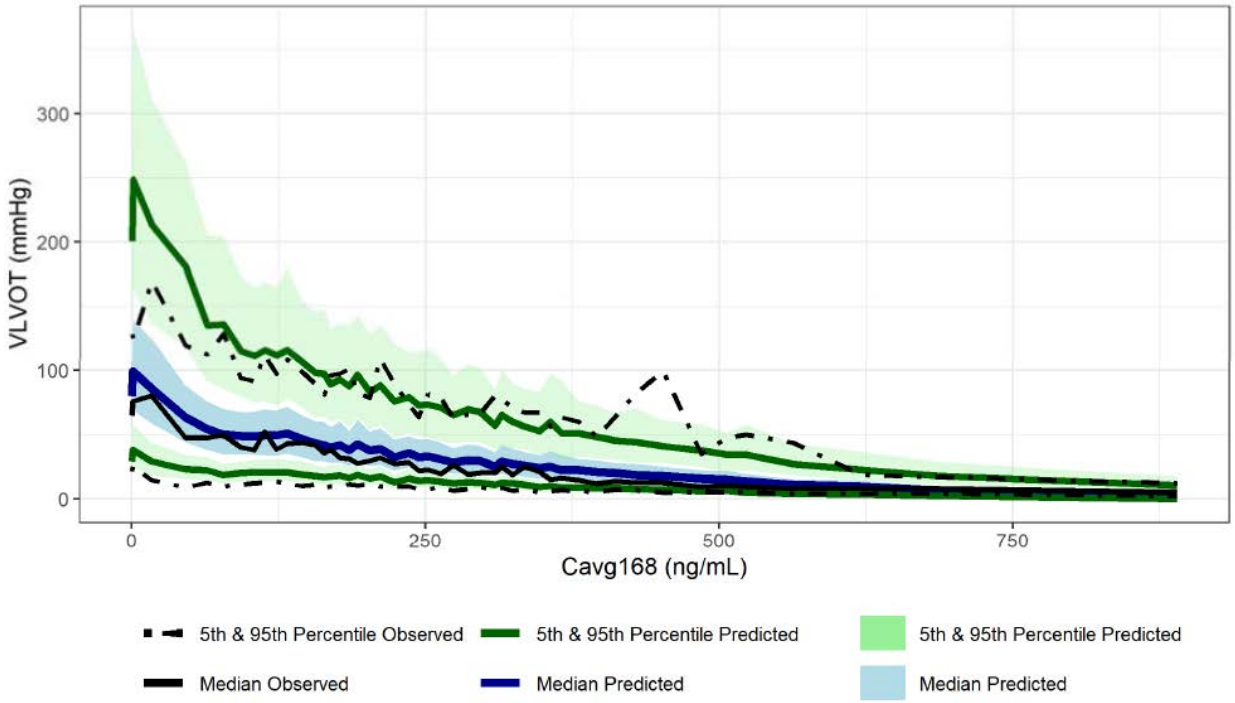
3.3.2 Is the proposed dosing regimen appropriate for the general population for which the indication is being sought?

Yes, one placebo-controlled, phase-3 study (Study # 005), one open-label, phase-2 study (Study # 004), and 2 on-going long-term extension studies (Studies # 006, and # 007) demonstrated that mavacamten administered as once daily capsule is superior to placebo for the treatment of oHCM (Section 3.3.1).

The Applicant conducted the exposure response analyses for efficacy and safety endpoints (Studies # 004, # 005, # 007, # 008) using a non-linear mixed effects modeling. Each of these studies included mavacamten as monotherapy or in addition to standard of care therapy. In general, hypertrophic cardiomyopathy is associated with patients who have unexplained left ventricular hypertrophy, hypercontractility, and impaired relaxation. Thus, HCM phenotypes are identified as

the presence (obstructive; oHCM) or absence (non-obstructive; nHCM) of obstruction of the left ventricular outflow tract (LVOT; where obstruction is defined as a peak LV outflow gradient ≥ 30 mm Hg; at rest or with provocation). Considering the targeted effect of mavacamten in reducing obstruction in outflow tract, the E-R model was developed to characterize the relationship between mavacamten exposure (trough) and VLVOT (LVOT gradient with provocation using Valsalva maneuver) in Figure 3-1. Since mavacamten is a cardiac myosin inhibitor, its treatment is also associated with undesirable effects on systolic function primarily due to its reduced cardiac contractility. For this purpose, the E-R model was also developed to characterize the relationship between mavacamten and LVEF (Figure 3-2). Analysis indicated a direct relationship between plasma concentrations (as Cavg at 168 h) and LVEF as well as between plasma concentrations (as Cavg at 168 h) and VLVOT.

Figure 3-1 Exposure-Response Relationship Between Mavacamten Concentrations and VLVOT (Efficacy; VPC)

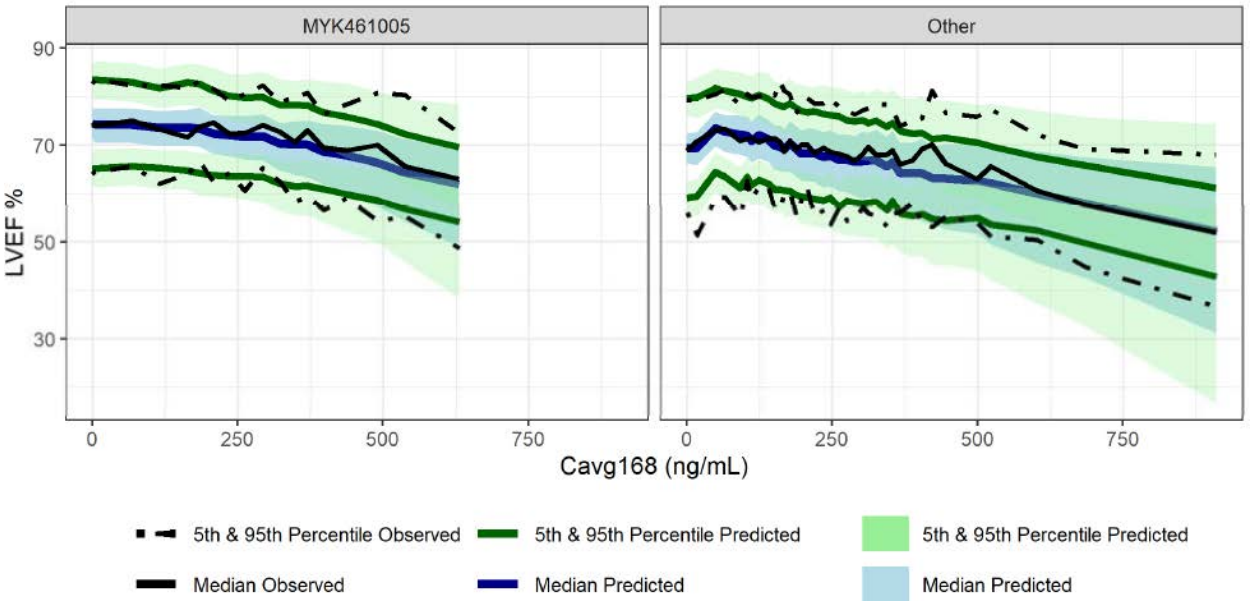


Source: Mavacamten-er-report.pdf, SN0038, Figure 16

The developed model adequately characterized the relationship between Cavg168 with LVEF using a power model. Baseline LVEF was found to have significant effect on the model steepness parameter. In addition, baseline LVEF, disease type (nHCM *vs*. oHCM), and sex were all found to have significant impact on model intercept. There was inadequate data to characterize in hysteresis between mavacamten concentrations and ejection fraction. Similarly, the development model also adequately characterized the relationship between Cavg168 with VLVOT using a decaying exponential model. Baseline VLOT and baseline NT-proBNP levels were found to have

significant effect on the model intercept parameter. As a model qualification, the simulation study outcomes for time-course data for concentrations, VLVOT, and LVEF were similar to those observed values (Study # 005; Figure 4-8).

Figure 3-2 Exposure-Response Relationship Between Mavacamten Concentrations and LVEF (Safety; VPC)



Source: Mavacamten-er-report.pdf, SN0038, Figure 10

Similar to the preliminary assessment (Study # 004), the final E-R analyses also demonstrated a concentration dependent reduction in VLVOT and LVEF. The analysis indicates that median mavacamten concentrations higher than 1000 ng/mL are associated with considerable decrease (≤ 50%) in LVEF. Combinedly, these relationships suggested use of mavacamten can be done with appropriate dose titrations based on the proposed PD marker of efficacy i.e., left ventricular outflow tract gradient (LVOT with Valsalva; <30 mm Hg) as well as the proposed PD marker of safety i.e., left ventricular ejection fraction (LVEF ≥ 50%).

However, mavacamten exhibits a high pharmacokinetic variability (Section 4.1) and it undergoes extensive CYP enzyme-mediated metabolism with a major contribution (fm: ~74%) from polymorphic CYP2C19 enzyme (Section 3.3.3.1). Significantly increased exposures of mavacamten were observed in the subjects who are PM of CYP2C19 compared to NM of CYP2C19. Steady-state simulations of mavacamten exposures in different CYP2C19 genotypes indicated that a considerable part of PK variability can be explained using CYP2C19 genotypes (Figure 3-3).

In addition to ECHO (LVEF and LVOT) monitoring based dose titrations, the phase-3 study (EXPLORER-HCM) also utilized concentrations (PK) based rules for dose titration instead of a prospective dose adjustment based on CYP2C19 genotypes. Most importantly, the Applicant

proposed a dose titration algorithm which neither includes PK monitoring nor does it considered a differential dosing of mavacamten based on prospective genotyping of CYP2C19. Considering the steep relationship between concentrations of mavacamten and LVEF and its pharmacokinetic variability, evaluation of the proposed dose titration scheme and monitoring plan is critical for optimal and safe use of mavacamten. Based on the available pharmacokinetic, exposure-response (for LVEF and LVOT), clinical safety efficacy data (Section 4.1), the FDA reviewers conducted additional PK/PD simulations using POP-PK and E-R models evaluating suitability of proposed dosing regimens. Additional clinical scenarios were explored to derive optimal dosing regimen, titration algorithm, and ECHO monitoring plan. For this purpose, proportions of patients exceeding pre-specified threshold of concentrations (>700 ng/mL and > 1000 ng/mL), LVEF (≤ 50%; as PD endpoint for safety), and LVOT (< 30 mm Hg; as PD endpoint for efficacy) were compared across all scenarios (Section 4.1.2).

The analyses results indicated that the proportions of patients below LVEF 50% with the proposed dosing regimen were consistently higher in PM of CYP2C19 compared to other genotypes of CYP2C19. These increased concentrations and lower LVEF in these patients may place them at higher risk for serious heart failure events. For this purpose, a modified dosing regimen is recommended for PM of CYP2C19 which includes an initial treatment with once daily doses for 4 weeks and followed by a three-time-per-week (TIW, on Monday, Wednesday and Friday) dosing from Week 5. This modified dosing regimen is supported by similar mavacamten exposures, response of VLVOT <30 mm Hg, and risk of LVEF<50% in PM patients as compared to non-PM patients (Section 4.1.2).

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

Yes, we have recommendations on alternate dosing regimens and management strategy for following sup-populations based on intrinsic factors as outlined below. The Applicant conducted dedicated clinical studies assessing the impact of CYP2C19 genotypes and hepatic function on the exposures of mavacamten (see below).

In addition, Population pharmacokinetic analysis did not reveal a significant impact of age, sex, body weight on the exposures of mavacamten. Dose adjustment is not necessary based on intrinsic factors such as age, sex, body weight.

3.3.3.1 CYP2C19 Genotype Status

Mavacamten undergoes extensive CYP enzymes mediated metabolism with a major contribution from polymorphic CYP2C19 (fm: ~74%) enzyme. The Applicant conducted a dedicated pharmacogenomic study (Study # 012) comparing the pharmacokinetics of mavacamten between NM (*1/*1, *1/*3) of CYP2C19 and PM (*2/*2, *2/*3) of CYP2C19. This was an open-label, parallel group study evaluating the pharmacokinetics of mavacamten in healthy subjects (n=16; 8 /cohort). Following prospective genotyping for CYP2C19 status, subjects were assigned to 2 parallel cohorts (Cohort 1: NM of CYP2C19 and Cohort 2: PM of CYP2C19) and received single dose of 15 mg mavacamten (capsule formulation) under fasting condition. Blood samples were

collected up to 60 days post-dose for the determination of mavacamten concentrations. The summary of pharmacokinetic parameters is presented in Table 3-4.

Table 3-4 Summary of PK Parameters [Study # MYK-461-012]

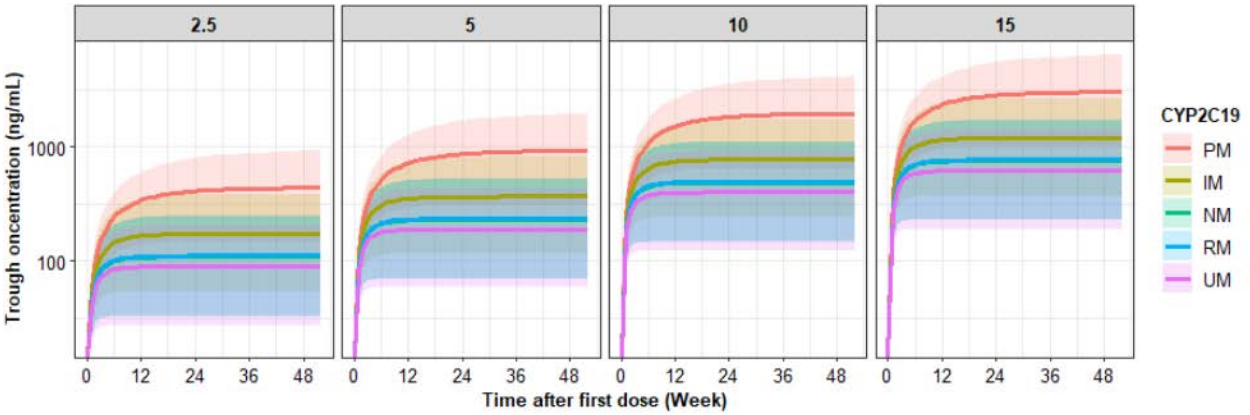
CYP2C19 Genotype	PK Parameters*		Geometric Mean Ratio (90% CI)	
	Cmax (ng/mL)	AUCinf (ng·h/mL)	Cmax (ng/mL)	AUCinf (ng·h/mL)
PM	509 (27%), n=8	43520 (18%); n=8	1.47 (0.93 – 2.33)	3.41 (2.44 – 4.79)
NM	397 (56%); n=8	14130 (57%); n=8		

**Data presented as mean (CV), number of subjects. NM: Normal (*1/*1, *1/*3) metabolizers of CYP2C19; PM: Poor (*2/*2, *2/*3) metabolizers of CYP2C19.*

Source: Reviewer's analysis.

Following a single dose, significant increase in the exposures of mavacamten (Cmax: 1.5-fold and AUCinf: 3.4-fold) were observed in the subjects who are PM of CYP2C19 compared to NM of CYP2C19. Similarly, the elimination half-life of mavacamten was significantly extended in PM compared to NM (PM: 572 *vs*. NM: 221 h) of CYP2C19. The FDA reviewers performed steady-state simulations in different CYP2C19 genotypes using population PK analysis (Figure 3-3).

Figure 3-3 Simulated Plasma (trough) Concentration versus Time Profiles following Multiple (Fixed at 2.5, 5, 10, and 15 mg Once Daily) Doses in Patients with Various CYP2C19 Genotypes [POP-PK]



PM: Poor Metabolizers of CYP2C19; IM: Intermediate Metabolizers of CYP2C19; NM: Normal Metabolizers of CYP2C19; RM: Rapid Metabolizers of CYP2C19; UM: Ultra-rapid Metabolizers of CYP2C19.

Source: Reviewer's Analysis

These simulations indicate significantly increased exposures of mavacamten in PM of CYP2C19 compared to other genotypes of CYP2C19 at all doses. Moreover, the time to steady-state was also longer for PM of CYP2C19 (~28 weeks for PM *vs*. ~6 weeks for NM) compared to NM of CYP2C19. In addition, these simulations indicate that higher doses (*viz.*, 10 and 15 mg; once daily) are associated with steady-state though concentrations of >1000 ng/mL in PM of CYP2C19.

3.3.3.2 Hepatic Impairment

The Applicant conducted a dedicated hepatic impairment study (Study # 015) evaluating the effect of hepatic function on the pharmacokinetics of mavacamten. This was an open-label, parallel group study evaluating the pharmacokinetics of mavacamten in subjects with hepatic impairment compared to that in subjects with normal hepatic function (healthy matched controls). Subjects with normal (n=11, cohort 3), mild (Child-Pugh Group A: 5 to 6 points; n=8, cohort 1), or moderate (Child-Pugh Group B: 7 to 9 points; n=8, cohort 1) hepatic impairment received a single 25 mg dose of mavacamten (using immediate-release capsule formulation under fasting condition). All subjects were extensive (EM) or rapid metabolizers (RM) of CYP2C19. Blood samples were collected up to 72 h post-dose for the determination of total mavacamten and unbound mavacamten concentrations. The summary of pharmacokinetic parameters is presented in Table 3-5.

Table 3-5 Summary of PK Parameters [Study # MYK-461-015]

Hepatic Impairment Group	PK Parameters*		Geometric Mean Ratio (90% CI)	
	Cmax (ng/mL)	AUCinf (ng·h/mL)	Cmax (ng/mL)	AUC (ng·h/mL)
Mild	596 (23%), n=8	71000 (12%); n=4	1.12 (0.86 to 1.45)	3.24 (2.25 to 4.68)
Matched control	534 (36%); n=8	18200 (67%); n=8		
Moderate	468 (31%); n=8	32800 (104%); n=4	1.10 (0.79 to 1.54)	1.87 (1.03 to 3.39)
Matched Control	426 (47%); n=8	19700 (85%); n=8		

*Data presented as mean (CV), number of subjects.

Source: Reviewer's analysis.

Relatively higher exposures of mavacamten (AUC) were observed in subjects with mild (Child-Pugh class A) and moderate (Child-Pugh class B) hepatic impairment compared to subjects with normal hepatic function (matched control). Similarly, half-life of mavacamten was increased subjects with hepatic impairment (mild: ~634 h and moderate: ~420 h) compared to their matched control (~171 h and ~189 h).

Although the Applicant states that no clinically meaningful differences in the pharmacokinetics of mavacamten were observed in subjects with mild and moderate hepatic impairment compared to

subjects with normal hepatic function, the exposure of mavacamten is increased significantly (~3-fold for AUCinf) in subjects with mild and moderate hepatic impairment compared to that with subject with normal hepatic function with proportionate increase in half-life. Moreover, there was a limited sample size and high variability to explore relationship between hepatic function and mavacamten concentrations. Considering ~3-fold increase in exposures, the lowest starting dose is expected to offer exposures equivalent to 7.5 mg once daily in subjects with normal hepatic function. Therefore, we recommend lower starting dose of 2.5 mg once daily with maximum daily dose of 10 mg once daily in patients with mild to moderate hepatic impairment.

Mavacamten has not been studied in patients with severe hepatic impairment (Child-Pugh Group C). Also, refer to clinical review (by Dr. Tzu-Yun McDowell and Dr. Preston Dunnmon) for safety of mavacamten in subjects with hepatic impairment. (b) (4) As mavacamten is extensively metabolized liver enzymes, considerably increased half-life of mavacamten is expected in subjects with severe hepatic impairment. Thus, no dosing recommendations can be made for these patients. It is recommended to avoid use of mavacamten in patient with severe hepatic impairment.

3.3.3.3 Renal Impairment

Considering that the renal elimination is not a major excretion pathway for mavacamten, the Applicant did not conduct a dedicated clinical study evaluating the effect of renal function on the pharmacokinetics of mavacamten. Population pharmacokinetic analysis did not reveal a significant impact of creatinine clearance (CrCl: 37.6 to 385 mL/min; n=435) on the exposures of mavacamten. No clinically meaningful differences in the pharmacokinetics of mavacamten were observed in subjects with mild and moderate renal impairment compared to subjects with normal renal function (Section 4.1).

However, mavacamten has not been studied in patients with severe renal impairment, ESRD (eGFR: < 15 mL/min/1.73 m^2), and in patients on dialysis. Reduced clearance of mavacamten with increased uremia associated with severe renal impairment and ESRD cannot be excluded. In absence of pharmacokinetic data, no dosing recommendations can be made for patients with severe renal impairment and ESRD. It is recommended to avoid use of mavacamten in patient with severe renal impairment or ESRD.

3.3.3.4 Sex and Age

Additional evaluation of the effect of intrinsic factors was conducted as part of the population pharmacokinetics analysis. Population pharmacokinetics analysis concluded that age, body weight, and sex are not expected to significantly affect the exposure of mavacamten (Section 4.1). Considering the safety and efficacy data from pivotal studies and the revised monitoring plan and dose titration scheme, the reported differences in the exposure of mavacamten across these intrinsic factors are not expected to be significant.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

The Applicant conducted in vitro studies suggesting that mavacamten is extensively metabolized primarily by oxidation with major contribution from CYP2C19 (fm: ~74%), followed by CYP3A (fm: ~18%), and to lesser extent by CYP2C9 (fm: ~7.6%). Concomitant administration of mavacamten with a strong and moderate inhibitor or inducer of CYP enzymes is expected to significantly impact mavacamten exposures. The Applicant conducted clinical drug interaction studies to assess the interaction potential with 1) Inhibitors of CYP2C19 (Study # 018) and inhibitors of CYP3A4 (Study # 009), and 2) Substrate of CYP3A4 (Study # 016 and # 010). In addition, PBPK assessments were conducted to evaluate the impact of concomitant administration of mavacamten with modulators of CYP2C19 and/or CYP3A4 (Section 4.3).

3.3.4.1 Drug Interactions – CYP2C19, CYP3A4, and CYP2C9 Modulators

3.3.4.1.1 Drug Interaction with Inhibitors of CYP2C19

Since mavacamten is primarily metabolized by CYP2C19, the Applicant conducted a clinical drug interaction study (Study # 018) evaluating the effect of weak to moderate inhibitor of CYP2C19 on the pharmacokinetics of mavacamten. This was an open-label, randomized, parallel-group study evaluating the effect of concomitant administration of omeprazole (multiple dose; 31-day course) on the pharmacokinetics of mavacamten (single dose) in healthy subjects.

The study included healthy subjects who are NM of CYP2C19 and RM of CYP2C19. Subjects (n=29) were randomized to receive a single 15 mg dose of mavacamten (n=15) or a single 15 mg dose of mavacamten after omeprazole course (n=14). Subjects in latter cohort received once daily 20 mg omeprazole from Day -3 until the Day 28 visit. Blood samples were collected for the determination of total mavacamten concentrations. The summary of pharmacokinetic parameters is presented in Table 3-6.

Table 3-6 Summary of PK Parameters [Study # MYK-461-018]

Treatment Group	PK Parameters*		Geometric Mean Ratio (90% CI)	
	Cmax (ng/mL)	AUCinf (ng·h/mL)	Cmax (ng/mL)	AUCinf (ng·h/mL)
Mavacamten+ omeprazole	280 (40%); n=13	14110 (35%); n=13	-	-
Mavacamten	284 (36%); n=15	8377 (36%); n=15	0.99 (0.75 to 1.30)	1.48 (1.16 to 1.88)

*Data presented as mean (%CV) number of subjects.

Source: Reviewer's analysis.

Concomitant administration of mavacamten with omeprazole (at steady state) resulted in increased exposures of mavacamten (AUC: ~50%) without a significant change in peak concentrations. The Applicant proposed no specific adjustment of dose or dosing frequency for concomitant administration of mavacamten with moderate to weak inhibitors of CYP2C19.

The effect of a strong CYP2C19 inhibitor on the PK of mavacamten was evaluated using the PBPK analyses in different genotypes of CYP2C19 (Section 4.3) by the FDA reviewers. The effect of a moderate CYP2C19 inhibitor was not evaluated due to the lack of a PBPK perpetrator model.

When mavacamten is concomitantly administered with fluconazole (a strong CYP2C19 and moderate CYP3A inhibitor), the steady state mavacamten Cmin,ss was predicted to increase by at least 5.4-foldin NM of CYP2C19. The effect of a strong CYP2C19 inhibitor on the PK of mavacamten in IM of CYP2C19 could not be evaluated due to lack of appropriate models. The proposed dosing recommendation in IM of CYP2C19 is based on a conservative approach. CYP2C19 strong inhibitors should be avoided in patients who are not PM (i.e., IM, NM, RM, UM) of CYP2C19 because a 5.4-fold increase in the current mavacamten dose that a patient is taken exceeds the recommended maximum therapeutic dose.

Although the effect of a moderate CYP2C19 inhibitor on mavacamten has not been evaluated, considerably increased exposures of mavacamten in patients who are not PM of CYP2C19 are expected for concomitant administration with a moderate inhibitor of CYP2C19 based on the effect of a strong CYP2C19 inhibitor. Significantly increased exposures of mavacamten were also observed in PM of CYP2C19 compared to NM of CYP2C19. Based on the available clinical data and considering the steep relationship between concentrations of mavacamten and left ventricle ejection fraction (Section 4.1), it is recommended to avoid concomitant administration of mavacamten with a moderate inhibitor of CYP2C19.

When mavacamten is co-administered with omeprazole (a weak CYP2C19 inhibitor), 50% increase in Cmin,ss was predicted in NM of CYP2C19. Therefore, we recommend dose reduction (i.e., 15 to 10 mg, 10 to 7.5 mg, 5 to 2.5 mg) and avoid using mavacamten for subject who are on 2.5 mg daily dose) during the concomitant administration of mavacamten with weak inhibitors of CYP2C19 in patients who are not PM (i.e., IM, NM, RM, UM) of CYP2C19.

The effect of a strong, moderate, or weak CYP2C19 inhibitor on the PK of mavacamten in PM of CYP2C19 is expected to be minimum because the CYP2C19 activity in PM of CYP2C19 is very low. Therefore, no dose adjustment is recommended for PM of CYP2C19 when mavacamten is co-administered with a CYP2C19 inhibitor.

3.3.4.1.2 Drug Interaction with Inhibitors of CYP3A4

The Applicant conducted a clinical drug interaction study (Study # 009) to evaluating the effect of moderate inhibitor of CYP3A4 on the pharmacokinetics of mavacamten. This was an open-label, randomized, parallel-group study evaluating the effect of concomitant administration of verapamil (multiple dose; 240 mg once daily; sustained release tablet) on the pharmacokinetics of mavacamten (single dose; 25 mg tablet) in healthy subjects.

Subjects (n=26) were randomized (1:1) to receive mavacamten alone or in combination with verapamil until Day 28. Blood samples were collected for the determination of total mavacamten concentrations. The study included NM (*1/*1; n=18), IM (*2/*1; n=4), and PM (*2/*3 and *2/*2; n=3) of CYP2C19. The summary of pharmacokinetic parameters is presented in in Table 3-7.

Table 3-7 Summary of PK Parameters [EM; Study # MYK-461-009]

Treatment Group	PK Parameters*		Geometric Mean Ratio (90% CI)	
	Cmax (ng/mL)	AUCinf (ng·h/mL)	Cmax (ng/mL)	AUCinf (ng·h/mL)
Mavacamten + Verapamil	504 (39%); n=11	20740 (40%); n=10	-	-
Mavacamten	358 (37%); n=11	17220 (38%); n=11	1.52 (1.16 to 1.99)	1.16 (0.84 to 1.58)

**Data presented as mean (%CV) and number of subjects; EM – includes normal and intermediate metabolizers of CYP2C19.*

Source: Reviewer's analysis.

Concomitant administration of mavacamten with verapamil (at steady state) resulted in increased exposures of mavacamten (Cmax: ~1.5-fold and AUC: ~1.16-fold) and increased elimination half-life (146 h to 174 h). In 2 PM of CYP2C19 who received mavacamten and verapamil, pharmacokinetics assessment indicated a significantly higher exposure of mavacamten (AUCinf: 27800 and 72600 ng·h/mL) compared to NM of CYP2C19 without a considerable impact on the peak concentrations (Cmax: 248 and 300 ng/mL). This higher exposure is likely mainly due to their PM OF CYP2C19 status. In the 3 PM of CYP2C19, there was no difference between control subject who received mavacamten (AUCinf: 112000 ng·h/mL; n=1) alone and subjects who received mavacamten and verapamil concomitantly (n=2). Considering that there was a high variability in these pharmacokinetics parameters with limited sample size (n=2 *vs*. n=1), these data for PM of CYP2C19 are inconclusive.

The Applicant's PBPK assessment of drug interaction with itraconazole indicated that the concomitant administration of mavacamten with a strong inhibitor of CYP3A4 results in ~2-fold increase in AUC of mavacamten in PM of CYP2C19. (b) (4)

The effect of strong and moderate CYP3A4 inhibitors on the PK of mavacamten was evaluated using the PBPK analyses in different genotypes of CYP2C19 (Section 4.3) by the FDA reviewers. Ketoconazole (a strong CYP3A4 inhibitor) is predicted to increase Cmin,ss of mavacamten by approximately 30% and 100% in NM of CYP2C19 and PM of CYP2C19, respectively. The effect

of a CYP3A4 inhibitor on the PK of mavacamten in IM of CYP2C19 has not been evaluated. The dose adjustment for IM of CYP2C19 is based on the evaluation for PM of CYP2C19 assuming CYP3A pathway contributes similarly to the total clearance in both populations. Based on the available clinical data and considering the steep relationship between concentrations of mavacamten and ejection fraction (Section 4.1), for subjects on 5, 10, or 15 mg daily doses we recommend dose reduction (i.e., 15 to 10, 10 to 7.5, 5 to 2.5) and avoid using mavacamten for subject who are on 2.5 mg daily dose) during the concomitant administration of mavacamten with strong inhibitors of CYP3A4 who are NM, RM, UR of CYP2C19. Similarly, for subjects on 5, 10, or 15 mg daily doses we recommend dose reduction (i.e., 15 to 7.5, 10 to 5, 5 to 2.5) and avoid using mavacamten for subject who are on 2.5 mg daily dose during the concomitant administration of mavacamten with strong inhibitors of CYP3A4 who are PM or IM of CYP2C19.

Following concomitant administration of mavacamten with a moderate CYP3A (e.g., diltiazem), the steady state Cmin are predicted to increase by approximately 60% and 20%, respectively, in PM of CYP2C19 and NM of CYP2C19. We recommend dose reduction (i.e., 15 to 12.5) and no dose adjustment for subjects who are on 2.5, 5 or 10 mg daily dose during the concomitant administration of mavacamten with moderate inhibitors of CYP3A4 who are NM, RM, and UM of CYP2C19. Similarly, for subjects on 5, 10, or 15 mg daily doses we recommend dose reduction (i.e., 15 to 7.5, 10 to 5, 5 to 2.5) and avoid using mavacamten for subjects who are on 2.5 mg daily dose during the concomitant administration of mavacamten with moderate inhibitors of CYP3A4 who are PM or IM of CYP2C19.

No dedicated drug interaction study was conducted to evaluate the drug interaction potential of mavacamten with weak inhibitors of CYP3A4. (b) (4) Since the expected increase in exposures (Cmax and AUC) of mavacamten is not clinically meaningful, no dose adjustment is recommended during concomitant administration of mavacamten with a weak inhibitor of CYP3A4.

3.3.4.1.3 Drug Interaction with CYP3A4 Substrate

In vitro studies indicated that mavacamten is an inducer of human CYP3A4. The Applicant conducted a clinical drug interaction study (Study # 016) evaluating the effect of mavacamten administration on the pharmacokinetics of the sensitive CYP3A4 substrate midazolam. This was an open-label, fixed-sequence, cross-over study evaluating the effect of concomitant administration of mavacamten (multiple dose) on the pharmacokinetics of midazolam (single dose) in healthy subjects (n=14). The study excluded PM of CYP2C19.

Healthy subjects (n=14) received: Period-1) a single 5 mg midazolam dose on Day 1, Period-2) 25 mg mavacamten was administered on Day 2 and 3 followed by 15 mg mavacamten on Day 4 to 16, Period-3) 15 mg mavacamten was administered with 45 mg midazolam on Day 17. Blood samples were collected for the determination of plasma mavacamten, midazolam and hydroxy-midazolam.

Table 3-8 Summary of PK Parameters [Study # MYK-461-016]

Analytes	PK Parameters		Geometric Mean Ratio (90% CI)	
	Cmax (ng/mL)	AUCinf (ng·h/mL)	Cmax	AUCinf
Midazolam	**P1:** 16.6 (22%); n=13	55.3 (62%); n=13	0.93	0.87
	P3: 15.5 (43%); n=12	48.8 (47%); n=9	(0.77 - 1.13)	(0.68 - 1.10)
OH-Midazolam	**P1:** 12.7 (47%); n=13	41.5 (24%); n=10	1.28	1.21
	P3: 16.2 (37%); n=12	47.8 (36%); n=7	(1.01 - 1.65)	(1.04 - 1.39)

**Comparisons of analytes in the absence* (P1) and presence (P3) of mavacamten doses.

Source: Reviewer's analysis.

Concomitant administration of mavacamten with midazolam resulted in slightly decreased midazolam exposures and increased hydroxy-metabolite exposures. In addition, the trough concentrations of mavacamten (~314 ng/mL) observed in the study were comparable to those observed in Phase-3 study at Week 18 (~342 ng/mL; Study # 005). Note that this study was conducted in healthy subjects, which have lower mavacamten concentration compared to patients and thus may not show the maximum interaction potential in patients who receive the maximum dose of 15 mg/day.

3.3.4.1.4 Drug Interaction with Oral Contraceptives

In vitro studies indicated that mavacamten is an inducer of human CYP3A4. CYP3A4-mediated metabolism is the major pathway of oxidative metabolism of estrogen- and progestin-hormonal oral contraceptives (i.e., ethinyl estradiol and norethindrone). Concomitant administration of mavacamten with oral contraceptives may induce metabolism of contraceptives leading to decreased concentrations potentially affecting their efficacy. The Applicant conducted a clinical drug interaction study (Study # 010) evaluating the effect of mavacamten on the exposures of hormonal oral contraceptives (Ortho-Novum®: 1 mg norethindrone, 35 µg ethinyl estradiol). This was an open-label, 2-period, single-sequence (2-cycle), crossover study in normal healthy adult female subjects (n=13). The study included mostly NM (n=10) with one RM of CYP2C19 and 2 UM of CYP2C19.

In this 2-period study, subjects received a single dose of 35 µg ethinyl estradiol and 1 mg norethindrone on Day 1. Period 2 started 7 to 10 days after the previous oral contraceptive administration. Subjects received a 25 mg loading dose of mavacamten on Day 1 and a second 25 mg loading dose on Day 2, followed by a daily dose of 15 mg on Days 3 through 17 (for a total of 17 doses). On Day 15, subjects received the last mavacamten dose with a single dose of 35 µg ethinyl estradiol and 1 mg norethindrone. Ethinyl estradiol and norethindrone pharmacokinetics were determined after the first mavacamten dose and after all 17 doses had been administered.

Mavacamten concentrations were determined on Day 16 and 17. The summary of pharmacokinetic parameters is presented in Table 3-9.

Table 3-9 Summary of PK Parameters [Study # MYK-461-013]

Analytes	PK Parameters		Geometric Mean Ratio (90% CI)	
	Cmax (ng/mL)	AUCinf (ng·h/mL)	Cmax	AUCinf
Ethinyl Estradiol	**P1:** 0.065 (26%); n=13 **P2:** 0.068 (30%); n=12	0.73 (41%); n=13 0.85 (44%); n=12	1.05 (0.95 - 1.16)	1.20 (1.08 - 1.33)
Norethindrone	**P1:** 7.22 (36%); n=13 **P2:** 7.93 (24%); n=12	40.4 (31%); n=13 45.5 (32%); n=12	1.14 (0.98 - 1.33)	1.12 (1.01 - 1.24)

**Comparisons of analytes in the absence* (P1) and presence (P2) of mavacamten doses.

Source: Reviewer's analysis.

The administration of a mavacamten did not affect pharmacokinetic of Ortho-Novum components considerably, as multiple dosing of mavacamten resulted in slightly increased exposures of ethinyl estradiol (AUC: ~1.20-fold) and norethindrone (AUC: ~1.12-fold). In addition, the study evaluated the pharmacokinetics of mavacamten on day 1 (25 mg as a single dose) and Day 15 (with once daily dosing of 15 mg).

3.3.4.1.5 Drug Interaction with Inhibitors of CYP2C9

The Applicant did not evaluate the effect of concomitant administration of mavacamten with inhibitor of CYP2C9 on the pharmacokinetics of mavacamten. However, considering that mavacamten is extensively and predominantly metabolized by CYP2C19 and to some extent by CYP3A4, no clinically meaningful differences in the pharmacokinetics of mavacamten are expected with concomitant administration CYP2C9 inhibitors.

3.3.4.1.6 Drug Interaction with CYP2C Substrates

The effects of mavacamten on the PK of CYP2C8/9/19 substrates were evaluated using PBPK analyses. The induction effects of mavacamten on probe substrates of CYP enzymes depend on mavacamten dose and the CYP2C19 phenotype, ranging from weak to moderate induction effects. Of note, there are uncertainties in these predictions which are described in the review (Section 4.3).

3.3.4.1.7 Drug Interaction with CYP2C19 and CYP3A Inducers

The Applicant did not evaluate the effect of concomitant administration of mavacamten with inducer of CYP2C19 and CYP3A on the pharmacokinetics of mavacamten. However, considering

that mavacamten is extensively and predominantly metabolized by CYP2C19 and to some extent by CYP3A4, mavacamten is susceptible to CYP induction.

PBPK analyses suggested that following concomitant administration of mavacamten with a strong CYP3A and CYP2C19 inducer (e.g., rifampin) the steady-state Cmin of mavacamten was predicted to decrease by ~40- and ~4- fold in NM and PM of CYP2C19, respectively. Therefore, we recommend avoiding concomitant administration with strong inducers of CYP3A4 and CYP2C19.

Concomitant administration of mavacamten with a moderate CYP3A (e.g., efavirenz), the steady state Cmin was predicted to decrease by ~2-fold in PM and NM of CYP2C19. It is recommended to avoid concomitant administration of mavacamten with moderate inducers of CYP3A4 and CYP2C19 for subject who are on higher doses (10 and 15 mg daily dose) because it is unlikely that an efficacious dose that is equal to or lower than the highest recommended dose (e.g., 15 mg once daily) can be achieved. However, for subject who are on lower doses of mavacamten (i.e., 2.5 and 5 mg), we recommend up titration, as needed, until the dose reaches the highest recommended dose (e.g., 15 mg once daily) during its concomitant administration with moderate inducers of CYP3A4 and CYP2C19.

3.3.4.2 Drug Interactions – Transporters

3.3.4.2.1 Drug Interactions – Transporters Substrate

The Applicant conducted in vitro studies to assess if mavacamten is a substrate of following transporters.

P-glycoprotein and BCRP:

Mavacamten was not found to be a substrate of P-glycoprotein and BCRP.

OATP1B1 and OATP1B3:

Mavacamten was not found to be a substrate of OATP1B1 and OATP1B3 (Study # NC-190014).

OAT, OCT, and MATE:

Mavacamten was not found to be a substrate of OAT, OCT, and MATE (Study # NC-190014).

3.3.4.2.2 Inhibition

The Applicant evaluated potential inhibitory effects of mavacamten on following transporters.

P-gp, BSEP and BCRP:

Mavacamten did not inhibit P-gp, BSEP, and BCRP suggesting that it is less likely to alter the absorption and distribution of drugs that are substrates these transporters (Study # NC-190017).

OATP1B1 and OATP1B3:

Mavacamten was not found to be a potent inhibitor of OATP1B1 and OATP1B3 (Study # NC-190017).

OAT, OCT, and MATE:

Mavacamten was not found to be a potent inhibitor of OAT1, OAT3, OCT1, OCT2, and MATE2-K (Study # NC-190019). However, mavacamten inhibited MATE1 (IC50 = 22.6 μM; 6200 ng/mL). Considering the peak concentrations at steady state with highest therapeutic doses and protein binding (~97%), clinically relevant drug interactions are less likely.

3.3.4.3 Food effect & Gastric pH Modifying Agents

3.3.4.3.1 Food Effect

The Applicant conducted a clinical study (Study # 014) evaluating the effect of food on the pharmacokinetics of mavacamten from intended commercial capsule (Capsule-2) formulation. This was an open-label, randomized (1:1:1), single-dose, cross-over (3-sequence; 3-period) study in healthy subjects (n=24; 16/group). This study also evaluated the relative bioavailability of mavacamten from 2 capsule formulations (Treatment A vs B; Section 3.3.5). All subjects were NM (n=10) or RM of CYP2C19. For assessment of food effect, the subjects received single oral administration of 15 mg capsule (Capsule-2) formulation under fasting condition (Treatment B) and fed condition (with a high-fat breakfast; Treatment C). The summary of pharmacokinetic parameters is presented in Table 3-11.

Table 3-10 Summary of PK Parameters [Study # MYK-461-014]

Treatment Group+	PK Parameters*		Geometric Mean Ratio (90% CI)	
	Cmax (ng/mL)	AUCinf (ng·h/mL)	Cmax (ng/mL)	AUCinf (ng·h/mL)
Fed	153.0 (56%)	9395 (50%)	-	-
Fasting	341.1 (28%)	10690 (48%)	0.44 (0.36 to 0.54)	0.88 (0.84 to 0.91)

*Data presented as mean (%CV), number of subjects +Intended commercial formulation (test product).

Source: Reviewer's analysis.

In summary, capsule formulation exhibited a negative food effect with decrease in the rate of mavacamten absorption (Cmax) and its extent of absorption (AUCinf) following its administration with a high-fat breakfast compared to that under fasting condition. The effect on the rate of absorption was prominent as administration of mavacamten capsule under fed condition resulted in delayed Tmax with a significant decrease in peak concentrations (Table 3-11). Thus, there was a flattening of the concentration time profile under fed condition and the magnitude of effect on the exposure of mavacamten (AUC: ~12%) was moderate. Considering the available data on impact of food effect and fact that the efficacy/safety studies were conducted without food

restrictions, the Applicant's proposal to use mavacamten capsule formulation without regard to food appears reasonable.

3.3.4.3.2 Gastric pH Modifying Agents

The Applicant evaluated effect of acid-reducing agents on the pharmacokinetics of mavacamten in their drug interaction study (Study # 018). Since omeprazole is an inhibitor of CYP2C19, the study primarily evaluated effect of CYP2C19 inhibition on the pharmacokinetics of mavacamten (Section 3.3.4.1.1). Concomitant administration of mavacamten with omeprazole (at steady state) resulted in increased exposures of mavacamten (AUC: ~50%) without a significant change in peak concentrations. It is important to highlight that mavacamten is extensively and mainly metabolized by CYP2C19.

Mavacamten exhibits a low solubility (pH 2 to 8: 0.02 mg/mL with (b) (4)) and high permeability (99.4 to 156 × 10^{-7} cm/sec between 1 to 200 µM; potential BCS Class II compound) profile and the immediate-release capsule formulation (b) (4). Mavacamten does not exhibits a pH dependent solubility profile between pH 2 to 8. In addition, the Applicant's dissolution profiles were not considerably different (b) (4) even at the highest dose proposed. Therefore, no clinically relevant changes in systemic exposures (Cmax or AUC) of mavacamten are expected when administered with acid-reducing agents.

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support approval of the to-be-marketed formulation?

Yes. The Applicant developed 2 immediate-release capsule (strengths: 2.5, 5, 10, 15 mg) formulations of mavacamten (Capsule 1 and Capsule 2, intended for commercialization) which were used in phase-3 safety and efficacy studies. Since the pivotal safety and efficacy study (# 005) mostly utilized intended commercialization formulation (Capsule 2), PK bridging study was not required (Section 5.2).

The Applicant conducted a clinical study (Study # 014) evaluating the relative bioavailability between the intended commercial capsule (Capsule-2) formulation versus the initial capsule (Capsule-1) formulation. It was an open-label, randomized, 3-way crossover study conducted in healthy subjects (n=24). All subjects were NM or RM of CYP2C19. For relative bioavailability assessment, the subjects received single oral administration of 15 mg capsule formulation under fasting conditions. The summary of pharmacokinetic parameters is presented in Table 3-11.

Table 3-11 Summary of PK Parameters [Study # MYK-461-014]

Treatment Group	PK Parameters*		Geometric Mean Ratio (90% CI)	
	Cmax (ng/mL)	AUCinf (ng·h/mL)	Cmax (ng/mL)	AUCinf (ng·h/mL)
Capsule-2+	341.1 (28%)	10690 (48%)	-	-

Treatment Group	PK Parameters*		Geometric Mean Ratio (90% CI)	
	Cmax (ng/mL)	AUCinf (ng·h/mL)	Cmax (ng/mL)	AUCinf (ng·h/mL)
Capsule-1	337.5 (38%)	10240 (47%)	1.01 (0.88 to 1.16)	1.06 (1.01 to 1.11)

*Data presented as mean (%CV), number of subjects [+]Intended commercial formulation (test product).

Source: Reviewer's analysis.

Both formulations indicated similar absorption rates and exposures with a bi-exponential decline after the peak concentration, and a long terminal elimination. The results from this study support bridging of data between Capsule-1 and intended commercial capsule formulation, Capsule-2.

4 APPENDICES

4.1 Pharmacometrics Analysis

4.1.1 Sponsor's Analysis

4.1.1.1 Objectives

- to develop a population pharmacokinetic (popPK) model for mavacamten that describes data pooled from healthy subjects (HS), patients with oHCM, and patients with nHCM
- to quantify the variation in mavacamten exposure due to intrinsic and extrinsic factors including study population (HS, oHCM, and nHCM), CYP2C19 phenotypes (PM with *2/*2, IM with *1/*2, *2/*17, NM with *1/*1, RM with *1/*17, and UM with *17/*17), body weight, age, sex, race, renal function, dose level and formulation
- to develop exposure-response (E-R) models that characterize the relationships between mavacamten exposure vs. LVEF and VLVOT in patients with oHCM
- to use the popPK model and E-R models to simulate and explore dose titration regimens based on periodic measurement of LVEF and VLVOT

4.1.1.2 Data

The source of data for the popPK modeling were from 12 clinical studies (studies 002, 003, 004, 005, 006, 007, 008, 009, 010, 011, 012, and 014). The evaluable subjects had received at least 1 dose of mavacamten and at least 1 measurable mavacamten concentration observation with associated sampling time and dosing information.

The source of data for the E-R modeling were from 5 clinical studies (studies 004, 005, 006, 007, and 008). The evaluable subjects had baseline and at least 1 post-treatment (including post-placebo treatment) response measurement (LVEF or VLVOT) with associated sampling time.

Table 4-1. Studies included in the popPK or E-R analysis.

Study Number [Name]; Phase	Study Design/Objective, Population	Number of subjects (Active/Placebo)
MYK-461-002 (002); Phase 1	Single ascending dose study in HS	36/12
MYK-461-003 (003); Phase 1	Multiple ascending dose study in HS	50/10
MYK-461-004 (004) [PIONEER]; Phase 2, open label	Pilot study: 12-week study in patients with oHCM; LVOT-guided dose titration	21/0
MYK-461-005 (005) [EXPLORER]; Phase 3	Pivotal placebo-controlled 30-week study in patients with oHCM; PK- and ECHO-guided dose titration	123/128
MYK-461-006 (006) [MAVERICK]; Phase 2	16-week study in patients with nHCM; PK-guided dose titration	39/20

MYK-461-007 (007) [EXPLORER] [a]; Phase 3 (LTE)	104-week open-label study in patients with oHCM (from Study 005); ECHO-guided dose titration	260/0
MYK-461-008 (008) [PIONEER][a]; Phase 2 (OLE-LTE)	116-week OLE study in patients with oHCM (from Study 004); PK- and LVOTg-guided dose titration	13/0
MYK-461-009 (009); Phase 1	DDI (verapamil); Single dose in HS	25/0 (12 - verapamil)
MYK-461-010 (010); Phase 1	DDI (oral contraception); Multiple-dose crossover study in HS	13/0
MYK-461-011 (011); Phase 1	Single dose; Japanese vs Caucasian HS	28/0
MYK-461-012 (012); Phase 1	PM OF CYP2C19 vs NM (*2/*2 vs *1/*1); Single dose in HS	16/0
MYK-461-014 (014); Phase 1	Food effect; initial capsule vs intended commercial capsule; Single-dose crossover study in HS	24/0

[a] *Study ongoing, partial study data to be included; data cut-off data: 30 Oct 2020. DDI: drug-drug interaction; HS: healthy subjects; LTE: long-term extension; LVOT: left ventricular outflow tract; nHCM: non-obstructive hypertrophic cardiomyopathy; NM: normal metabolizer; PM: poor metabolizer (CYP2C19 *2/*2); oHCM: obstructive hypertrophic cardiomyopathy; OLE: open-label extension.*

Source: Adapted from Table S1 in Applicant's popPK report (mavacamten-poppk-report.pdf, SN0038).

4.1.1.3 **Method**

PopPK modeling was conducted using the nonlinear mixed effect modeling approach with NONMEM Version 7.4 facilitated by PsN Version 4.8.1 and R Version 4.0. First-order conditional estimation method with interaction was used for popPK model development. The structural base model was selected based on prior experience and included body weight, CYP2C19, and formulation (solution vs. tablet and capsule). Additional covariate selection was conducted in a stepwise process using SCM (significance levels: forward 0.01; backward 0.001).

The following covariates were tested: ALT, LBW, TBIL, EGFR, CRCL, dose, race, sex, study population, tablet formulation, NYHA classification, concomitant omeprazole, esomeprazole, lansoprazole, or pantoprazole administration, and fed status (in HS only). Concomitant medications were evaluated without regard to the N=15 threshold. Age and AST were not tested because of high correlation with EGFR and ALT, respectively. Standard diagnostic plots were used to access each model in describing the observations. Prediction-corrected visual predictive checks (pcVPCs) were used to evaluate the predictive ability of the final model.

E-R analyses were conducted using R Version 4.0. Direct-effect model was selected for LVEF (decreasing power model) and VLVOT (exponential model) based on prior experience and preliminary analysis. The primary exposure measure considered was the average concentration for the 7-day period prior to the endpoint measure (Cavg168). The selection of covariates for evaluation focused on clinical relevance and statistical significance. Standard diagnostic plots were used to access each model in describing the observations.

Simulations were performed as a qualification tool and to compare study 005 and ECHO-guided titration regimens based on LVEF and VLVOT measures. VLVOT <30 mm Hg was selected as

the threshold for the efficacy biomarker because in graphical analysis comparing VLVOT and the primary clinical endpoint NYHA classification, the best outcomes, consisting of improvement of 1 to 2 levels in NYHA classification, were clustered at VLVOT levels below about 30 mm Hg. Simulations of different ECHO-guided titration regimens were also compared to results from study 005. Simulation was conducted in 4000 subjects for all scenarios.

4.1.1.4 Results

Population PK Analysis

Mavacamten PK was best described by a 2-compartment model, including rapid first-order absorption with a short lag time, followed by rapid distribution, and a long terminal (first-order) elimination phase. The model included the effects of baseline body weight (WT) on clearances (apparent clearance [CL/F] and apparent inter-compartmental clearance [Q/F]) and volumes (apparent central volume of distribution [V2/F] and apparent peripheral volume of distribution [V3/F]); CYP2C19 phenotype on CL/F; HS, omeprazole and esomeprazole administration, and sex on CL/F; solution formulation on absorption rate constant (KA) and relative bioavailability (F); dose level on absorption lag time (ALAG1) and F; fed status on KA and F; and sex on F.

Based on formal and exploratory covariate analysis, there was no significant effect of age (range: 18-82 years), race (Caucasian 80%, Black/African American 5%, Asian 12.5%), and mild to moderate renal impairment (eGFR 29.5-148 mL/min/1.73m^2) on mavacamten PK.

The Parameter estimates of the Applicant's Final PopPK model for mavacamten are listed in Table Table 4-2. The goodness-of-fit (GOF) plots are presented in Figure 4-4. The pcVPC plots are illustrated in Figure 4-5.

Table 4-2. Parameter Estimates of Applicant's Final Population PK Model of Mavacamten

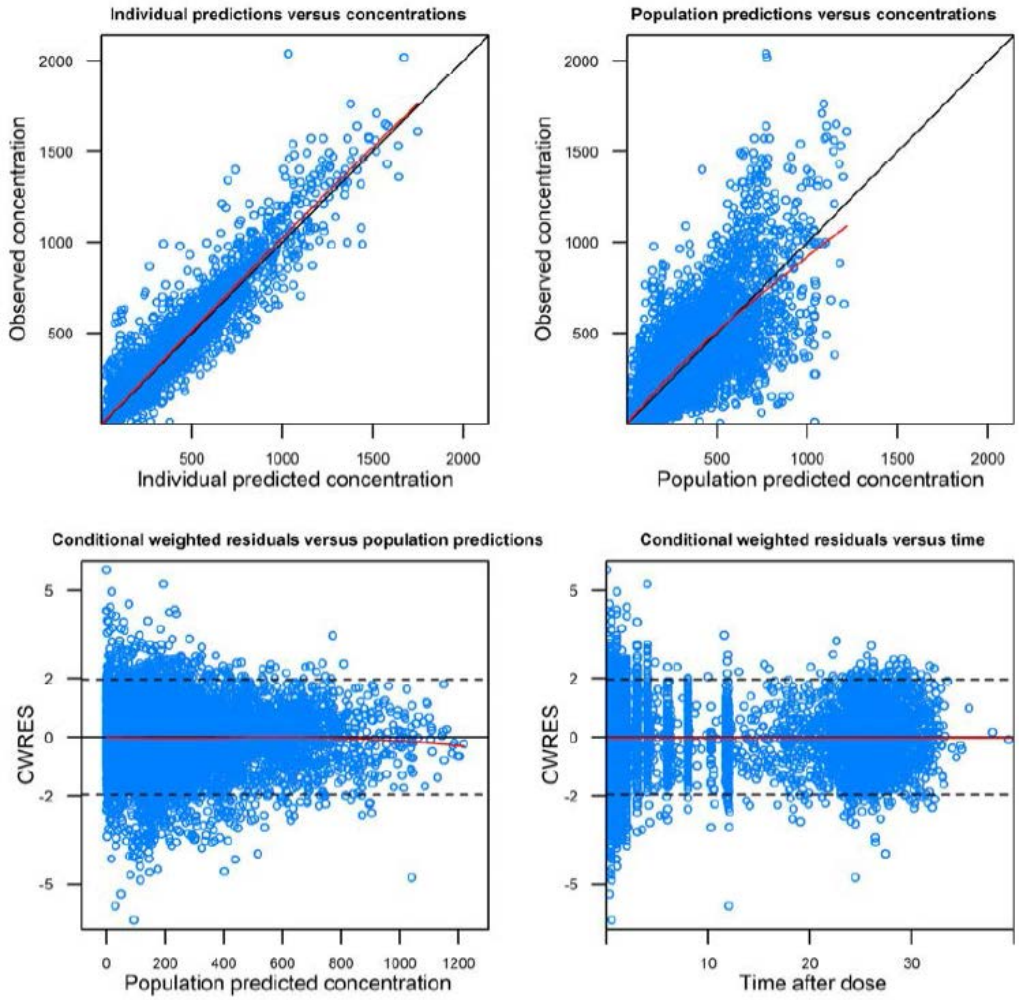
Fixed effect Parameters	Estimate	%RSE	Parameter	Estimate	%RSE
CL/F (L/hr)	0.914	3	V3/F (L)	252	2
WT-CLx/F	0.75 [Fixed]	--	Q/F (L/hr)	16.3	4
2C19:PM-CL/F	-0.722	3	KA (hr^{-1})	0.301	25
2C19:IM-CL/F	-0.331	10	Solution-KA	0.681	23
2C19:RM-CL/F	-0.0022	2050	Fasted HS-KA	0.873	63
2C19:UM-CL/F	0.253	51	Dose-KA	-0.135	20
2C19:Missing	-0.14	41	Log(ALAG1 (hr))	0.192	5
HS-CL/F	0.272	21	Dose-ALAG1	-0.087	43
OMEP-CL/F	-0.332	10	F	1 [Fixed]	--
EGFR-CL/F	0.205	42	Solution-F	-0.194	21
ESOMEP-CL/F	-0.421	6	Dose-F	0.0777	15
Female-CL/F	0.273	20	Fasted HS-F	-0.314	7
V2/F (L)	6.63	14	Fed HS-F	-0.433	7
WT-Vx/F	0.813	9	Female-F	0.0945	27

Random Effect	Estimate	%RSE	Shrinkage (%)
IIV on CL/F	53.2%	3	1
CL-V2/F correlation	-2%		
IIV on V2/F	131.9%	9	37
CL-V3/F correlation	58%		
V2-V3/F correlation	3%		
IIV on V3/F	22.6%	5	13
IIV on KA	41.1%	14	45
IIV on Q/F	23%	8	43
IIV on RUV	46.6%	8	1
Residual Error	**Estimate**	**%RSE**	
EP	0.0292	5	1
EP14	0.478	22	1

Abbreviations: 2C19=cytochrome P450 2C19; ALAG1=absorption lag time; CL=clearance; CLx=clearances; CV=coefficient of variation; EP=exponential residual error; EP14 exponential residual error for Study MYK-461-014 data; ESOMEP=esomeprazole; F=relative bioavailability; HS=healthy subject; IIV=inter-individual variability; IM=intermediate metabolizer; KA=absorption rate constant; OMEP=omeprazole; PM=poor metabolizer; Q=inter-compartmental clearance; RSE=relative standard error; RUV=residual unexplained variability; UM=ultra-rapid metabolizer; V2=central volume of distribution; V3=peripheral volume of distribution; Vx=volumes; WT=body weight.

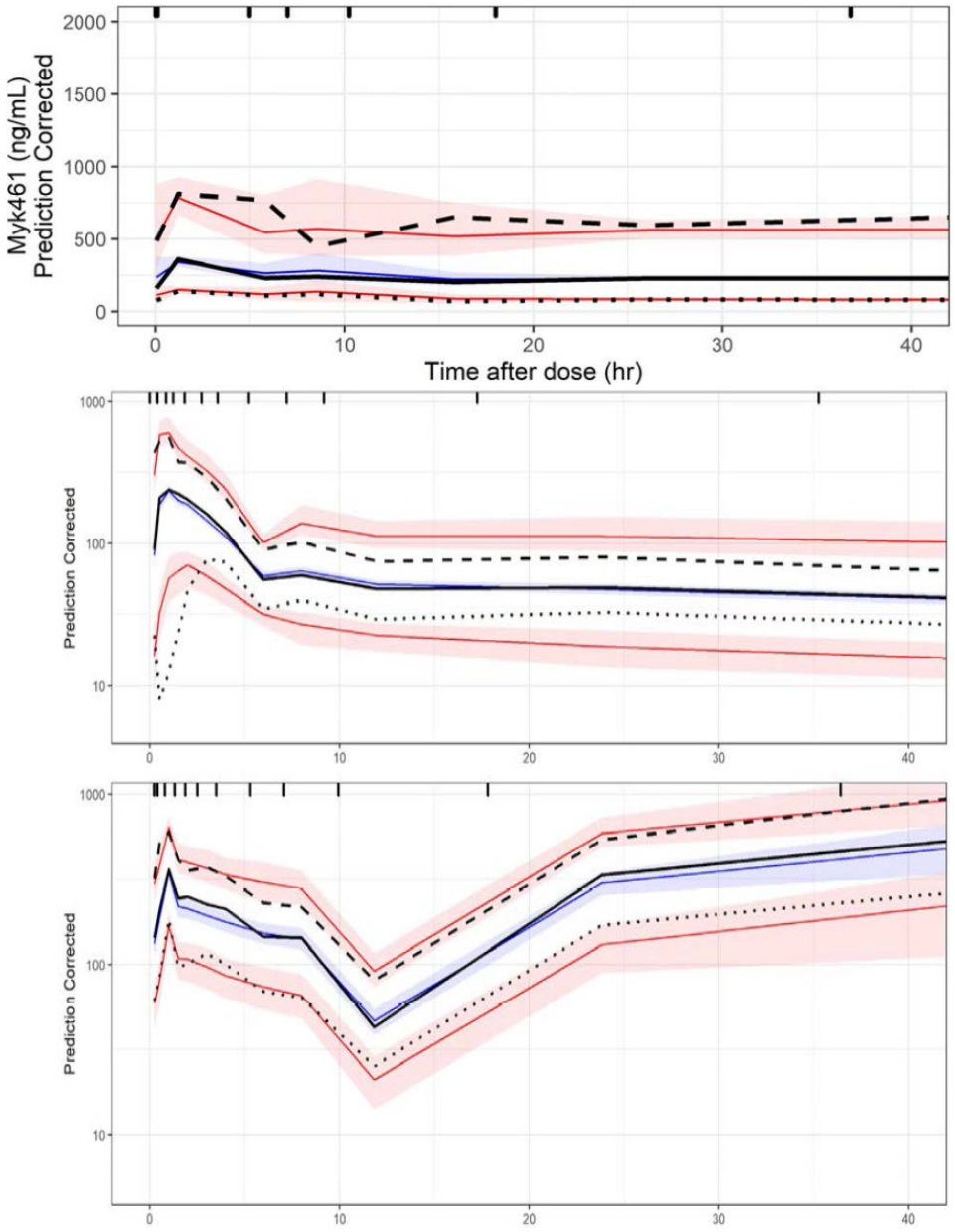
Source: Applicant's final model run117. Table 11 in Applicant's PopPK study report.

Figure 4-4. Goodness-of-Fit plots for the Applicant's Final Model



Source: mavacamten-poppk-report.pdf, SN0038, Figure 8

Figure 4-5. pcVPC Plots for the Final PopPK Model (Top: study 005; Middle: single dose in healthy subjects; Bottom: multiple dose in healthy subjects)



Source: mavacamten-poppk-report.pdf, SN0038, Figure 11 and Figure 20.

The popPK model was used to simulate the effect on exposures of covariates on a univariate basis. Compared to the reference subject (a patient with oHCM, 84 kg male, NM of CYP2C19, with an eGFR of 95 mL/min/1.73 m^2 without any concomitant medication on 5 mg QD mavacamten treatment for 30 weeks). Median steady state average concentration (C_{avg-SS}) was most influenced

by dose level (0.45-fold with 2.5 mg QD to 3.6-fold with 15 mg QD) and CYP2C19 phenotype (from 0.8-fold in UM to 3.6-fold in PM). The effect of WT on $C_{avg\text{-}SS}$ ranged from 0.68-fold (140 kg) to 1.6-fold (45 kg). Healthy subjects had higher apparent clearance and reduced $C_{ave\text{-}SS}$ relative to the reference subject with oHCM. Similar covariate influence was seen on trough concentration at daily dosing interval (Ctrough) and maximum concentration (Cmax).

Reviewer's comments:

- *The dataset has minor issues such as including non-zero concentration before the first dose. There were potential outlier observations with extremely long follow up time after the last dose.*
- *Intensive PK data were collected in healthy subject studies. Studies 005 and 006 collected 1 post-dose PK data per study subject at 1-2 hours post-dose after repeated dosing; otherwise, only trough concentrations were collected in the patient population. Considering significant food effect on Cmax and a lack of control of meal intake in the patient studies, the population PK model cannot be used to predict Cmax in the target patient population.*
- *The large IIV on RUV suggested uncertainties in the prediction of individual concentrations. On the other hand, considering the small shrinkage on CL (~1%), which was set for the patient population, the model appears reasonable to predict average overall exposure and average concentration to support further exposure-response analysis.*
- *Reviewer's independent analyses on revised datasets (e.g., remove pre-dose concentration, shorter follow-up from long term extension studies) and modified covariate models resulted in similar estimates on key parameters (e.g., CL/F, V2/F) and key covariate effect by CYP2C19 genotype.h*

Exposure-Response Analyses

The base model for exposure-LVEF analysis has the mathematical representation: $E = E0 \times (1 - \exp(kk) \times (C_{avg168})^{qq})$ with the exponent qq fixed to 1. The final model included baseline LVEF (centered at 74%), study population (nHCM versus oHCM) and sex on intercept parameter E0, and baseline LVEF and Study MYK-461-005 on steepness parameter kk and power model exponent qq. Random effects were retained on both E0 (additive) and kk (proportional). The parameter estimates of the Applicant's final E-R model for LVEF are presented in Table 4-3. The VPC plots stratified by studies (Study 005 and others) are presented in Figure 4-6.

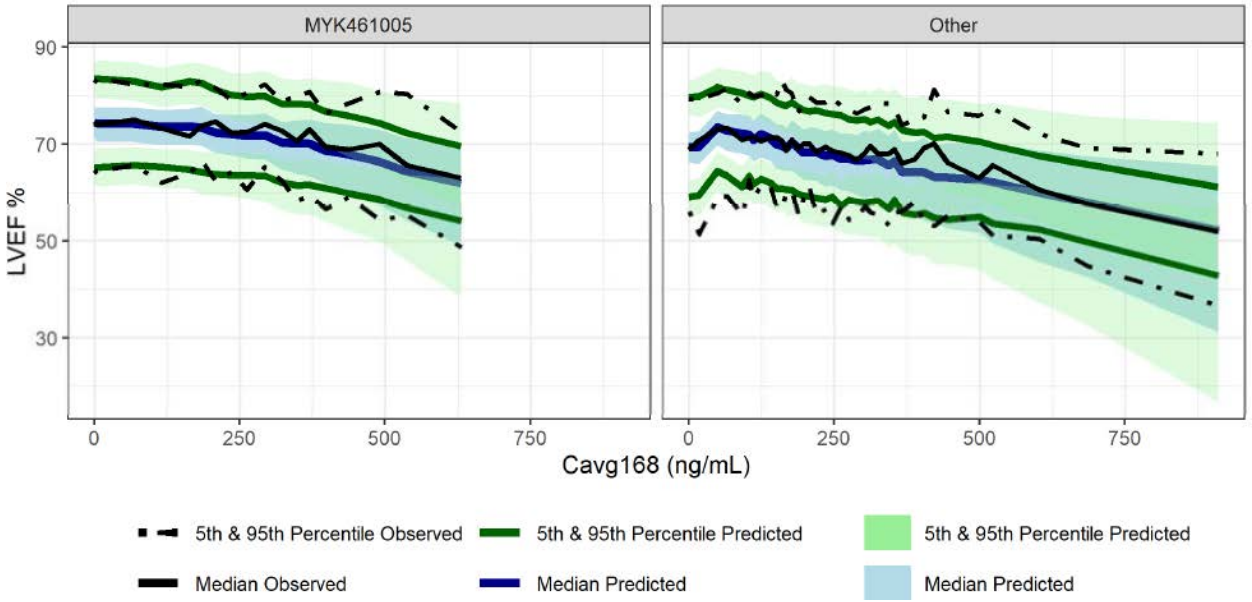
Table 4-3. Parameter Estimates of Applicant's Final Exposure-Response Model for LVEF

Parameter	Unit	Value	Standard Error
E0.(Intercept)	%	74.0	0.243
E0.I(log(BL.LVEF/74))	%	33.6	1.73
E0.POPnHCM	%	-3.24	0.485
E0.SEXFEMALE	%	1.40	0.345
Log(kk.(Intercept)) (for Study MYK-461-005)	1/(ng/mL)	-12.8	0.901
Log(kk.(Intercept)) (Additive value, other studies relative to study 005)		4.29	0.869

kk.I(log(BL.LVEF/74))	1/(ng/mL)	1.73	0.418
qq.(intercept) (for Study MYK-461-005)		1.69	0.146
qq.(intercept) (Additive value, other studies relative to study 005)		-0.64	0.142
Random effects			
SD (E0.(Intercept))	%	2.38	
SD (kk.(Intercept))	1/(ng/mL)	0.616	
Corr (E0,kk)	-	-0.062	
Residual SD	%	4.8	

Source: Mavacamten-er-report.pdf, SN0038, Table 9

Figure 4-6. VPC for the Final E-R Model for LVEF



Source: Mavacamten-er-report.pdf, SN0038, Figure 10

Reviewer's comments:

- *Dose adjustment based on PD response may introduce bias into the evaluation of the E-R relationships. The reviewer conducted sensitivity analysis using data on or before the first potential dose adjustment (Week 4 in study 004 and Week 6 in studies 005-008). The reviewer's final model based on these early data points follows the mathematical representation: E = E0 × (1 - kk × Cavg168). Baseline LVEF, patient population and sex were identified as significant covariates on E0, and baseline LVEF, pacemaker and study 005 were significant covariates on kk. The predicted drug effects on LEVF were similar to the Applicant's final model for patients with oHCM in studies other than study 005. Study 005 has a shallower E-R slope as compare to the other studies.*
- *The Applicant's final model included study specific effect on key model parameters. In a typical patient with oHCM, the predicted LVEF is higher with study 005 parameters than with non-study 005 parameters at concentrations below ~800 ng/mL; the predicted LVEF values was*

lower with study 005 parameters at concentrations above 800 ng/mL. In reviewer's analyses, the confidence interval of the percent of patients with LVEF<50% highly overlap in simulations when using study 005 or non-study 005 parameters.

- *Overall, reviewer's analyses do not present major concerns of under-estimating the risks of reaching LVEF<50% threshold. It appears reasonable to use study 005 parameters in Applicant's final model for simulation in further analysis.*

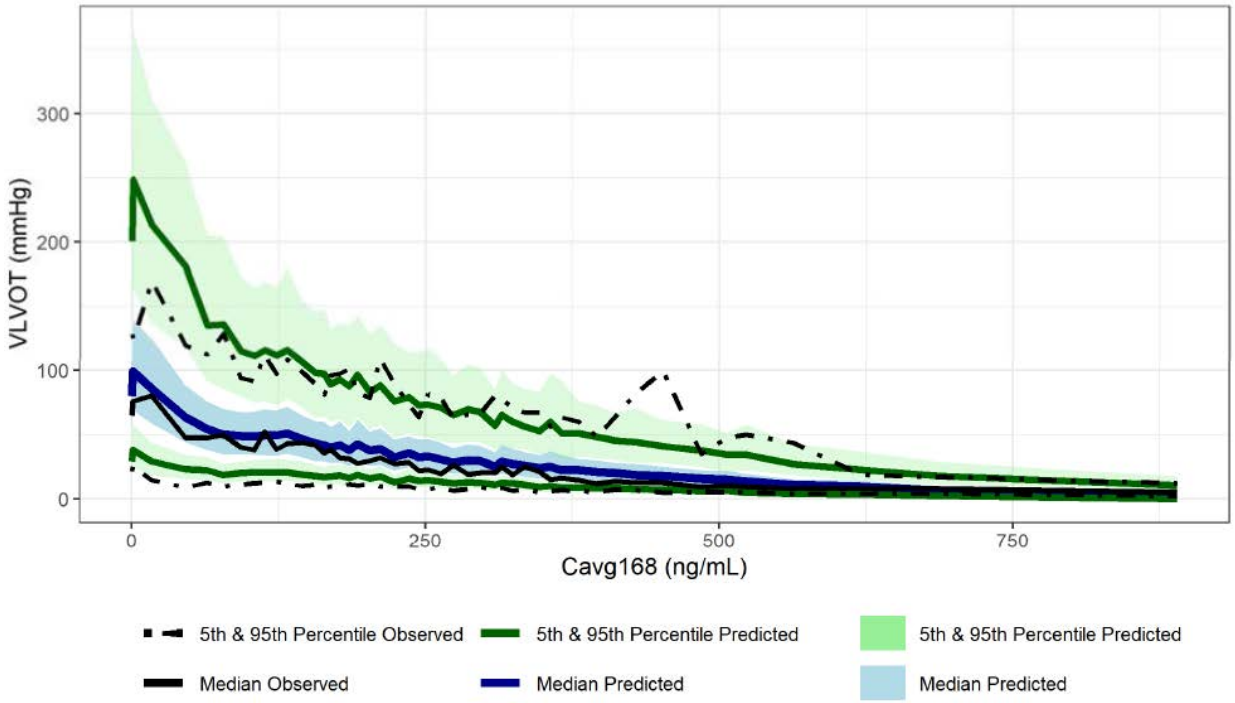
The base model for exposure-VLVOT analysis has the mathematical representation: E = exp(E0) × exp(-exp(kk) × C_{avg168}). The final model included baseline VLVOT (centered at 69 mm Hg) on both intercept parameter E0 and steepness parameter kk and baseline NT-proBNP (centered at 736 pg/mL) on E0. Proportional random effects were retained on both E0 and kk. The model also included placebo effect in time. The parameter estimates of the Applicant's final E-R model for VLVOT are presented in Table 4-3. The VPC plot for VLVOT is presented in Figure 4-7.

Table 4-4. Parameter Estimates of Applicant's Final Exposure-Response Model for VLVOT

Parameter	Unit	Value	Standard Error
Log(E0.(Intercept))	mm Hg	4.22	0.0248
E0.I(log(VLVOT_BL/69)		0.521	0.0319
E0.I(log(NTPROBNP_BL/736))		0.108	0.0152
Log(kk.(Intercept))	1/(ng/mL)	-5.66	0.0343
kk.I(log(VLVOT_BL/69))		0.438	0.0506
Placebo parameters			
kt	1/wk	0.0373	0.0205
aa (Fixed)		0.8767	-
Random effects			
SD (E0.(Intercept))	mm Hg	0.245	
SD (kk.(Intercept))	1/(ng/mL)	0.433	
Corr (E0,kk)		0.010	
Residual SD (exponential error)		0.468	

Source: Mavacamten-er-report.pdf, SN0038, Page 68; Table 10

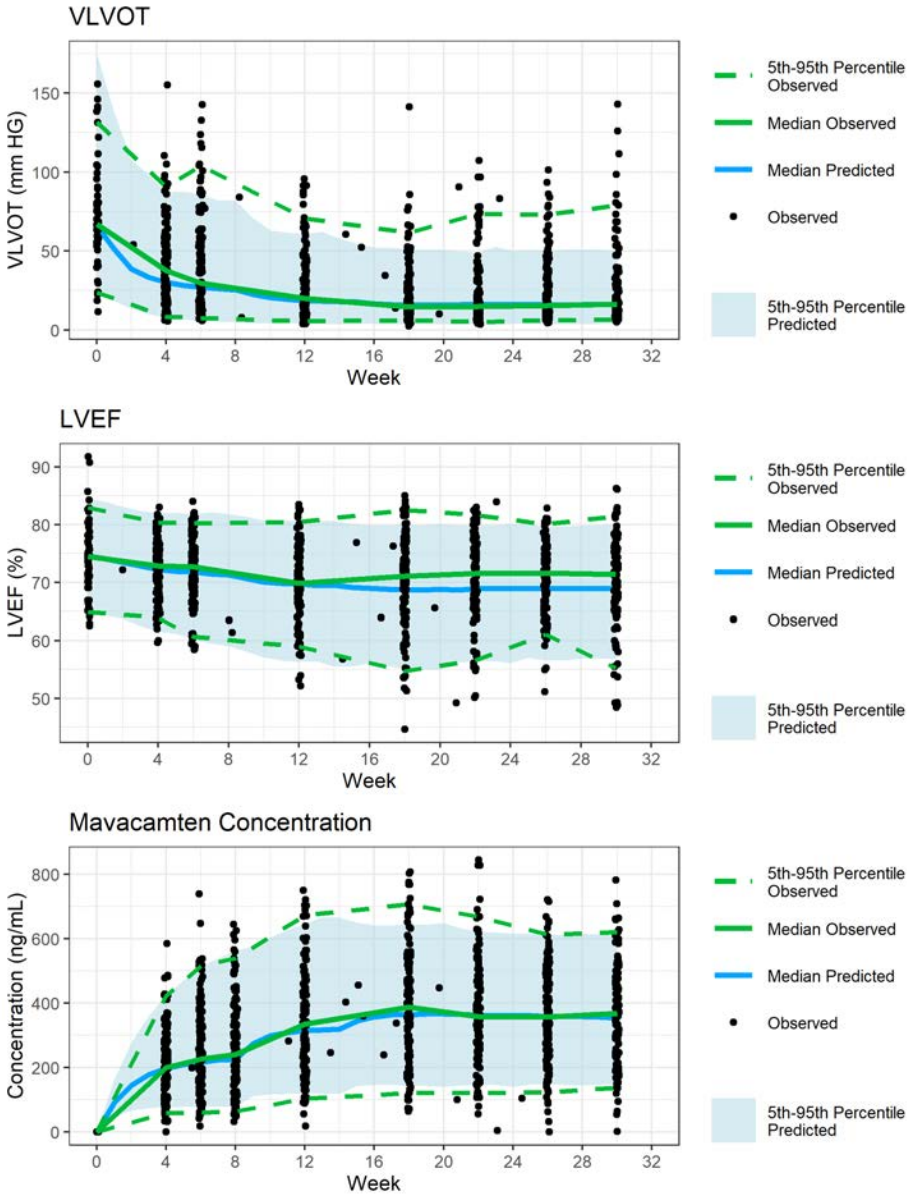
Figure 4-7. VPC for the Final E-R Model for VLVOT



Source: Mavacamten-er-report.pdf, SN0038, Figure 16

Comparison of the time-course of study 005 data (VLVOT, LVEF, and concentration) with the simulation results using study 005 titration regimen suggested that models represent the data well (Figure 4-8).

Figure 4-8. Predictive Check Comparing the Dose-Titration Simulation.



Source: Mavacamten-er-report.pdf, SN0038, Figure 20.

Simulations to Support the Applicant's Proposed Dosing Regimen

The Applicant's proposed dosing regimen in the labeling was different from that was studied in Study 005. The proposed dosing regimen included potential down-titration at Week 4 if VLVOT <20 mm Hg, a scheduled return visit every 12 weeks for potential up-titration (if VLVOT gradient ≥30 mm Hg and LVEF ≥55%; maximum dose: 15 mg QD) followed by an additional visit 4 weeks after, and temporary dose interruption at all visits for LVEF <50% followed by re-start at the next

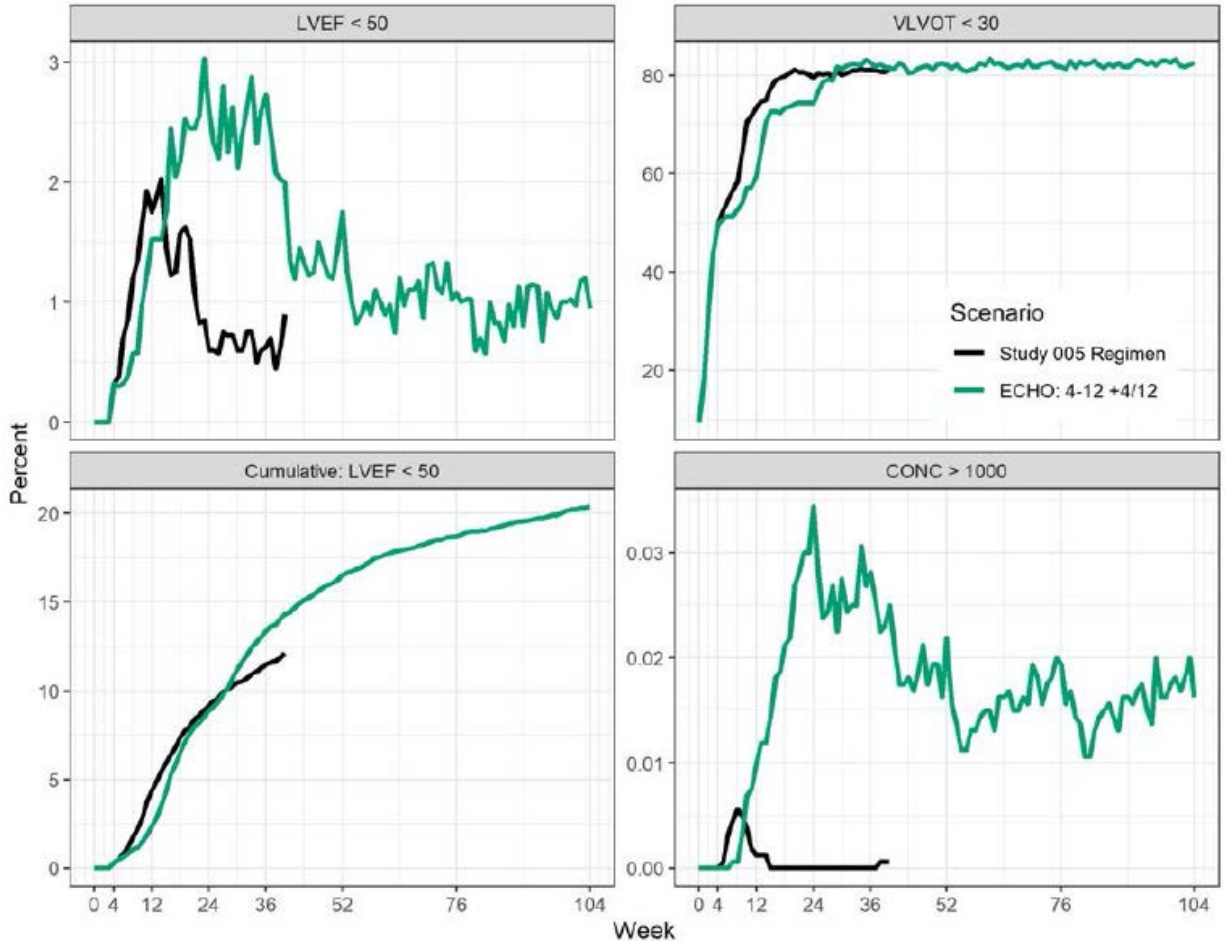
lower dose after LVEF ≥50%. This dosing regimen was selected based on primarily similar dose distribution (Table 4-5) and percentage of patients with LVEF<50% (Figure 4-9 upper left panel) or VLVOT<30% (Figure 4-9 upper right panel) at Week 30 in comparison to study 005 regimen, and secondly on visit frequency and feasibility considerations.

Table 4-5. Final (Week 30) Observed and Predicted Percent at Each Dose Level in Study MYK-461-005

Final Dose	Observed (%)	Predicted (%) – 005 regimen	Predicted (%) – proposed regimen
0	1.65	0.725	1.75
2.5 mg	4.96	5.9	2.58
5 mg	49.6	44.6	44.6
10 mg	33.1	38.6	39.8
15 mg	10.7	10.2	11.2

Source: adapted from Mavacamten-er-report.pdf, SN0038, Table 12 and Table 13.

Figure 4-9. Time Course of Percent of Patients Achieving Key LVEF, VLVOT, and Concentration Thresholds for Long-term Dosing and Comparison to Study 005 Regimen.



Source: Mavacamten-er-report.pdf, SN0038, Figure 25

Reviewer's comments:

- *The Reviewers conducted independent simulations based on Applicant's popPK and E-R models to verify the Applicant's proposed dosing regimen for mavacamten. Refer to Section 4.1.2 for more details. In general, the reviewers agree that the Applicant's proposed dosing regimen is expected to achieve similar benefit-risk to the dose titration regimen in study 005 (based upon similar incidence of LVEF <50% and VLVOT <30 mm Hg), and the benefit-risk is predicted to be maintained over 2 years in patients with CYP2C19 non-PM genotypes.*
- *However, given the significant difference in PK characteristics in patients with PM OF CYP2C19 genotype vs. other genotypes, the Applicant's proposed dosing regimen is expected to result in a high percent of patients with PM genotype experiencing LVEF<50% during the course of treatment. To reduce the risk of LVEF<50% in patients with PM of CYP2C19, the reviewers recommend a modified dosing regimen with a reduced dosing frequency for PM patients based on the FDA's simulations. The modified dosing regimen for PM patients includes an initial treatment with once daily doses for 4 weeks and followed by a three-time-per-week (TIW, on Monday, Wednesday and Friday) dosing from Week 5. Dose levels and dose adjustment criteria are the same as proposed by the Applicant in the labeling. This modified dosing regimen for PM patients was supported by similar mavacamten PK exposure, response of VLVOT <30 mm Hg, and risk of LVEF<50% in PM patients as compared to non-PM patients. Refer to Section 4.5.2 Reviewer's Analysis for more details.*
- (b) (4) *. However, the reviewers do not agree with such a dosing regimen without prospective CYP2C19 genotype due to the following reasons: 1) the proposed ECHO-guided criteria were not studied in any of clinical studies, and 2) this complicated modified dosing regimen brings potential compliance issues for the majority of patients (non-PM patients) without a significant improvement in the control of risk of LVEF<50%.*

4.1.2 Reviewer's Analysis

Introduction: Patients with PM of CYP2C19 is expected to accumulate drug at a slower rate and achieve significantly higher exposure as compare to the other genotype groups. The performance of the Applicant's proposed dosing regimen in patients with UM, RM, NM, IM, and PM of CYP2C19 could be different due to variations in systemic exposure.

Objectives: To evaluate the need of differential dosing regimen in patients with different CYP2C19 genotypes.

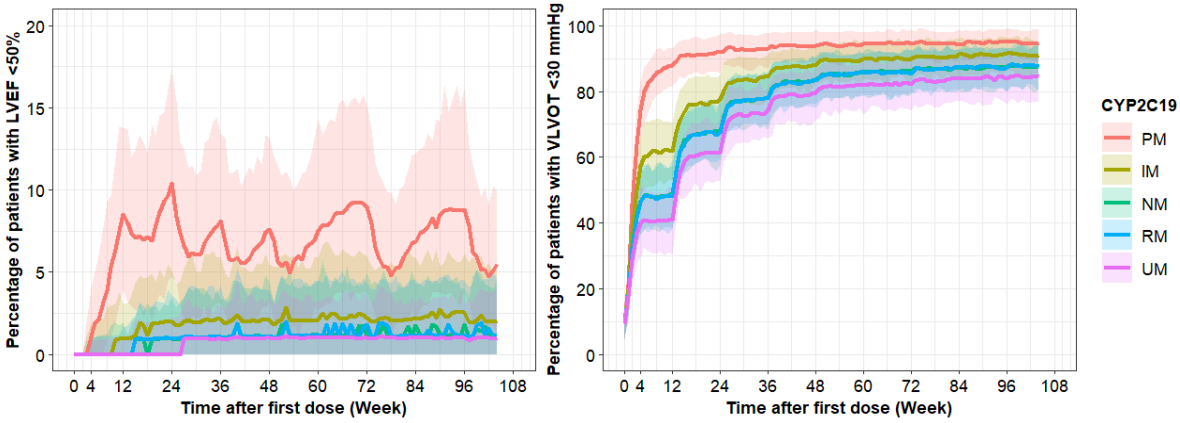
Methods: The simulation analysis used the Applicant's final popPK and E-R models. For each proposed dosing regimen and monitoring plan, simulations were conducted in 200 virtual trials

with each trial containing 500 patients equally distributed to 5 genotype groups. In the simulations, routine visits are scheduled every 12 weeks or 24 weeks with additional visit 4 weeks later for patients had an up-titration in any of the routine visit.

Results:

The Applicant's proposed dosing regimen in the labeling results in a remarkably higher proportion of patients with PM of CYP2C19 experiencing LVEF<50% during the course of treatment, despite of a slightly higher response of VLVOT <30 mm Hg (Figure 4-10).

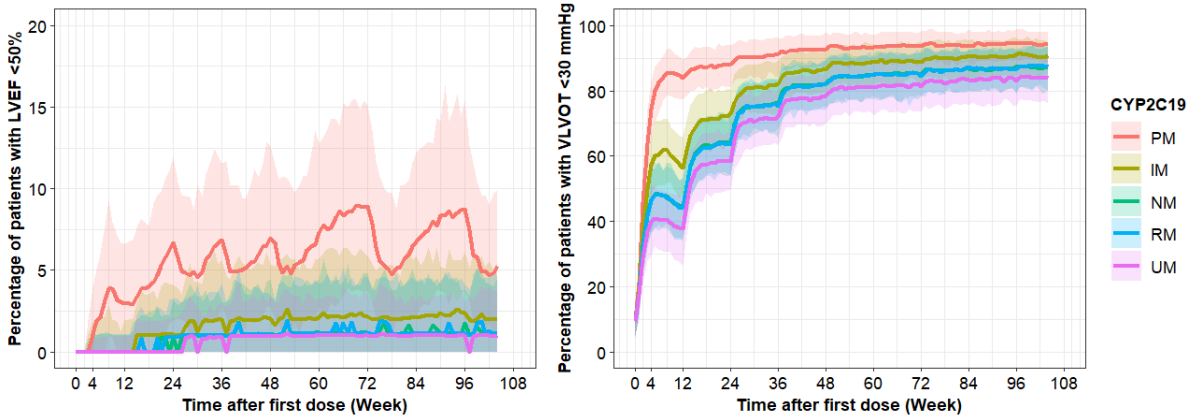
Figure 4-10. Time Course of Percent of Patients Reaching LVEF (Left Panel) and VLVOT (Right Panel) Thresholds at the Applicant's Proposed Dosing Regimen.



Source: Reviewer's analysis.

One additional visit at Week 8 with potential down titration (VLVOT<20 mm Hg, same as Week 4) reduces the percent of patients experience LVEF<50% in the PM group between weeks 12 to 36; however, the risk is still significantly higher than the other groups (Figure 4-11).

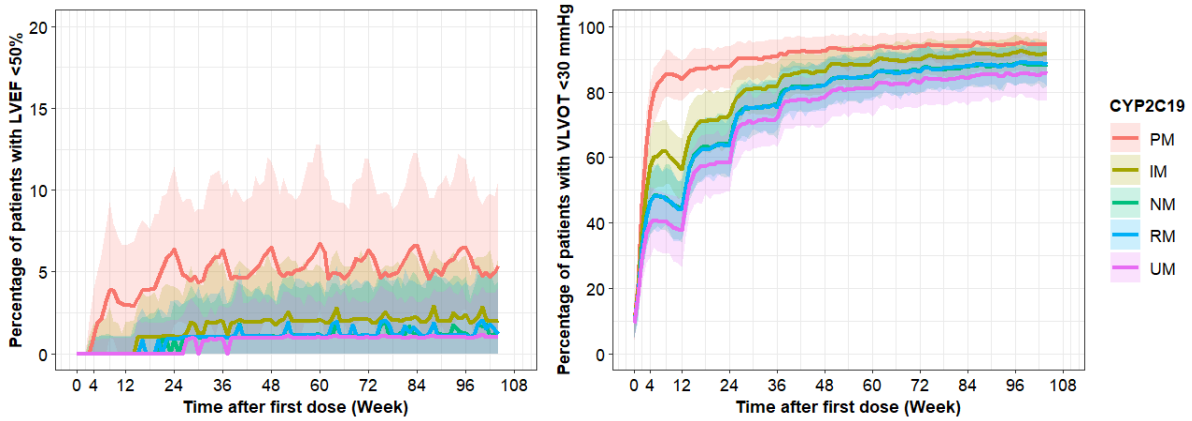
Figure 4-11. Time Course of Percent of Patients Reaching LVEF (Left Panel) and VLVOT (Right Panel) Thresholds at the Applicant's Proposed Dosing Regimen with an Additional Visit at Week 8.



Source: Reviewer's analysis.

More frequent visits after 1 year (changing from Q6M to Q3M) reduces the percent of patients with LVEF<50% in the PM group, but the risk is still unacceptably high (Figure 4-12). In addition, there does not appear to be major improvement in the percent of patients with LVEF<50% in the other genotypes.

Figure 4-12. Time Course of Percent of Patients Reaching LVEF (Left Panel) and VLVOT (Right Panel) Thresholds at the Applicant's Proposed Dosing Regimen with Additional Visits at Week 8 and After 1 Year.

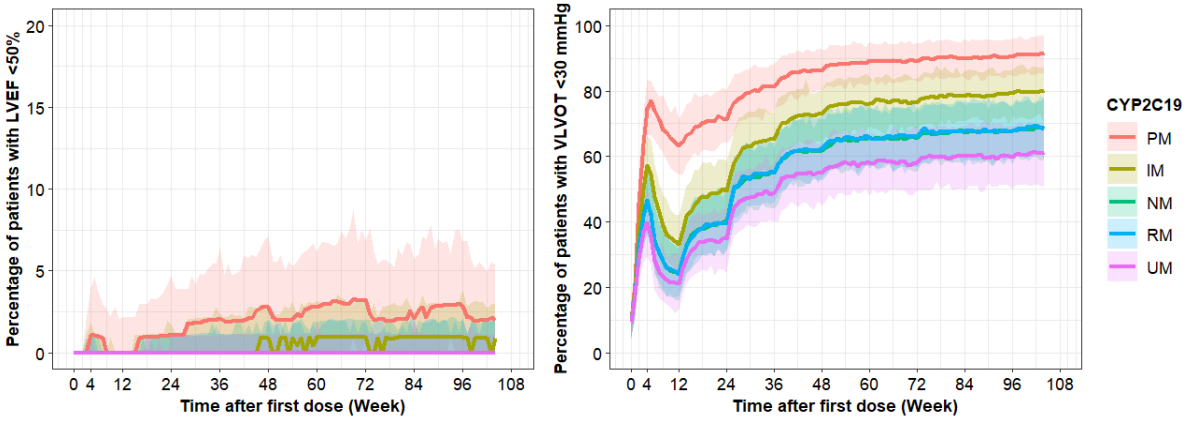


Source: Reviewer's analysis.

To further reduce the percent of patients with LVEF<50%, we simulated a scenario, in which all patients start with 5 mg QD, following the Applicant's proposed ECHO-based dose adjustment criteria in the labeling, and receive doses on a three-times per week (TIW; Monday, Wednesday and Friday) basis from Week 5. The reduced dosing frequency lowered the maximum percent of patients with LVEF<50% to approximately 2.5% in patients with PM genotype, however, it also

resulted in a significant reduction in percent of patients with VLVOT<30 mm Hg in the other genotype groups (Figure 4-13).

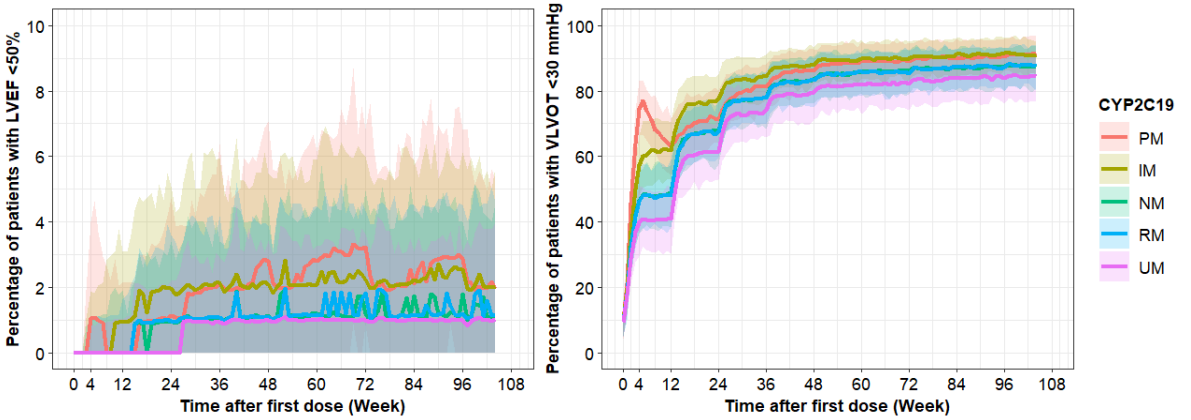
Figure 4-13. Time Course of Percent of Patients Reaching LVEF (Left Panel) and VLVOT (Right Panel) Thresholds with a Reduced Dosing Frequency from Week 5.



Source: Reviewer's analysis.

Overall, we recommend prospective genotyping before mavacamten treatment. Patients with non-PM genotypes should follow the Applicant's proposed dosing regimen, while patients with PM genotype should follow a modified dosing regimen with a reduced dosing frequency after 4-week treatment with the same ECHO-guided dose adjustment criteria as the Applicant proposed in the labeling. Such a prospective genotyping doing regimen is expected to achieve similar benefit-risk (based upon similar incidence of LVEF <50% and VLVOT <30 mm Hg) across different CYP2C19 genotypes (Figure 4-14).

Figure 4-14. Time Course of Percent of Patients Reaching LVEF (Left Panel) and VLVOT (Right Panel) Thresholds at the Reviewers' Recommended Dosing Regimens.



Source: Reviewer's analysis.

4.2 Pharmacogenomics Analysis

4.2.1 Background

Mavacamten is predominantly cleared by CYP2C19 (~74%), CYP3A4 (~18%), and CYP2C9 (~7.6%). Many metabolites are formed; the most abundant metabolite MYK-1078 is <4% of the exposure of mavacamten.

The CYP2C19 gene is highly polymorphic. Alleles are categorized into functional groups as follows: normal function (e.g., CYP2C19*1), decreased function (e.g., CYP2C19*9), no function (e.g., CYP2C19*2-*8), and increased function (e.g., CYP2C19*17). An individual carrying two increased function alleles is considered an UM of CYP2C19. An individual carrying one normal function allele and one increased function allele is a RM of CYP2C19. An individual carrying two normal function alleles is a NM of CYP2C19. An IM of CYP2C19 is defined as an individual carrying one normal function allele and one no function allele, or one increased function allele and one no function allele. PM of CYP2C19 is an individual carrying two no function alleles. The phenotype frequencies differ across ancestrally diverse populations (Table 4-6).

Table 4-6 Frequency of the CYP2C19 Phenotypes Across Racial/Ethnic Populations

Racial/Ethnic Population	CYP2C19 Phenotype Frequency (%)				
	Ultrarapid	Rapid	Normal	Intermediate	Poor
African-American	4	24	33	31	4
American†	0.7	14	63	21	1
Central/South Asian	3	19	30	41	8
East Asian	<1	3	38	46	13
European	5	27	40	26	2
Latino	3	24	52	19	1

Source: Reviewer-generated table based on PMID: 32770672. Racial/Ethnic Population categorization based on PMID: 30506572. †The American genetic ancestry group includes populations from both North and South America with ancestors predating European colonization, including American Indian, Alaska Native, First Nations, Inuit, and Métis in Canada, and Indigenous peoples of Central and South America.

The purpose of this review is 1) to determine if the CYP2C19 phenotype assignments as performed by the Applicant are acceptable and 2) to evaluate the Applicant's analyses of mavacamten efficacy in various HCM genotype pathogenicity subgroups.

4.2.2 Contents

4.2.2.1 CYP2C19 Genotyping Assessment and Phenotype Categorization

Different CYP2C19 allele combinations are categorized into the following phenotypes (Table 4-7).

Table 4-7 Assignment of the CYP2C19 Phenotype Based on Genotype

Phenotype	Examples of CYP2C19 Diplotypes
CYP2C19 ultrarapid metabolizer (UM)	*17/*17
CYP2C19 rapid metabolizer (RM)	*1/*17
CYP2C19 normal metabolizer (NM)	*1/*1
CYP2C19 intermediate metabolizer (IM)	*1/*2, *1/*3, *2/*17, *3/*17
CYP2C19 poor metabolizer (PM)	*2/*2, *2/*3, *3/*3

Source: Reviewer-generated table based on PMID: 32770672

Table 4-8 contains studies with available CYP2C19 genotype data and assigned phenotypes status. In addition, Table 4-8 provides genotyping methods where available.

Table 4-8 Listing of Clinical Studies with Available CYP2C19 Genotypes and CYP2C19 Assigned Phenotypes Status

Study Number, Study Design	Number of Subjects*	Genotyping Information	CYP2C19				
			UM	RM	NM	IM	PM
MYK-461-009, Phase 1, open label, randomized, parallel group	MYK, N=25 V	The (b) (4) characterized CYP2C19 metabolizer phenotypes; no additional genotyping methods were provided	---	---	*1/*1, n=11 (MYK) *1/*1, n=7 (MYK+V)	*1/*2, n=4 (MYK+V)	*2/*3, n=1 (MYK) *2/*2, n=2 (MYK+V)
MYK-461-018, Phase 1, open label, randomized, parallel group	Cohort 1: MYK, Day 1 Cohort 2: MYK and OMEP, Day -3 to 28; N=27	Enrolled subjects with NM and RMs as determined by the central laboratory during the prescreening period; no additional genotyping methods were provided	---	*1/*17, n=6 (MYK) n= 6, (MYK+OMEP)	*1/*1, n=9 (MYK) n=8, (MYK+OMEP)	---	---
MYK-461-016, Phase 1, open label, fixed sequence	MYK, Days 2 and 3, MYK, Days 4 to 17 MDZ, Day 1 and 17; N=12	Enrolled subjects with NM and RMs as determined by the central laboratory during the prescreening period; no additional genotyping methods were provided	---	*1/*17, n=5	*1/*1, n=8	---	---
MYK-461-010, Phase 1, open label, 2 period, 1-sequence crossover	MYK, Days 1 and 2, MYK, Days 3 to 17, Hormonal contraceptive, Day 1 and 15; N=13	The (b) (4) characterized CYP2C19 metabolizer phenotypes defined as: NM (*1/*1), RMs (*1/*17), UM (*17/*17) or IM (*1/*2, *1/*3, *17/*2, *17/*3); no additional genotyping methods were provided	*17/*17, n=2	*1/*17, n=1	*1/*1, n=10	---	---
MYK-461-011, Phase 1, open label, parallel group	MYK, N=28	The (b) (4) characterized CYP2C19 metabolizer phenotypes defined as: NM (i.e., have 2 copies of the functional allele *1) or IM (i.e., have 1 copy of the functional allele *1 and 1 copy of a loss-of-function allele [*2 - *8]; no additional genotyping methods were provided	*17/*17, n=2	*1/*17, n=1	*1/*1, n=13	*1/*2, n=6 *1/*3, n=6	---
MYK-461-004, Phase 2, open label	MYK, Part A: N=11 Part B:	Genotyping methods were not provided	Part A: *17/*17, n=0 Part B:	Part A: *1/*17, n=3 Classified as UM by the Applicant	Part A: *1/*1, n=5 Part B:	Part A: *1/*2B, n=2 *2A/*17, n=1	Part A: n=0 Part B:

	N=10		*17/*17, n=1	Part B: *1/*17, n=2 Classified as UM by the Applicant	*1/*1, n=5	Part B: n=0	*2A/*9, n=1
MYK-461-005, Phase 3, randomized, double blind, placebo controlled	MYK, N=123 PLB, N=128	CYP2C19 genotyping performed by (b) (4) no additional genotyping methods were provided Missing: n=8 (MYK), n=12 (PLB) Not PM: *1/*9 or *9/*9, n=1 (MYK) *2A/*17 or *2B/*17, n= 2 (MYK), n=1 (PLB)	*17/*17, n=4 (MYK), n=3 (PLB)	*1/*17, n=22 (MYK), n=32 (PLB)	*1/*1, n=48 (MYK), n=44 (PLB)	Overall: n=31 (MYK), n=33 (PLB) *1/*17 or *9/*17, n=1 (PLB) *1/*2A, n=16 (MYK), n=19 (PLB) *1/2A or *1/*2B, n=7 (MYK), n=3 (PLB) *1/2A or *1/*9, n=1 (PLB) *1/*3, n=1 (MYK) *1/*4, n=2 (PLB) *1/*6, n=2 (PLB) *1/*8, n=1 (MYK) *2A/*17, n= 5 (MYK), n=3 (PLB) *6/*17, n=1 (PLB) *8/*17, n= 1 (PLB) *9/*17, n=1 (MYK)	*2A/*2A, n= 2 (MYK), n=2 (PLB) *2A/*2B, n=1 (PLB)
MYK-461-006, Phase 2, randomized, double blind, placebo controlled	MYK, N=40 PLB, N=19	CYP2C19 genotyping performed by (b) (4) no additional genotyping methods were provided	---	n=8, (200ng/ml MYK) n=5, (500ng/ml MYK)	n=7, (200ng/ml MYK) n=7, (500ng/ml MYK)	n=3, (200ng/ml MYK) n=5, (500ng/ml MYK)	---
MYK-461-012, Phase 1, open label, parallel group	MYK, N=14	The (b) (4) characterized CYP2C19 metabolizer phenotypes; NM and PM were enrolled; no additional genotyping methods were provided	---	---	(*1/*1), n=8	---	(*2/*2), n=4 (*2/*3), n=4

MYK-461-013, Phase 1, open label, single dose	MYK, N=6	Preferred participants will NM. RM may be enrolled with Applicant's approval; no additional genotyping methods were provided	---	---	(*1/*1), n=6	---	---
MYK-461-015, Phase 1, open label, nonrandomized, parallel group	MYK, N=27	Genotyping was performed at a single central laboratory; alleles detected: *1,*2,*3,*17 by the LUMINEX XTAG(R) CYP2C19 KIT V3 US-IVD	---	*1/*17, n= 12	---	---	---
MYK-461-014, Phase 1, randomized, open label, 3-way crossover	MYK, N=24	Enrolled subjects with NM, RM or UM as determined by the central laboratory during the prescreening period; the CYP2C9 genotype was collected as part of subject characterization only; no additional genotyping methods were provided	---	*1/*17, n=5	*1/*1, n=19	---	---

*Source: Reviewer-generated table based on data submitted in the NDA package. *Number of subjects completed the study. MYK= Mavacamten; V= Verapamil; OMEP= Omeprazole; MDZ= Midazolam; PLB= Placebo. Genotypes CYP2C19*2A and CYP2C19*2B are considered to be no function alleles and can be categorized as CYP2C19*2. PM: Poor Metabolizers of CYP2C19; IM: Intermediate Metabolizers of CYP2C19; NM: Normal Metabolizers of CYP2C19; RM: Rapid Metabolizers of CYP2C19; UM: Ultra-rapid Metabolizers of CYP2C19.*

Reviewer's Comments:

*The Applicant's CYP2C19 variant selection (i.e., *1, *2, *3, *9, *17) seems to be adequate to cover the most common and relevant genotypes of the CYP2C19 gene to adequately determine a patient's CYP2C19 phenotype. The Applicant utilized categorization of the CYP2C19 alleles into the phenotype groups as presented in Table 2. The reviewer agrees with the proposed categorization. Of note, the CYP2C19 *1/*17 genotype was classified as UM in study MYK-461-004 (n=3), which is not in agreement with established categorization approach, that classifies *1/*17 as RMs. All other phenotype assignments seem to be adequate. In most instances, limited information about genotype methods were provided in the submitted NDA package.*

4.2.2.2 HCM Genotype Assessment

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder defined by left ventricular (LV) hypertrophy that cannot be explained by another cardiac or systemic disease. According to the Applicant, approximately 40% of affected individuals overall and 60% of those with a family history of clinical disease have a mutation in one or more sarcomeric structural genes.

Pivotal study MYK-461-005 enrolled patients diagnosed with obstructive hypertrophic cardiomyopathy (oHCM). Clinical diagnoses of patients with oHCM were based on current clinical guidelines. In addition, blood samples were collected for optional HCM genotyping for subjects who provided separate, specific consent. In vitae performed HCM genotyping using a 60-gene panel. A by-subject listings of the results from current and historical HCM genotype testing was provided by the Applicant.

The 251 subjects randomized into the study were included in the intention to treat (ITT) population, including 123 subjects in the mavacamten group and 128 subjects in the placebo group. HCM genotyping was optional. Overall, 76% of subjects had HCM genotype assayed, including 73% (90/123 subjects) in the mavacamten group and 78% (100/128 subjects) in the placebo group. In the mavacamten group, 31% of subjects had at least 1 pathogenic or likely pathogenic mutation and 22% in the placebo group.

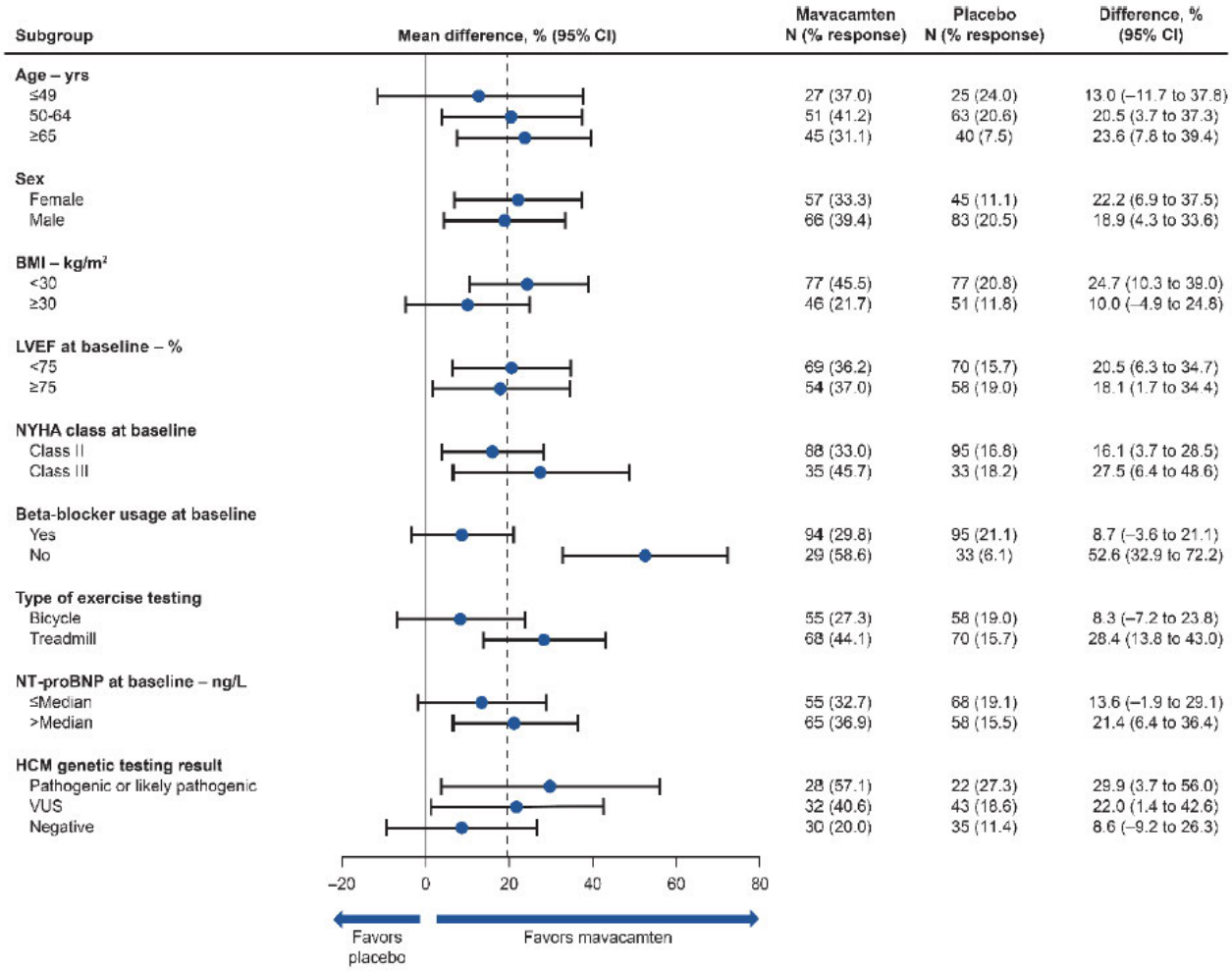
The most common mutations identified were in the MYBPC3 (12% of mavacamten subjects and 13% of placebo subjects) and MYH7 (8% of mavacamten subjects and 3% of placebo subjects) genes. More than 50% of subjects had at least 1 variant of uncertain significance (VUS) (59% of mavacamten subjects and 52% of placebo subjects). The most common VUSs were identified in the following genes:

- Mavacamten: FLNC (8%), MYH7 (6%), and MYBPC3 (4%)
- Placebo: MYBPC3 (7%), MYH6 (5%), FLNC (4%), and TPM1 (4%)

Subjects with any HCM pathogenic, likely pathogenic, or VUS mutations were included in a subgroup analyses of efficacy endpoints. According to the Applicant analyses, there was an increase in magnitude of effect on the primary endpoint observed for the subgroup of subjects with a pathogenic or likely pathogenic mutation (28 subjects in the mavacamten group vs. 22 subjects in the placebo group; difference mavacamten vs. placebo 30% [95% CI, 3.7 to 56.0]) compared

with those without pathogenic, likely pathogenic or VUS mutations (30 subjects in the mavacamten group vs. 35 subjects in the placebo group; difference mavacamten vs. placebo 9% [95% CI, -9.2 to 26.3]; Table 4-9). Minimal to no interaction was seen for the secondary endpoints.

Table 4-9 Between-Group Differences in the Composite Functional Endpoint at Week 30 by Baseline Characteristics and Stratification Factors (ITT Population, Study MYK-461-005)



Source: The Applicant-generated Figure 6; Mavacamten Clinical Study Report MYK-461-005 (EXPLORER-HCM). BMI = body mass index; HCM = hypertrophic cardiomyopathy; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro b-type natriuretic peptide; NYHA = New York Heart Association; VUS = variant of uncertain significance. The dotted vertical line represents the overall estimate. The 95% CIs of the response differences between mavacamten and placebo groups are based on normal approximation. The subgroups by stratification factors were determined using data in the eCRF.

4.2.3 Labeling Recommendations

Please refer to labeling for a final labeling recommendation.

4.2.4 Summary of Findings

The approach and methodologies utilized by the Applicant for determination of the metabolizer status based on the CYP2C19 genotype results seem generally acceptable. Of note, the CYP2C19 *1/*17 genotype was classified as UM of CYP2C19 in study MYK-461-004, which is not in agreement with the established categorization and should be classified as RM of CYP2C19. However, we do not anticipate meaningful impact on results given phenotype classification of only three patients was affected.

Based on the Applicant analyses, there seems to be an increase in magnitude of effect on the primary endpoint observed for the subgroup of subjects with the pathogenic or likely pathogenic HCM associated mutations compared to patients with no mutations. However, sample collection for HCM genotyping was optional and obtained from 76% of patients in study MYK-461-005, which limits interpretation of the results presented by the Applicant.

4.3 PBPK Analysis

4.3.1 Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's physiologically based pharmacokinetic (PBPK) analyses to evaluate the drug-drug interaction (DDI) potentials:

- as a victim of CYP3A in PM OF CYP2C19
- as an inducer of CYP2B6, CYP3A4, and CYP2C8/9/19

The Division of Pharmacometrics has reviewed the PBPK analyses reports (myo-1-b-simcyp and NC-20-0047), the response to FDA's information requests submitted on March 19th (SN0009), June 23rd (seq 0030), and June 29th, 2021 (seq 0032), and PBPK report addendum (SN0038) submitted on August 6th, 2021, and the modeling supporting files, and concluded the followings based on the reviewer's simulation results.

- The induction effects of mavacamten on probe substrates of CYP3A4 and CYP2Cs in patients with obstructive hypertrophic cardiomyopathy (oHCM) ranged from weak to moderate induction effects depending on mavacamten dose and the CYP2C19 genotype.
- The PBPK analysis of the effect of mavacamten on CYP2B6 is inadequate due to the uncertainty about the relative contribution of CYP2B6 in the elimination of the CYP2B6 probe substrate bupropion.
- The effects of CYP3A and CYP2C19 modulators was evaluated/simulated in healthy subjects listed below. There is uncertainty about applying the predicted DDI effects to patients due to the unknown mechanism for higher exposure in this patient population.
    - In PM OF CYP2C19, the strong CYP3A inhibitors itraconazole and ketoconazole were predicted to increase mavacamten $AUC_{0\text{-}24h,ss}$ and $C_{min,ss}$ by approximately 2-fold.
    - In NM of CYP2C19, strong CYP2C19 inhibitor and moderate CYP3A inhibitor fluconazole was predicted to increase mavacamten $AUC_{0\text{-}24h,ss}$ by at least 3-fold and $C_{min,ss}$ by at least 5.4-fold**.**
    - The strong CYP3A and CYP2C19 inducer rifampin was predicted to reduce mavacamten $AUC_{0\text{-}24h,ss}$ by approximately 3- and 8-fold, and $C_{min,ss}$ by 4- and 40-fold in PM of CYP2C19 and NM of CYP2C19, respectively. The moderate CYP3A and CYP2C19 inducer efavirenz was predicted to reduce mavacamten $AUC_{0\text{-}24h,ss}$ by approximately 1.5-fold and $C_{min,ss}$ by approximately 2-fold.

4.3.2 Background

Mavacamten (MYK-461, SAR439152) is a novel small molecule selective allosteric inhibitor of cardiac myosin and is being investigated for treatment of symptomatic obstructive hypertrophic cardiomyopathy. The available dose strengths are 2.5-, 5-, 10- and 15-mg. It was proposed that each patient starts from the lowest effective dose of 5-mg once daily regardless of food, age, sex,

CYP2C19 genotype, organ impairment (mild or moderate), or concomitant medication. Dose-titration is based on each patient's clinical response. The maximum recommended dose is 15-mg once daily. Following oral administration of multiple-dose of mavacamten, its average concentration at the steady-state, $C_{avg,ss}$, increased dose proportionally across the dose range of 2- to 15-mg in healthy subjects and in patient population (mavacamten-poppk-report.pdf), and $C_{avg,ss}$ in oHCM patients with the NM of CYP2C19 was approximately 2.7-fold higher than that in healthy NM of CYP2C19 (mavacamten-poppk-report.pdf). Its AUC accumulated approximately 7-fold at steady-state in NM of CYP2C19. PM of CYP2C19 had 3.4-fold higher in AUC compared to NM of CYP2C19. Its terminal half-life was approximately 3 days in UM of CYP2C19, 8 days in NM of CYP2C19, and 23 days in PM of CYP2C19.

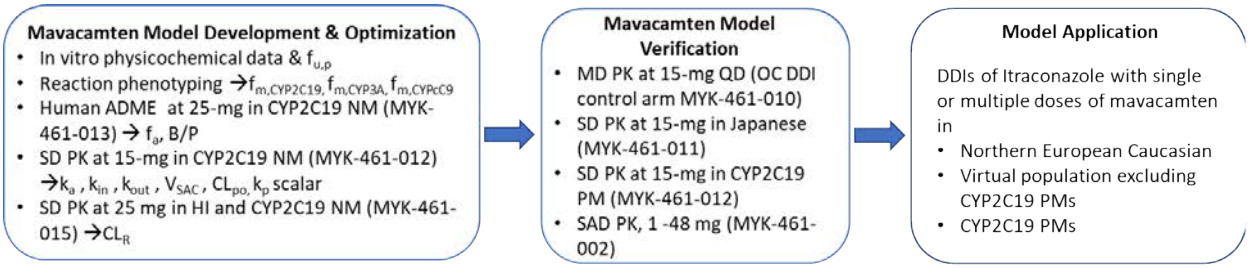
Mavacamten appears to be a BCS class II compound. It is well-absorbed and is extensively metabolized primarily through CYP2C19 (74%), CYP3A4 (18%), and CYP2C9 (7.6%) (NC-17-0018). In the human ADME study, approximately 7% and 85% of radioactivity were recovered in the feces (1% unchanged parent) and the urine (3% unchanged parent), respectively. Mavacamten is not a substrate of P-gp, BCRP, OATP1B1 and OATP1B3. Mavacamten is determined in vitro to be a mechanism-based inhibitor of CYP2D6 and CYP2C19, and a competitive inhibitor of CYP3A (IC_{50} =175 µM), CYP2C9 (K_i =59.5 µM) and CYP2C19 (K_i = 46.2 µM). Mavacamten is also an inducer of CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 in vitro. The Applicant conducted clinical DDI studies with omeprazole, verapamil, oral contraceptives and midazolam, and a clinical PK study in NM of CYP2C19 to evaluate some of the *in vitro* findings. Refer to the Clinical Pharmacology review Section for detail information on mavacamten regarding ADME properties, *in vitro* and clinical studies used in PBPK modeling.

4.3.3 Methods

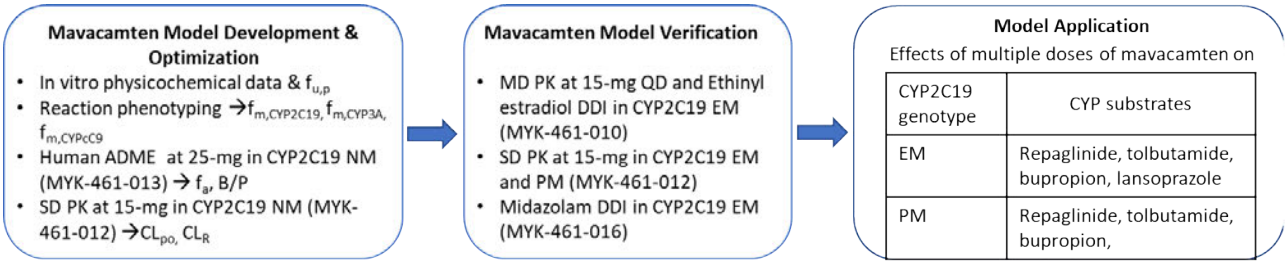
Simulations related to evaluation of mavacamten as a victim of strong CYP3A inhibitors and inducers were performed using the PK/PD Profiles mode in the Simcyp® Simulator (Version 19 Certara, Sheffield, UK). Simulations related to evaluation of mavacamten as an inducer of CYP enzymes were performed in GastroPlus 9.7. Schemes of the PBPK simulation strategy are shown in Figure 4-15, which summarizes the studies used for mavacamten model development and verification, and model applications in DDI predictions. For mavacamten PBPK model, based on results from *in vitro* metabolism and human ADME studies, fraction of mavacamten metabolized was assigned to be 74% for CYP2C19 ($f_{m,CYP2C19}$), 18% for CYP3A ($f_{m,CYP3A}$), and 8% for CYP2C9 ($f_{m,CYP2C9}$). The Simcyp library files itraconazole_Fasted soln and SV-rifampin-MD were used for DDI simulations without any modification by the Applicant. The GastroPlus library files of midazolam, repaglinide, tolbutamide, ethinyl estradiol, lansoprazole and bupropion were used for simulating the effects of mavacamten.

Figure 4-15. Modeling and Simulation Strategy

a) Mavacamten as a victim (Simcyp V19)



b) Mavacamten as a perpetrator (GastroPlus V9.7)



** NM or EM = normal or extensive metabolizer, PM = poor metabolizer*

Source: This flow chart was generated by the reviewer based on myo-1-b-simcyp, NC-20-0047 and PBPK report addendum.

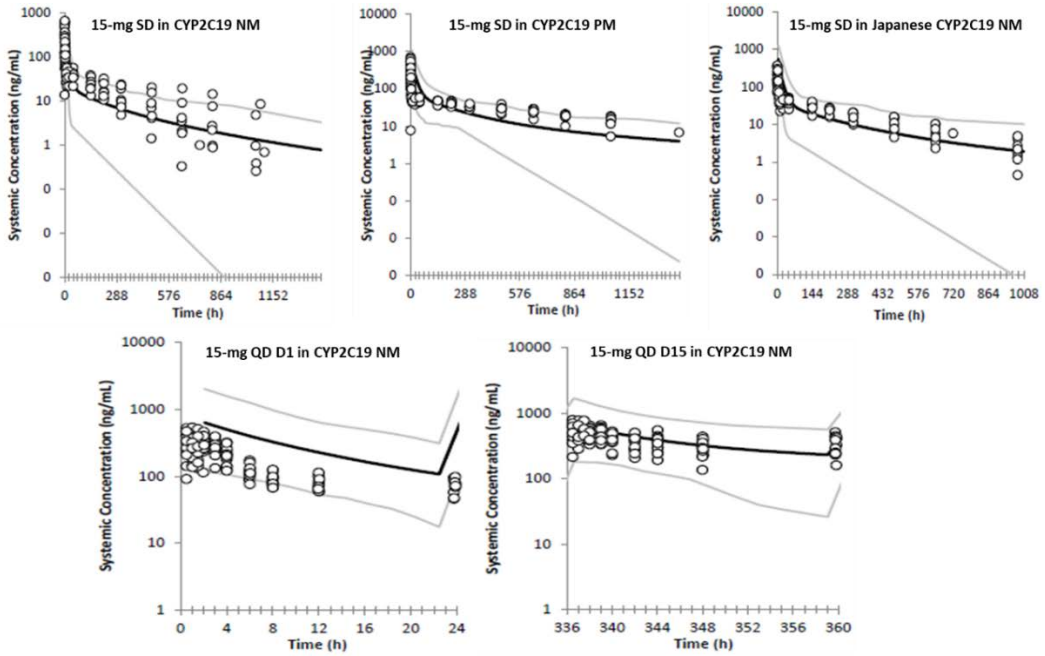
4.3.4 Results

4.3.4.1 Can the PBPK model adequately describe the PK profiles of mavacamten?

Yes. The mavacamten PBPK models using both Simcyp and GastroPlus could describe mavacamten PK following administration of single and multiple doses of mavacamten in healthy subjects (Figure 4-16 and Table 4-10).

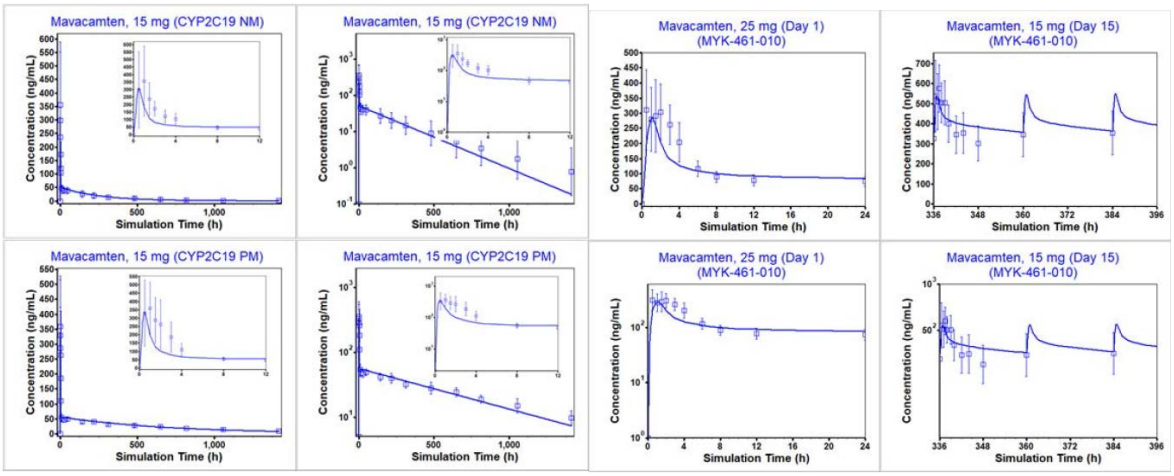
Figure 4-16. Simulated and Observed PK Profiles following Oral Administration of 15-mg Mavacamten in Healthy Subjects

c) Simcyp



Source: Figures 3 - 6 in the PBPK report (myo/1/b).

d) GastroPlus



Source: Figures 6 and 7 in rsp-fda-pharmacology-request-20210616.pdf (SN0030)

Table 4-10 Simulated and Observed PK Parameters following Oral Administration of Mavacamten in Healthy Subjects

e) Simcyp

Study #	Populations	Dose (mg)	Dosing frequency	Study day	AUC (h*ng/mL) GM (CV%)			C_{max} (ng/mL) GM (CV%)			$t_{1/2}$ (h) GM (CV%)			Table # in the Report
					simulated	observed	Sim/obs	simulated	observed	Sim/obs	simulated	observed	Sim/obs	
MYK-461-012	CYP2C19 NM	15	SD	D1	10630	12530	0.85	365	333	1.04	173	193	0.9	3
MYK-461-012	CYP2C19 PM	15	SD	D1	37130	42800	0.9	439	490	0.87	318	553	0.58	7
MYK-461-010	CYP2C19 NM	15	QD	D1	5043	2768	1.82	446	391	1.14	ND	ND	ND	4
MYK-461-010	CYP2C19 NM	15	QD	D15	7286	8313	0.86	512	596	0.86	ND	ND	ND	5
MYK-461-011	CYP2C19 NM JPN	15	SD	D1	15010	15410	0.97	588	289	2.03	156	216	0.72	6
MYK-461-011	CYP2C19 NM JPN	5	SD	D1	5395	6277	0.86	196	141	1.39	156	216	0.72	reviewer
MYK-461-011	CYP2C19 NM JPN	25	SD	D1	26689	17370	1.54	979	504	1.94	156	141	1.10	reviewer
MYK-461-011	CYP2C19 NM NEC	25	SD	D1	18404	19280	0.95	462	516	0.90	214	144	1.49	reviewer

JPN: Japanese population, NEC: Caucasian population, ND: not determined.

Source: Tables 3-7 in the PBPK report (myo/1/b) and reviewer's analyses

a) GastroPlus

CYP2C19 Phenotype	Mavacamten Dose Regimen	PK Parameters, Geometric Mean (CV%), Median [Min – Max]					Reference and Comments
		Name (Unit)	Unit	Predicted	Observed	Predicted/ Observed	
NM	QD 25 mg Days 1-2 15 mg Days 3-17	$AUC_{0\text{-}24,\ Day1}$	ng*h/mL	2358 (25.4)	2768 (12.9)	0.852	Observed data from Study MYK-461-010 (N=13). Comparison was made with data from 13 (out of 100) virtual subjects simulated by Population Simulation.
		$C_{max,Day1}$	ng*h/mL	337.3 (20.1)	390.8 (19.7)	0.863	
		$AUC_{0\text{-}24,Day\ 15}$	ng*h/mL	8350 (61.0)	8313(29.2)	1.004	
		$C_{max,Day15}$	ng/mL	537.2 (36.0)	595.7 (22.2)	0.902	
		$C_{trough,Day15}$	ng/mL	302.6 (70.6)	312.1 (33.9)	0.970	
NM	15 mg single dose	$AUC_{0\text{-}\infty}$	ng*h/mL	12380 (49.4)	12530 (53.8)	0.988	Observed data from Study MYK-461-012 (N=8) (Virtual population N=100).
		$AUC_{0\text{-}last}$	ng*h/mL	12240 (46.3)	12120 (49.4)	1.010	
		C_{max}	ng/mL	283.0 (20.0)	333.2 (75.3)	0.849	
		T_{max}	h	0.5 [0.3 – 0.8]	1.00 [0.50 – 4.00]	-	
		[a]Terminal $t_{1/2}$	h	111.8 (55.2) [35.8 - 353.5]	192.7(58.6) [86.70-473.8]	-	
PM	15 mg single dose	$AUC_{0\text{-}\infty}$	ng*h/mL	41100(33.1)	42800 (20.3)	0.920	
		$AUC_{0\text{-}last}$	ng*h/mL	36400 (24.9)	35310 (13.6)	0.976	
		C_{max}	ng/mL	326.9 (16.5)	489.9 (31.4)	0.665	
		T_{max}	h	0.7 [0.5 – 1.1]	0.75 [0.50- 3.00]	-	
		[a]Terminal $t_{1/2}$	h	434.6 (36.0) [179.9-840.0]	552.8 (30.1) [291.2 – 740.6]	-	

[a] Terminal $t_{1/2}$ were not available from GastroPlus simulation output data files and were obtained from noncompartmental analysis of simulated plasma concentrations-time data in Phoenix WinNonlin (Version 8.2).
Abbreviations: $AUC_{0\text{-}\infty}$, area under the plasma drug concentration-time curve from time zero to infinity; $AUC_{0\text{-}last}$, area under the plasma drug concentration-time curve from time zero to last time point with measurable concentration or simulation length; $AUC_{0\text{-}24}$, area under the plasma drug concentration-time curve from time zero to 24 hours; C_{max}, maximum plasma concentration; C_{trough}, minimum plasma concentration during dose interval; CV, Coefficient of variation (%); NM, normal metabolizer; PM, poor metabolizer; QD, once daily.

Source: Table 6 in rsp-fda-pharmacology-request-20210616.pdf (SN0030)

f) Observed and predicted PK parameters of mavacamten following oral administration of single and multiple doses of mavacamten (MYK-461-002 and -003) in healthy subjects (Simcyp V19)

Dose (mg)	Geometric Mean Parameters	Simulated	Observed	Simulated/Obse
1	AUC_{0-T} (h*ng/mL)	575	296	1.94
	C_{max} (ng/mL)	24.0	20.9	1.15
2	AUC_{0-T} (h*ng/mL)	1150	1368	0.84
	C_{max} (ng/mL)	48.0	62.0	0.77
6	AUC_{0-T} (h*ng/mL)	3445	3245	1.06
	C_{max} (ng/mL)	136	101	1.35
12	AUC_{0-T} (h*ng/mL)	6881	5333	1.29
	C_{max} (ng/mL)	272	204	1.33
24	AUC_{0-T} (h*ng/mL)	13518	14555	0.93
	C_{max} (ng/mL)	556	492	1.13
48	AUC_{0-T} (h*ng/mL)	27370	32990	0.83
	C_{max} (ng/mL)	1089	894	1.22

Dose (mg)	Parameters	Simulated	Observed	Simulated/Obs
1	AUC_{0-12} (h*ng/mL)	173	81.0	2.14
	$C_{max,0-12}$ (ng/mL)	22.8	29.0	0.79
	$AUC_{648-660}$ (h*ng/mL)	581	577	1.01
	$C_{max,648-660}$ (ng/mL)	67.0	76.0	0.88
3	AUC_{0-12} (h*ng/mL)	519	177	2.93
	$C_{max,0-12}$ (ng/mL)	68.5	52.9	1.29
	$AUC_{648-660}$ (h*ng/mL)	1721	1387	1.24
	$C_{max,648-660}$ (ng/mL)	199	159	1.25
12.5	AUC_{0-24} (h*ng/mL)	2999	1195	2.51
	$C_{max,0-24}$ (ng/mL)	285	208	1.37
	$AUC_{648-672}$ (h*ng/mL)	7077	6185	1.14
	$C_{max,648-672}$ (ng/mL)	544	412	1.32
18.5	AUC_{0-24} (h*ng/mL)	4437	2220	2.00
	$C_{max,0-24}$ (ng/mL)	422	362	1.17
	$AUC_{648-672}$ (h*ng/mL)	10345	15819	0.65
	$C_{max,648-672}$ (ng/mL)	798	944	0.85
25	AUC_{0-24} (h*ng/mL)	5995	2748	2.18
	$C_{max,0-24}$ (ng/mL)	571	451	1.27
	$AUC_{576-672}$* (h*ng/mL)	28871	NA	
	$C_{max,576-672}$* (ng/mL)	1052	NA	

Source: PBPK addendum (SN0038)

4.3.4.2 Can PBPK analyses be used to estimate the induction effects of mavacamten on substrates of CYP2Cs and CYP2B6?

The Applicant conducted DDI simulations to predict the effects of mavacamten on probe substrates of CYP enzymes in healthy subjects, but the analyses were inadequate for the following reasons:

(b) (4)

The reviewer simulated the effects of mavacamten on probe substrates of CYP enzymes using the doses at which mavacamten $AUC_{0\text{-}24,ss}$ matched to that estimated from the oHCM patients in the phase 3 study and induction parameters calibrated to the induction parameters of rifampin that could reproduced its observed effects on substrates of CYP3A and CYP2Cs. Details of the reviewer's analyses are discussed below in the Additional Comments. The results showed that the effects of mavacamten on the exposure of the probe substrates depended on mavacamten dose and CYP2C19 phenotype, ranging from weak to moderate induction effects (Table 4-11). Because there is no correlation between CYP2C19 mRNA and activity in vitro[2] and no correlation between

in vitro data and clinical observations, the confidence in the predicted effects of mavacamten on CYP2C19 substrates in NM of CYP2C19 is low (data not shown). In PM of CYP2C19, the predicted effects of mavacamten on the CYP2C19 substrate omeprazole was similar to that on the CYP3A substrate midazolam (Table 4-11). This is mainly because the fraction of omeprazole metabolized by CYP3A in the model increased to 100% in PM of CYP2C19.

Table 4-11 Predicted Effects of Mavacamten on Single-dose Pharmacokinetics of CYP-substrates following Concomitant Administration of Multiple Doses of Mavacamten in oHCM Patients with different CYP2C19 Phenotypes.

Populations & Mavacamten Dosing regimen	Interacting CYP	CYP substrate	AUC Ratio	C_{max} Ratio
25 mg QD 2d, 15 mg QD 14d in CYP2C19 NM	CYP3A	midazolam	0.76	0.86
CYP2C19 PM & 15 mg QD 210d	CYP3A	midazolam	0.36	0.52
	CYP2C8/CYP3A	repaglinide	0.61	0.7
	CYP2C9	tolbutamide	0.35	0.7
	CYP2C19/CYP3A	omeprazole	0.33	0.7
CYP2C19 PM & 5 mg QD 210d and CYP2C19 NM & 15 mg QD 50d	CYP3A	midazolam	0.55	0.76
	CYP2C8/CYP3A	repaglinide	0.73	0.81
	CYP2C9	tolbutamide	0.46	0.77
CYP2C19 PM & 5 mg QD 210d	CYP2C19/CYP3A	omeprazole	0.52	0.83
CYP2C19 NM & 5 mg QD 50d	CYP3A	midazolam	0.79	0.87
	CYP2C8/CYP3A	repaglinide	0.88	0.92
	CYP2C9	tolbutamide	0.67	0.89

Source: reviewer's analyses. 100 virtual subjects (20-50-year-old, 50% females) were given mavacamten once daily for either 50 days in NM of CYP2C19 or 210 days in PM OF CYP2C19. A single dose of CYP substrates midazolam (2 mg), repaglinide (0.25 mg), and tolbutamide (500 mg) was given 24h before the last dose of mavacamten. Simulations were performed using Simcyp V19 by the Reviewer.

Additional Comments:

- *In NM of CYP2C19, the steady-state exposure of mavacamten is more than two-fold higher in the oHCM patients compared to the healthy subjects following once daily dosing of 5-mg mavacamten (Table 4-12). The mechanism for higher exposure in patients is unknown. This may pose uncertainty about the predicted DDI effects.*

Table 4-12 Comparison of Mavacamten Steady-state Exposure in Healthy Subjects with its Exposure in Patients following Multiple Doses of Mavacamten

Dose (mg)	Populations	AUC_{ss} (h*ng/mL)	C_{max-SS} (ng/mL)	C_{min-SS} (ng/mL)	Equivalent dose in patients (mg)	Sources
5	Healthy Subject, CYP2C19 NM	2100	128	78	5	popPK estimates
	oHCM patient, CYP2C19 NM	5568	273	216		
	oHCM patient, CYP2C19 PM	19272	842	785		
15	oHCM patient, CYP2C19 NM	19272	945	745	15	
	oHCM patient, CYP2C19 PM	57816	2526	2355		
10	Healthy Subject, CYP2C19 NM	5795	407		5	PBPK simulation†
15	Healthy Subject, CYP2C19 PM	19786	1081			
30	Healthy Subject, CYP2C19 NM	14715	1097		15	
60	Healthy Subject, CYP2C19 PM	54259	3285			

Median values are reported. PopPK estimated AUCss were calculated from Cavg-ss x 24h. PopPK estimates were based on a subject weighing 84 kg. †Reviewer's analyses: 100 virtual subjects (20-50-year-old, 50% females) were given mavacamten once daily for 49 days in NM of CYP2C19 and for 210 days in PM of CYP2C19.

- *To ensure sufficient exposures of parent drug for simulating the effect of multiple doses of mavacamten on single dose PK of a CYP substrate, the steady-state exposure of mavacamten in oHCM patients following once daily dosing of 5- or 15-mg mavacamten was simulated using higher doses of mavacamten in virtual healthy subjects (sim-healthy subject population) so that the simulated AUC was matched to that estimated by popPK analyses (Table 4-12).*
- *In the hepatocyte induction study (NC-19-0012), the CYP induction parameters (Emax and EC50) of rifampin, the positive control, estimated based on changes in CYP mRNA using the hepatocytes from the same donors were also available. It is possible to calibrate the induction parameters of mavacamten on CYP enzymes based on the relationship between rifampin induction of corresponding CYPs in vitro and in vivo. The optimized induction parameters of rifampin (Indmax and IndC50) in the SV-Rifampin MD model could capture the induction effects of rifampin observed in clinical DDI studies thus could be considered as in vivo induction parameters of rifampin. Therefore, the induction parameters of mavacamten on CYP enzymes (Table 4-13) were calibrated using the following equations:*

$$Calibrated\ Ind_{max}\ (mavacamten) = 1+E_{max}(mavacamten)/E_{max}(RIF)*(Ind_{max}(RIF)-1)$$

$$Calibrated\ IndC_{50}\ (mavacamten) = EC_{50}(mavacamten)/EC_{50}(RIF)*IndC_{50}(RIF)$$

***Note**: The original induction parameters of CYP2C19 in the SV-rifampin MD model under-predicted the effects on CYP2C19 substrate omeprazole* [redacted](b) (4) *. The values in Table 4-13 were optimized by the reviewer based on clinical DDI studies of rifampin with omeprazole 3-6. In addition, nonspecific binding of rifampin in the incubation medium was not incorporated in the calibration. The predicted induction effect of rifampin may be underpredicted.*

Table 4-13 In vitro CYP Induction Parameters and Calibrated Model Parameters of Mavacamten and Rifampin

CYP mRNA	Hepatocyte induction parameters			Induction parameters in Simcyp models			
	Induction parameters	RIF	Mavacamten	Model parameters	RIF	Mavacamten Calibrated	$f_{u,inc}$†
CYP3A4	EC_{50}	0.47	3.94	$IndC_{50}$	0.32	2.68	0.7
	E_{max}	12.1	7.7	Ind_{max}	16	10.55	0.7
CYP2C8	EC_{50}	0.3	2.88	$IndC_{50}$	0.3	2.88	0.7
	E_{max}	3.34	3.25	Ind_{max}	6.7	6.55	0.7
CYP2C9	EC_{50}	1.05	4.47	$IndC_{50}$	0.1	0.43	0.7
	E_{max}	3.34	2.14	Ind_{max}	6	4.20	0.7
CYP2C19	EC_{50}	0.89	3.55	$IndC_{50}$	0.11*	0.44	0.7
	E_{max}	3.37	2.25	Ind_{max}	22*	15.02	0.7

**Reviewer optimized parameters. †Nonspecific binding of mavacamten. RIF: rifampin*

Source: reviewer's analyses

4.3.4.3 Can PBPK analyses predict the effects of strong CYP3A and CYP2C19 inhibitors and inducers on the PK of mavacamten?

The simulated mavacamten PK in both healthy NM of CYP2C19 and PM of CYP2C19 was consistent with clinical observations (Figure 4-16 and Table 4-10). The Applicant also provided additional evidence to demonstrate the predictive performance of the NM of CYP2C19 and PM of CYP2C19 populations (rsp-fda-pharmacology-request-20210616, SN0030). Therefore, fraction metabolized by CYP2C19 (fm, CYP2C19), 74% based on the in vitro reaction phenotyping study, in the mavacamten model is considered verified. Subsequently, it is reasonable to assume that the in vivo fm, CYP3A4 value of mavacamten is similar to the 18% estimated from the same in vitro studies. Therefore, the mavacamten PBPK model could be used to predict the effects of CYP3A and CYP2C19 perpetrators in healthy subjects. As mentioned above, however, the steady-state exposure of mavacamten is more than two-fold higher in the oHCM patients compared to the healthy subjects, and the mechanism for higher exposure in patients is unknown. This poses uncertainty about applying the predicted DDI effects in healthy subjects discussed below to oHCM patients.

In PM OF CYP2C19, when 15 mg mavacamten was co-administered with the strong CYP3A inhibitors itraconazole, the AUC of mavacamten was predicted to increase approximately 2-fold

(Table 4-15), which is similar to the results submitted by the Applicant (Table 4-14). Greater effect was predicted when ketoconazole was co-administered (Table 4-15). Of note, the Applicant-simulated itraconazole DDI studies only lasted 59 days, which has not reached steady state considering the long half-life in PM OF CYP2C19. In NM of CYP2C19, the reviewer simulated the DDI study of mavacamten with the strong CYP2C19 inhibitor and moderate CYP3A inhibitor fluconazole. Fluconazole was predicted to increase mavacamten AUC by approximately 3.1-fold (Table 4-15), which was similar to the observed 3.4-fold difference in AUC between NM of CYP2C19 and PM of CYP2C19, therefore provided additional verification of fm, CYP2C19. Of note, fluconazole was predicted to have a greater effect on mavacamten exposure when CYP2C19 induction parameters of mavacamten were incorporated in its model (Table 4-15).

The Applicant didn't investigate the potential effects of CYP induction on mavacamten in the initial submission. Mavacamten is a substrate of CYP2C19, CYP3A and CYP2C9, and is susceptible to CYP induction. The analyses conducted by the reviewer showed that the strong CYP3A and CYP2C19 inducer rifampin was predicted to reduce steady-state mavacamten AUC0-24h and Cmin by approximately 3- and 4-fold in PM of CYP2C19 and 8-and 40-fold in NM of CYP2C19, respectively (Table 4-15). The moderate CYP3A and CYP2C19 inducer efavirenz was predicted to reduce mavacamten AUC by approximately 1.5- fold and Cmin,ss by approximately 2-fold regardless of CYP2C19 phenotype (Table 4-15).

Table 4-14 Summary of Mavacamten DDI Simulations as a Victim of CYP3A4 Inhibitor Itraconazole in Various Virtual Northern European Caucasian Populations

Virtual Population	Mavacamten	C_{max} GMR (90% CI)	AUC[1] (90% CI)
Representative Northern European Caucasian	Single dose	1.01 (1.01 – 1.01)	1.30 (1.24 – 1.35)
	Steady state	1.16 (1.13 – 1.18)	1.26 (1.23 – 1.29)
Northern European Caucasian population excluding CYP2C19 PMs	Single dose	1.01 (1.01 – 1.01)	1.19 (1.17 – 1.21)
	Steady state	1.13 (1.11 – 1.14)	1.23 (1.21 – 1.25)
Northern European Caucasian population of 100% CYP2C19 PMs	Single dose	1.01 (1.01 – 1.01)	2.18 (2.07 – 2.28)
	Steady state	1.40 (1.37 – 1.43)	1.59 (1.54 – 1.64)

[1]represents AUC_{0-inf} ratio after single dose mavacamten and AUC_{0-24h} ratio under steady state conditions
Simulated population geometric mean ratio (90% CI) [source: myo-1-b-model-app-25.xlsx; myo-1-b-model-app-24.xlsx, myo-1-b-model-app-47.xlsx; myo-1-b-model-app-48.xlsx, myo-1-b-model-app-27.xlsx; myo-1-b-model-app-28.xlsx].

Source: Table 8 in the PBPK report (myo/1/b)

Table 4-15 Predicted Drug Interactions of Mavacamten as a Victim of Strong CYP Inhibitors and Inducer in Healthy Subjects

	Perpetrator dosing regimen	Mavacamten dosing regimen	AUC† ratio	C_{max} ratio	C_{min} ratio	CYP2C19 phenotype
Strong CYP3A	Ketoconazole	15 mg SD D8	1.96	1.01		CYP2C19 PM

inhibitors	400 mg QD 210d	15 mg QD 210d	2.27	1.92	2.56	
	Itraconazole 200 mg QD 210d	15 mg SD D8	2.14	1.01		
		15 mg QD 210d	1.72	1.51	1.82	
Moderate	Diltiazem 60 mg TID 210d	15 mg QD 210d	1.42	1.32	1.55	
Moderate	Diltiazem 60 mg TID 60d	15 mg QD 60d	1.14	1.07	1.19	CYP2C19 NM
Strong CYP2C19 inhibitor	Fluconazole 200 mg QD 60d	15 mg SD D10	3.77	1.04		CYP2C19 NM
		15 mg QD 60d‡	3.10	2.08	5.35	
		15 mg QD 60d‡	4.13	2.30	9.48	CYP2C19 UM
Strong CYP3A and CYP2C19 inducer	Rifampin 600 mg QD 60d	5 mg SD D15	0.3	0.96		CYP2C19 PM
		5 mg QD 60d	0.33	0.49	0.23	
		15 mg QD 60d	0.39	0.56	0.23	
		5 mg SD D15	0.13	0.78		CYP2C19 NM
		5 mg QD 60d	0.13	0.42	0.025	
		15 mg QD 60d	0.13	0.43	0.025	
Moderate CYP3A and CYP2C19 inducer	Efavirenz* 600 mg QD 60d	15 mg QD 60d	0.68	0.77	0.57	CYP2C19 PM
			0.61	0.78	0.46	CYP2C19 NM
			0.63	0.81	0.43	CYP2C19 UM

*The optimized induction parameters (Indmax and IndC50) of rifampin for CYP2C19 in Table 4-13 were used in the simulations. Sim-Healthy Subject population aged 20 -50 with female ratio of 0.5 was used in these simulations. Geometric mean was reported. Simulations were performed using Simcyp V19. †AUC, AUC0-24h for steady-state, AUC0-inf for single dose. ‡ The induction parameters of mavacamten for CYP2C19 were not calibrated with rifampin. When the calibrated parameters were used, the AUC, Cmax and Cmin ratios were predicted to be 3.52, 2.02 and 7.62, respectively. * The default SV-Efavirenz model was used except that the Indmax and IndC50 of efavirenz for CYP2C19 used in the simulation were 1.86 and 0.005 mM7.*

Source: Reviewer's analyses

Note: The Applicant submitted additional simulations to evaluate the effects of rifampin on mavacamten in NM of CYP2C19 after the mid-cycle review communication (PBPK report addendum, SN0038). However, the default induction parameters for CYP2C19 in the SV-rifampin-MD model were used. Therefore, the effects of rifampin on mavacamten were underestimated.

4.3.5 Conclusions

- The induction effects of mavacamten on probe substrates of CYP enzymes depend on mavacamten dose and the CYP2C19 phenotype, ranging from weak to moderate induction effects (Table 4-11).

- In CYP2C19PM, when 15 mg mavacamten was co-administered with the strong CYP3A inhibitors itraconazole and ketoconazole, the steady-state AUC0-24h and Cmin of mavacamten were predicted to increase by approximately 2-fold (Table 4-15).
- In NM of CYP2C19, co-administration of mavacamten with the strong CYP2C19 and moderate CYP3A inhibitor fluconazole was predicted to increase mavacamten AUC0-24h and Cmin by at least 3- and 5-fold, respectively (Table 4-15).
- The strong CYP3A and CYP2C19 inducer rifampin was predicted to reduce mavacamten AUC0-24h and Cmin by approximately 3- and 4-fold in PM of CYP2C19 and 8-and 40-fold in NM of CYP2C19, respectively (Table 4-15). The moderate CYP3A and CYP2C19 inducer efavirenz was predicted to reduce mavacamten AUC by approximately 1.5- fold and Cmin,ss by approximately 2-fold regardless of CYP2C19 phenotype.

4.3.6 References

1. Fahmi OA et al. Evaluation of CYP2B6 Induction and Prediction of Clinical Drug–Drug Interactions: Considerations from the IQ Consortium Induction Working Group—An Industry Perspective. *Drug Metab Dispos* (2016), 44:1720–1730
2. Hariparsad N et al. Considerations from the IQ Induction Working Group in Response to Drug-Drug Interaction Guidance from Regulatory Agencies: Focus on Downregulation, CYP2C Induction, and CYP2B6 Positive Control. *Drug Metab Dispos*. (2017);45(10):1049-1059
3. Bosilkovska M et al. Geneva Cocktail for Cytochrome P450 and P-Glycoprotein Activity Assessment Using Dried Blood Spots. *Clinical Pharmacology & Therapeutics* (2014); **96** (3): 349–359
4. Kamiya C et al. Effect of co-administered inducer or inhibitor on omeprazole pharmacokinetics based on CYP2C19 genotype. J Pharmacol Sci. (2019); 139(4):361-366.
5. Park GJ et al. Drug-drug interaction of microdose and regular-dose omeprazole with a CYP2C19 inhibitor and inducer. *Drug Des Devel Ther*.(2017);11:1043-1053
6. Derungs A et al. Effects of Cytochrome P450 Inhibition and Induction on the Phenotyping Metrics of the Basel Cocktail: A Randomized Crossover Study. *Clin Pharmacokinet*. (2016) ;55(1):79-91.
7. Nagai M et al. Characterization of CYP2C Induction in Cryopreserved Human Hepatocytes and Its Application in the Prediction of the Clinical Consequences of the Induction. *J Pharm Sci* (2018) 107: 2479 -2488.

5 Additional Assessments

5.1 Bioanalytical Method validation

For the determination of mavacamten concentrations in human plasma, the Applicant used validated high-performance liquid chromatographic (HPLC) methods with tandem mass spectrometry detection methods (LC-MS/MS; (b) (4)) with multiple reaction monitoring transitions. In addition, the Applicant used LC-MS/MS methods ((b) (4)) method for the determination of [^{14}C]-mavacamten concentrations in human plasma from the mass balance study. Since no major metabolites were detected in human plasma, no other analytical methods were developed for determination of metabolite concentrations in human plasma.

Plasma samples containing K_2EDTA as an anticoagulant and internal standard (MYK-1320 and MYK-1316) were processed using liquid-liquid extraction (b) (4) and protein precipitation (b) (4) prior to LC-MS/MS analysis. Summary of bioanalytical methods used in the clinical development program is provided in Table 5-1.

Table 5-1 Summary of Analytical Methods Utilized in Clinical Development

Study Numbers	Validation Summary	Clinical Studies
Studies # AD15-610, AD15-493, AD15-569, AD17-699, AD20-1064, AD18-984, AD20-1083, AD20-1058, AD17-658, AD18-755, AD17-668, AD18-908, AD20-1006, AD20-1044, AD20-1090, AD20-1068	Range: 0.2 to 200 ng/mL Accuracy: ±10.3% (max) Precision: ≤ 14.8% (max)	Studies # 001, 002, 003, 004, 005, 006, 007, 008, 009, 010, 011, 012, 014, 015, 016, 018. Validation Report # AV15-MYK461-01 & Its Addendum Reports
8391620	Range: 0.2 to 200 ng/mL Accuracy: -4.2% to 0.2%* Precision: ≤ 11.7%	Study # 013 Validation Report # NC-20-0041 & Its Addendum Reports

** Between run accuracy bias*

Analytical validation evaluated extraction recovery, stability (whole blood, benchtop, freeze-thaw, re-injection, long-term stability), carryover effects, matrix effects.

Summary of bioanalytical method used in the relative bioavailability study is provided below (Table 5-2). Accuracy and precision of QC samples were ≤15% (and ≤20% at LLQ), and calibration curves for the LC-MS/MS bioanalytical assay were within acceptable limits. Incurred samples reanalysis was carried out on approx. 10% of randomly selected samples from above

studies. More than 2/3rd of the incurred sample reanalysis were within 20% deviation. Results of incurred sample reanalysis were within acceptable limits.

Table 5-2 Summary of Bioanalytical Method [Study # 014]

Report Details	Matrix and Analyte	Range and QCs	Accuracy and Precision	Study Number	Method Reports
Report Number AD20-1006 (b) (4) Analysis Dates: 2019/10/18 to 2019/12/18	Matrix: Plasma (K_2 EDTA) Analyte: Mavacamten IS: MYK-1320 Method: HPLC-MS/MS (API-5500)	LLOQ: 0.2 ng/mL DQC: 160 ng/mL QCs: (0.6, 10, and 160 ng/mL)	8 CSs (0.2-200 ng/mL): (CS Levels: 0.2, 0.4, 1, 5, 50, 100, 180, and 200) Accuracy: -1.5 to 1.0% Precision: 3.2 to 6.6% 4 QCs (with 1 DQC) Accuracy: -5.0 to -0.6% Precision: 4.1 to 6.0%	Study No. MYK-461-014 (total samples 1120 from 24 subjects) Storage: 113 days	Validation Report AV15-MYK461-01 Method TM15-311.006 ISR 107/108 (99.1% met criteria ≤ 20%) SOP AA-312

CSs: Calibration Standards, QCs: Quality Control Samples, LLOQ: Lower Limit of Quantification, ULOQ: Upper Limit of Quantification; DQC: Dilution Quality Control Samples.

Reviewer's Comments:

The bioanalytical methods used in analysis of pharmacokinetic samples fulfill the required criterion for 'method validation' and 'application to routine analysis' provided in the 'Guidance for Industry: Bioanalytical Method Development' and is acceptable.

5.2 Summary of Formulations Utilized in Clinical Studies

During the development, three oral formulation, viz. an oral suspension, immediate release tablets (tablet 1 and 2) and immediate release capsules (capsule 1 and 2), were utilized. Since mavacamten exhibits a low solubility and high permeability (potential BCS Class II compound), (b) (4) were selected for clinical development.

Table 5-3 Summary of Formulations Utilized in Clinical Studies

Formulations	Clinical Studies
Oral suspension†	Studies # 001 and 002
Tablet (1 and 2)	Study # 003 (Tablet 1: 0.25, 1, 2.5 mg) Studies # 009, 010, 011 (Tablet 2: 2, 5, 10, and 20 mg)
Capsule (1 and 2)	Study # 006 (Capsule 1) Studies # 005, 007, 008, 012 (mostly Capsule 2‡) Study # 014* (Capsule 1 vs Capsule 2‡)

(b) (4) *‡intended commercial formulation; *Relative bioavailability / Food effect study using capsule 1 and capsule 2 formulations.*

Both capsule 1 and capsule 2 (mostly capsule 2) were used in Phase 3 and Phase 2/3 studies (Studies # 005, 007, 008). The Applicant conducted a relative bioavailability study (Study # 014) to assess bioavailability between 2 capsule formulations (single dose). The study results indicated that the exposure of mavacamten (GMR for AUC: 1.06 and Cmax: 1.01; capsule 2 vs. capsule 1) from both formulations were comparable.

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/

GIRISH K BENDE
10/15/2021 11:52:39 AM

NAN ZHENG
10/15/2021 11:55:20 AM

YING-HONG WANG
10/15/2021 11:57:18 AM

CHRISTIAN GRIMSTEIN
10/15/2021 12:01:39 PM
Signed also on behalf of Katarzyna Drozda.

XINYUAN ZHANG
10/15/2021 12:13:55 PM

LIANG LI
10/15/2021 12:17:42 PM

MANOJ KHURANA
10/17/2021 09:59:05 PM

DOANH C TRAN
10/18/2021 09:48:31 AM