CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214998Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 12, 2022

To: Maryann Gordon, M.D., Medical Officer
Division of Cardiology and Nephrology (DCN)

Alexis Childers, Regulatory Project Manager (DCN)

From: Charuni Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for CAMZYOS (mavacamten) capsules for oral use (Camzyos)

NDA: 214998

In response to DCN's consult request dated February 18, 2022, OPDP has reviewed the proposed product labeling (PI) and Medication Guide (MG) for CAMZYOS (mavacamten) capsules for oral use (Camzyos). This supplement provides for a new application indicated for the treatment of adults with symptomatic New York Heart Association (NYHA) class II-III obstructive hypertrophic cardiomyopathy (HCM) to improve functional capacity and symptoms.

PI, MG: OPDP's comments on the proposed labeling are based on the draft version received by electronic mail from DCN on March 31, 2022, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed and comments on the proposed MG will be sent under separate cover at a later time.

Thank you for your consult. If you have any questions, please contact Charuni Shah at (240) 402-4997 or charuni.shah@fda.hhs.gov.

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CHARUNI P SHAH
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	April 12, 2022
To:	Alexis Childers RAC, CQIA Regulatory Project Manager **Division of Cardiology and Nephrology (DCN)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Charuni Shah, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	CAMZYOS (mavacamten)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 214998
Applicant:	MyoKardia Inc.

1 INTRODUCTION

On January 28, 2021, MyoKardia Inc., submitted for the Agency's review a New Drug Application (NDA) 214998 for CAMZYOS (mavacamten) capsules, for oral use, for the proposed indication of the treatment of symptomatic obstructive hypertrophic cardiomyopathy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Cardiology and Nephrology (DCN) on February 4, 2021, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for CAMZYOS (mavacamten) capsules, for oral use.

2 MATERIAL REVIEWED

- Draft CAMZYOS (mavacamten) capsules MG received on January 28, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 30, 2022.
- Draft CAMZYOS (mavacamten) capsules Prescribing Information (PI) received on January 28, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 30, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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BARBARA A FULLER
04/12/2022 12:44:20 PM

LASHAWN M GRIFFITHS
04/12/2022 01:04:14 PM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Template

Date:	April 1, 2022
Reviewer:	Margie Goulding, PhD, Epidemiologist Division of Epidemiology II
Acting Team Leader:	Benjamin Booth, PhD Division of Epidemiology II
Deputy Director:	Monique Falconer, MD, MS Division of Epidemiology II
Director:	Judith Zander, MD Office of Pharmacovigilance and Epidemiology
Acting Team Leader:	Sarah Dutcher, PhD Sentinel Program
Deputy Director:	Robert Ball, MD, MPH Office of Surveillance and Epidemiology
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name(s):	Mavacamten (Tradename: Camzyos)
Application Type/Number:	NDA 214998
Applicant/sponsor:	MyoKardia Inc.
OSE RCM #:	2021-189 (& RCM 2021-1251 for the SAM mtg)

Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

NDA 214998 is being reviewed for mavacamten, a cardiac myosin inhibitor, proposed for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in adults (b) (4)

Mavacamten is a novel small molecule allosteric inhibitor of striated muscle myosin that selectively targets cardiac myosin and reversibly inhibits its binding to actin. Its mechanism of action results in the reduction of sarcomeric hypercontractility and is predicted to facilitate ventricular relaxation, which should improve both dynamic LVOT obstruction and LV compliance (diastolic dysfunction) in patients with hypertrophic cardiomyopathy (HCM).

Mavacamten was granted both orphan drug and breakthrough therapy designations for the treatment of symptomatic oHCM.

1.2. Describe the Safety Concern

In rat and rabbit reproductive toxicology studies, mavacamten was found to cause developmental abnormalities. It was found to cause increased post-implantation loss, lower mean fetal body weight, slightly reduced fetal skeletal ossification, heart malformation, and increased incidences of skeletal malformations when compared to controls in developing rats, and increased incidences of cleft palate, great vessel malformations, and fused sternebrae in rabbit fetuses at the same doses that cause maternal toxicity in rabbits. In sum, mavacamten has a high probability of being a teratogen when administered during gestation.

The trial supporting this application was a phase-3, double-blind, randomized, placebo-controlled trial [EXPLORER-HCM] conducted in cardiovascular centers in 13 countries over 2018-2020.[1] A total of 251 patients with HCM with an LVOT gradient of 50 mm Hg or greater and NYHA class II-III symptoms were assigned (1:1) to receive mavacamten starting at 5 mg or placebo for 30 weeks. The mean age of participants was 58.5 years, with 21% aged younger than 50 years, 45% aged 50-64 years, and 34% aged 65 years or older. Mavacamten treatment showed positive results on both the primary and secondary endpoints.[1] No information on the occurrence or outcome of pregnancy in the study population was reported.

A systematic review of studies on outcomes and complications of pregnancy in HCM found that pregnancy in women with HCM carries maternal and fetal risks.[2] The maternal mortality rate was 0.5%, and any complication or worsening of symptoms occurred in 29% of the patients. Premature birth was observed in 26%. In conclusion, maternal mortality related to pregnancy in women with HCM is low and appears to be confined to women with a high-risk profile before pregnancy. Fetal mortality is comparable to that in the general population; however, the risk of premature birth is increased.[2]

The draft label includes this Warnings and Precautions language:

(b) (4)

The draft label also includes these sections under 8. USE IN SPECIFIC POPULATIONS:

8.1. Pregnancy

Risk Summary

(b) (4) Based on animal data, CAMZYOS may cause fetal harm when administered to a pregnant female. (b) (4)

(b) (4)

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

There is a pregnancy (b) (4) for CAMZYOS. If CAMZYOS is administered during pregnancy, or if a patient becomes pregnant while receiving

CAMZYOS or within 4 months [(b) (4)] the last dose of CAMZYOS, healthcare providers should report CAMZYOS exposure by [(b) (4)] Bristol-Myers Squibb at 1-800-721-5072.

Data

Animal Data

When mavacamten was administered orally to pregnant rats ([(b) (4)] mg/kg/day) during the period of organogenesis, decreased mean fetal body weight, and increases in post implantation loss and fetal malformations (visceral and skeletal) were observed in the high dose group (1.5 mg/kg/day). Visceral malformations (heart malformation in fetuses, including one total situs inversus) and increased incidences of skeletal malformations (mainly fused sternebrae) were observed. Plasma exposure (AUC) at the no effect dose for embryo-fetal development in rats [(b) (4)] in humans at the MRHD.

When mavacamten was administered orally to pregnant rabbits ([(b) (4)] mg/kg/day) during the period of organogenesis, fetal malformations (visceral and skeletal) were increased at doses of 1.2 mg/kg/day and higher. Visceral findings consisted of malformations of the great vessels (dilatation of pulmonary trunk and/or aortic arch) [(b) (4)] Skeletal malformations consisted of higher incidences of fused sternebrae [(b) (4)] Plasma exposure (AUC) at the no effect dose for embryo-fetal development in rabbits is [(b) (4)] in humans at the MRHD.

In a pre/postnatal development study, mavacamten was administered orally to pregnant rats ([(b) (4)] mg/kg/day) from gestation Day 6 to lactation/post-partum Day 20. No adverse effects were observed in the dams or offspring exposed daily from before birth (in utero) through lactation. 1.5 mg/kg/day (the highest dosage level tested) was considered to be the no-observed-adverse-effect level (NOAEL). [(b) (4)]

8.3. Females and Males of Reproductive Potential

Pregnancy Testing

Confirm [(b) (4)] in females of reproductive potential prior to initiation of [(b) (4)] CAMZYOS [(b) (4)]

Contraception

Females

Advise females of reproductive potential [redacted] (b) (4) to use effective contraception during treatment with CAMZYOS and for [redacted] (b) (4) 4 months after [redacted] (b) (4)

[redacted] (b) (4)

The number of women expected to become pregnant while on mavacamten is expected to be small as oHCM presents mostly in patients who are beyond reproductive age, and pregnancy is contraindicated in women with severe LVOT obstruction due to prohibitively high maternal risks.[3] The Applicant estimates that in the U.S. there would be only approximately 14 women of ages 18-44 with HCM per year who are pregnant and using mavacamten[a]. Thus, while mavacamten exposure in pregnant women is expected to be rare, it is advisable to obtain more information on the risks to the pregnancy, fetus and infant, given the birth defects seen in the animal reproductive toxicology studies on mavacamten. A Risk Evaluation and Mitigation Strategy for teratogenicity is not planned.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)

Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

[a] MyoKardia pregnancy study proposal in IND121904 Mavacamten post approval mtg package 10.26.20, pg. 19.

☒ No approved indication, but use in women of childbearing age is a general concern

Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty

☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †

☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† ***If checked, please complete General ARIA Sufficiency Template.***

2.2. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☐ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☐ Electronic database study with chart review
☐ Electronic database study without chart review
☒ Other, please specify: A descriptive pregnancy safety study (See 2.4 below).

2.3. Which are the major areas where ARIA is not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population
☐ Exposures
☒ Outcomes
☐ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Outcomes
The Agency requested descriptive pregnancy safety study seeks broad-based surveillance, including on pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on infants in pregnancies where the woman was exposed to mavacamten. (b) (4) [redacted]

(b) (4) The chart review needed to validate the reported outcomes is also outside of ARIA's scope.

Analytical Tools

ARIA analytic tools are not sufficient to assess the regulatory question of interest because ARIA data mining methods have not been fully tested and implemented for post-marketing surveillance of birth defects and other pregnancy outcomes.

2.4. Please include the proposed PMR language in the approval letter.

Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to CAMZYOS (mavacamten) during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

References

1. Olivotto, I., et al., *Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial.* Lancet, 2020. **396**(10253): p. 759-769.
2. Schinkel, A.F., *Pregnancy in women with hypertrophic cardiomyopathy.* Cardiol Rev, 2014. **22**(5): p. 217-22.
3. Pieper, P.G. and F. Walker, *Pregnancy in women with hypertrophic cardiomyopathy.* Neth Heart J, 2013. **21**(1): p. 14-8.

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SARAH K DUTCHER
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04/01/2022 04:34:58 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 03, 2022
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214998
Product Name and Strength:	Camzyos (mavacamten) capsules, 2.5 mg, 5 mg, 10 mg, and 15 mg
Applicant/Sponsor Name:	Bristol Myers Squibb
OSE RCM #:	2021-190-1
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on March 1, 2022 for Camzyos (mavacamten) capsules. We reviewed the revised container labels for Camzyos (mavacamten) (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Aidoo, M. Label and Labeling Review for Camzyos (mavacamten) (NDA 214998). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUN 22. RCM No.: 2021-190.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Disease, Pediatrics, Urology, and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatrics and Maternal Health PLLR Addendum

Date: February 14, 2022 **Date Consulted:** June 3, 2021

From: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Lynne Yao, MD, DPMH Director

To: Alexis Childers, Regulatory Project Manager (RPM)
Division of Cardiology and Nephrology (DCN)

Drug: Camzyos (mavacamten)

NDA: 214998

Proposed Indication: Treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in adults to improve functional capacity, (b) (4) and symptoms.

Applicant: MyoKardia Inc.

Subject: Pregnancy and Lactation Labeling Rule (PLLR) compliance

Materials Reviewed:

- DPMH Memorandum regarding Postmarketing Requirement (PMR) for descriptive pregnancy safety study, NDA 214998, by K. Baisden, DO, dated August 20, 2021. DARRTS Reference ID: 4833004.

Consult Question: DCN requests input regarding proposed PLLR labeling subsections

BACKGROUND

On January 28, 2021, the applicant, MyoKardia Inc., submitted a new NDA (214998) for a new molecular entity (NME), Camzyos (mavacamten). On June 3, 2021, the Division of Cardiology

and Nephrology (DCN) consulted the Division of Pediatric and Maternal Health (DPMH) to assist in developing a postmarketing study to assess pregnancy exposure to mavacamten based on concerns for teratogenic effects observed in animal reproduction studies. DCN did not request DPMH to provide Pregnancy and Lactation Labeling Rule (PLLR) labeling recommendations. On August 20, 2021, the DPMH finalized memorandum recommended a postmarketing descriptive pregnancy safety study.

On November 18, 2021, DCN issued a major amendment to the application, extending the user fee goal date to April 28, 2022. On January 28, 2022, DCN requested DPMH input on PLLR labeling. This addendum provides DPMH labeling recommendations for PLLR compliance.

Drug Characteristics

Mechanism of action: cardiac myosin inhibitor

- *Half-life:* terminal half-life is 6-9 days in CYP 2C19 normal metabolizers (NM). Mean half-life is prolonged in CYP 2C19 poor metabolizers (PM) compared to NM (23 days versus 6-9 days, respectively). (b) (4)
- *Molecular weight:* 273.33 g/mol
- *Plasma protein binding:* 97-98%

Condition: Hypertrophic Cardiomyopathy (HCM) Pregnancy[1,2]

- *HCM:* chronic, progressive disease of the cardiomyocyte, defined by left ventricular (LV) hypertrophy, with a diverse clinical presentation and course. There are two common types of HCM: obstructive hypertrophic cardiomyopathy (oHCM) and nonobstructive hypertrophic cardiomyopathy. In a general population of young adults, the prevalence of HCM is approximately 1 per 500.
- *HCM and pregnancy:* pregnancy places a significant burden on the cardiovascular system (such as marked increases in circulating blood volume, stroke volume, and heart rate) which may lead to heart failure, arrhythmias, and, rarely, maternal mortality in women with a pre-existent cardiomyopathy. For women with HCM and resting or provocable LVOT obstruction ≥50 mm Hg and/or cardiac symptoms not controlled by medical therapy, pregnancy is associated with increased risk; while pregnancy is contraindicated in women with HCM and advanced heart failure symptoms.
    - A systemic review of 11 observational studies which included 9 patient cohorts (a total of 237 women with HCM and 408 pregnancies), demonstrated that most pregnancies in women with HCM are uneventful.[1] Nevertheless, pregnancy in women with HCM carries maternal and fetal risks. The maternal mortality rate was low at 0.5% and any complication or worsening of symptoms occurred in 29% of the patients. Fetal mortality caused by spontaneous abortion (15%), therapeutic abortion (5%), and stillbirth (2%), was comparable with that in the general population. However, the observed risk of premature birth (26%) was increased.

[1] Schinkel, Arend F.L. MD, PhD. Pregnancy in Women with Hypertrophic Cardiomyopathy. Cardiology in Review. September/October 2014-Volume 22-Issue 5-p 217-222.
[2] Pieper, PG, et al. Pregnancy in Women with Hypertrophic Cardiomyopathy. Neth Heart J (2013) 21:14-18.

REVIEW
The reader is referred to the prior DPMH review by K. Baisden, DO, which includes a full assessment of the available clinical data on mavacamten use during pregnancy and lactation, as well as potential effects on human fertility.[3]

LABELING RECOMMENDATIONS
DPMH revised subsections 2.X, 5.4, 8.1, 8.2, 8.3, and section 17 of the labeling for compliance with the PLLR. DPMH labeling recommendations are below and reflect input from the DCN Nonclinical team and Clinical Pharmacology. Subsection 7.2 is included to provide context. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

(b) (4)

[3] DPMH Memorandum regarding Postmarketing Requirement (PMR) for descriptive pregnancy safety study, NDA 214998, by K. Baisden, DO, dated August 20, 2021. DARRTS Reference ID: 4833004

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/s/

TAMARA N JOHNSON
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LYNNE P YAO
02/16/2022 08:21:00 AM

CDRH/OHT7/DCTD

Memo

TO: Alexis Childers, Senior Regulatory Health Project Manager, OND/ORO/DROCHEN

FROM: Joey Kotarek, CDRH/OHT7/DCTD

Joseph A. Kotarek -S

Digitally signed by Joseph A. Kotarek -S
Date: 2021.10.07 08:55:26 -04'00'

DATE: October 6, 2021

RE: ICCR case number 00785959

A. BACKGROUND

Mavacamten is predominantly metabolized by the CYP2C19 (~75%). CYP2C19 is a polymorphic enzyme, leading to a high degree of variability for metabolism of mavacamten because of underlying genetic differences in CYP2C19 activity. Because of this variability, depending on CYP2C19 activity, patients may be at risk for mavacamten-related toxicity (poor metabolizers [PMs]"). PMs may have increased risk of reduced left ventricular ejection fraction (LVEF) which may cause heart failure due to systolic dysfunction (symptomatic LVEF< 50%).

While the applicant proposes to utilize the same dosage and monitoring approach regardless of the patient's metabolizer status, FDA is considering a differential dosage and monitoring approach in CYP2C19 poor metabolizers. Under the FDA proposed dose and monitoring regimen, CYP2C19 genotype testing would be essential for the safe and effective use of mavacamten.

B. Specific Questions

1. Are the in vitro diagnostics that are currently FDA-cleared for CYP2C19 genotyping adequate to support the proposed use of mavacamten in CYP2C19 PMs?

   CDER has indicated that the relevant alleles for mavacamten dosing would be CYP2C19 *1, *2, *3 and *17, to help identify normal, poor, intermediate, rapid and ultrarapid metabolizers. There are several in vitro diagnostics that are currently FDA

cleared for detection of these CYP2C19 variants, such as the Spartan RX CYP2C19 Test System (k123891), the Verigine® CYP2C19 Nucleic Acid Test (CYP2C19) (k120466), and the Infiniti CYP2C19 Assay (k101683). However, while these devices are indicated for identifying *2, *3, and *17 alleles, these devices are not intended for establishing differential dosage and monitoring regimen.

Of note, the accuracy of presently cleared 510(k) assays in determining rare CYP2C19 variants is supported by a very limited number of samples, and sometimes only a single measurement was used to support the accuracy of detection (for example, *3/*3 and *3/*17), therefore the confidence in the assay to measure this genotype is nil. While this was determined to be adequate to support the present intended use of these devices, informing the dose decisions for mavacamten constitutes a new intended use and the benefit risk profile of such an intended use should be assessed to determine whether the performance of a presently marketed assay would be adequate to support mavacamten dosing as a companion diagnostic (e.g., in the event of erroneous device results, are there other factors that would mitigate the risk of adverse events related to mavacamten overdosing or underdosing). It may be possible for the drug sponsor to collaborate with the manufacturer of an existing 510(k) device such that companion diagnostic claims (to support the safe and effective dosing of mavacamten) could be added to a presently marketed CYP2C19 assay. However, additional validation studies (e.g., a more robust accuracy study with better confidence) may be needed to support such claims for a presently cleared 510(k) assay. If the risks associated with misidentification of 2C19 variants were minor (e.g., if there were no *3/*3 specific dosing recommendations in drug labeling) then it may be adequate to leverage an existing assay as a companion diagnostic for mavacamten therapy; however, CDRH would need to review the details of such a proposal, as well as the benefit-risk assessment associated with mavacamten dose decisions, in order to provide feedback on any specific regulatory pathway.

Additionally, CDER has referenced the regulatory path used to support assays which measured CYP2D6 variants to support eliglustat therapy (for Gaucher Disease). At the time of drug approval, cleared tests for CYP2D6 variant testing were available, and these tests were used to facilitate eliglustat dosing strategies (rather than explicitly call for use of a companion diagnostic assay in drug labeling). However, eliglustat is an orphan drug with a relatively small patient population. When a therapeutic product is intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists and the benefits from the use of the therapeutic product are so pronounced as to outweigh the risks from the lack of an approved or cleared IVD companion diagnostic device, it may be appropriate to approve a therapeutic product even if an IVD companion diagnostic device is not yet approved or cleared. As noted above, CDRH would need more information describing the benefit-risk profile associated with mavacamten dose decisions in order to provide more specific feedback.

2. If adequate, how should labeling for the drug product reference the available tests (e.g., as detected by an FDA-cleared test)?

   Per the Companion Diagnostic Devices guidance, a companion diagnostic device is defined as "an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product." If this device would be essential for the safe and effective use of mavacamten, then it would be considered a companion diagnostic. The use of an IVD companion diagnostic device with a therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, including the labeling of any genetic equivalents of the therapeutic product.

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/s/

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Template

Date:	January 19, 2022
Reviewer:	Margie Goulding, PhD, Epidemiologist Division of Epidemiology II
Acting Team Leader:	Benjamin Booth, PhD Division of Epidemiology II
Deputy Director:	Monique Falconer, MD, MS Division of Epidemiology II
Director:	Judith Zander, MD Office of Pharmacovigilance and Epidemiology
Acting Team Leader:	Sarah Dutcher, PhD Sentinel Program
Deputy Director:	Robert Ball, MD, MPH Office of Surveillance and Epidemiology
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name(s):	Mavacamten
Application Type/Number:	NDA 214998
Applicant/sponsor:	MyoKardia Inc.
OSE RCM #:	2021-189 (& RCM 2021-1251 for the SAM mtg)

Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

NDA 214998 is being reviewed for mavacamten, a cardiac myosin inhibitor, proposed for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in adults (b) (4) [redacted]

Mavacamten is a novel small molecule allosteric inhibitor of striated muscle myosin that selectively targets cardiac myosin and reversibly inhibits its binding to actin. Its mechanism of action results in the reduction of sarcomeric hypercontractility and is predicted to facilitate ventricular relaxation, which should improve both dynamic LVOT obstruction and LV compliance (diastolic dysfunction) in patients with hypertrophic cardiomyopathy (HCM).

Mavacamten was granted both orphan drug and breakthrough therapy designations for the treatment of symptomatic oHCM.

1.2. Describe the Safety Concern

In rat and rabbit reproductive toxicology studies, mavacamten was found to cause developmental abnormalities. It was found to cause increased post-implantation loss, lower mean fetal body weight, slightly reduced fetal skeletal ossification, heart malformation, and increased incidences of skeletal malformations when compared to controls in developing rats, and increased incidences of cleft palate, great vessel malformations, and fused sternebrae in rabbit fetuses at the same doses that cause maternal toxicity in rabbits. In sum, mavacamten has a high probability of being a teratogen when administered during gestation.

The trial supporting this application was a phase-3, double-blind, randomized, placebo-controlled trial [EXPLORER-HCM] conducted in cardiovascular centers in 13 countries over 2018-2020.[1] A total of 251 patients with HCM with an LVOT gradient of 50 mm Hg or greater and NYHA class II-III symptoms were assigned (1:1) to receive mavacamten starting at 5 mg or placebo for 30 weeks. The mean age of participants was 58.5 years, with 21% aged younger than 50 years, 45% aged 50-64 years, and 34% aged 65 years or older. Mavacamten treatment showed positive results on both the primary and secondary endpoints.[1] No information on the occurrence or outcome of pregnancy in the study population was reported.

A systematic review of studies on outcomes and complications of pregnancy in HCM found that pregnancy in women with HCM carries maternal and fetal risks.[2] The maternal mortality rate was 0.5%, and any complication or worsening of symptoms occurred in 29% of the patients. Premature birth was observed in 26%. In conclusion, maternal mortality related to pregnancy in women with HCM is low and appears to be confined to women with a high-risk profile before pregnancy. Fetal mortality is comparable to that in the general population; however, the risk of premature birth is increased.[2]

The draft label includes this Warnings and Precautions language:

(b) (4)

The draft label also includes these sections under 8. USE IN SPECIFIC POPULATIONS:

8.1. Pregnancy

Risk Summary

(b) (4) Based on animal data, [TRADENAME] may cause fetal harm when administered to a pregnant female. (b) (4)

(b) (4)

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

There is a pregnancy [redacted] for [TRADENAME]. If [TRADENAME] is administered during pregnancy, or if a patient becomes pregnant while receiving [TRADENAME] or within 4 months [redacted] the last dose [TRADENAME], healthcare providers should report [TRADENAME] exposure by [redacted] Bristol-Myers Squibb at 1-800-721-5072.

Data

Animal Data

When mavacamten was administered orally to pregnant rats ([redacted] mg/kg/day) during the period of organogenesis, decreased mean fetal body weight, and increases in post implantation loss and fetal malformations (visceral and skeletal) were observed in the high dose group (1.5 mg/kg/day). Visceral malformations (heart malformation in fetuses, including one total situs inversus) and increased incidences of skeletal malformations (mainly fused sternebrae) were observed. Plasma exposure (AUC) at the no effect dose for embryo-fetal development in rats [redacted] in humans at the MRHD.

When mavacamten was administered orally to pregnant rabbits ([redacted] mg/kg/day) during the period of organogenesis, fetal malformations (visceral and skeletal) were increased at doses of 1.2 mg/kg/day and higher. Visceral findings consisted of malformations of the great vessels (dilatation of pulmonary trunk and/or aortic arch) [redacted] Skeletal malformations consisted of higher incidences of fused sternebrae [redacted] Plasma exposure (AUC) at the no effect dose for embryo-fetal development in rabbits is [redacted] in humans at the MRHD.

In a pre/postnatal development study, mavacamten was administered orally to pregnant rats ([redacted] mg/kg/day) from gestation Day 6 to lactation/post-partum Day 20. No adverse effects were observed in the dams or offspring exposed daily from before birth (in utero) through lactation. 1.5 mg/kg/day (the highest dosage level tested) was considered to be the no-observed-adverse-effect level (NOAEL). [redacted]

8.3. Females and Males of Reproductive Potential

Pregnancy Testing

Confirm [redacted] in females of reproductive potential prior to initiation of treatment with [TRADENAME] [redacted]

Contraception

Females

Advise females of reproductive potential [redacted] (b) (4) to use effective contraception during treatment with [TRADENAME] and for [redacted] (b) (4) months after [redacted] (b) (4).

[redacted] (b) (4)

The number of women expected to become pregnant while on mavacamten is expected to be small as oHCM presents mostly in patients who are beyond reproductive age, and pregnancy is contraindicated in women with severe LVOT obstruction due to prohibitively high maternal risks.[3] The Applicant estimates that in the U.S. there would be only approximately 14 women of ages 18-44 with HCM per year who are pregnant and using mavacamten[a]. Thus, while mavacamten exposure in pregnant women is expected to be rare, it is advisable to obtain more information on the risks to the pregnancy, fetus and infant, given the birth defects seen in the animal reproductive toxicology studies on mavacamten. A Risk Evaluation and Mitigation Strategy for teratogenicity is not planned.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

☒ No approved indication, but use in women of childbearing age is a general concern

[a] MyoKardia pregnancy study proposal in IND121904 Mavacamten post approval mtg package 10.26.20, pg. 19.

Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †
☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† ***If checked, please complete General ARIA Sufficiency Template.***

2.2. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☐ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☐ Electronic database study with chart review
☐ Electronic database study without chart review
☒ Other, please specify: A descriptive pregnancy safety study (See 2.4 below).

2.3. Which are the major areas where ARIA is not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population
☐ Exposures
☒ Outcomes
☐ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Outcomes
The Agency requested descriptive pregnancy safety study seeks broad-based surveillance, including on pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on infants in pregnancies where the woman was exposed to mavacamten. (b) (4) The chart review needed to validate the reported outcomes is also outside of ARIA's scope.

Analytical Tools
ARIA analytic tools are not sufficient to assess the regulatory question of interest because

ARIA data mining methods have not been fully tested and implemented for post-marketing surveillance of birth defects and other pregnancy outcomes.

2.4. Please include the proposed PMR language in the approval letter.

Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Tradename (mavacamten) during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

References

1. Olivotto, I., et al., *Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial.* Lancet, 2020. **396**(10253): p. 759-769.
2. Schinkel, A.F., *Pregnancy in women with hypertrophic cardiomyopathy.* Cardiol Rev, 2014. **22**(5): p. 217-22.
3. Pieper, P.G. and F. Walker, *Pregnancy in women with hypertrophic cardiomyopathy.* Neth Heart J, 2013. **21**(1): p. 14-8.

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/s/

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COA Tracking ID: C2021051
NDA Number/referenced IND: NDA 214998 (ref IND 121904)

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2021051
NDA#/referenced IND#:	NDA 214998 (referenced IND 121904)
Sponsor:	MyoKardia, Inc.
Established Name/Trade Name:	Mavacamten
Indication:	Obstructive hypertrophic cardiomyopathy (oHCM) ☒**Rare Disease/Orphan Designation** ☐Pediatrics
Meeting Type:	NDA Review
Review Division:	Division of Cardiology and Nephrology
Clinical Reviewer	Preston Dunnmon
Clinical Team Leader (TL)	Preston Dunnmon
Regulatory Project Manager:	Alexis Childers
COA Reviewer:	Susan Pretko
COA Division Director:	David Reasner
Date Consult Request Received:	February 3, 2021
Date COA Briefing Package/Submission Received:	January 28, 2021
Instruments reviewed:	Kansas City Cardiomyopathy Questionnaire-23 Clinical Summary Score ☒ Patient-reported outcome (PRO)
	Hypertrophic Cardiomyopathy Symptom Questionnaire ☒ Patient-reported outcome (PRO)

1. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) consult review is related to NDA 214998 for mavacamten. The proposed indication is treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in adults to improve functional capacity, (b) (4) and oHCM symptoms.

The applicant used the following patient-reported outcome (PRO) measures in their single 30-week, randomized, double-blind, placebo-controlled, multicenter, multinational, parallel-group phase 3 clinical trial (Study MYK-461-005 (EXPLORER-HCM)) in adult patients aged ≥ 18 years with symptomatic oHCM:

- Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ) Shortness of Breath (SoB) Domain (HCMSQ-SB), which assesses the severity and frequency of SoB (Secondary endpoint). The HCMSQ is in Appendix 1.
- Kansas City Cardiomyopathy Questionnaire-23 Clinical Summary Score (KCCQ-23 CSS), which assesses severity and frequency of heart failure symptoms and functional impacts of patients' cardiovascular disease (Secondary endpoint). The KCCQ-23 CSS is in Appendix 2.

This submission included a PRO Evidence Dossier. The Division seeks DCOA input on the assessment of missing baseline data and proposed labeling claims in the mavacamten draft label. The review concludes the following:

- The evidence submitted by the applicant is sufficient to demonstrate that the HCMSQ-SB score is fit-for-purpose[1] to measure severity and frequency of SoB for the context of use in this drug development program.
- The evidence submitted by the applicant is sufficient to demonstrate that the KCCQ-23 CSS is fit-for-purpose to measure severity of physical limitations, symptom frequency, and symptom burden of oHCM symptoms for the context of use in this drug development program.
- The evidence submitted by the applicant appears to support proposed labeling claims for the HCMSQ-SB score and the KCCQ-23 CSS, with some revisions.

2 BACKGROUND AND CORRESPONDENCE ON CLINICAL OUTCOME ASSESSMENT(S)

2.1 Regulatory Background

- MyoKardia, Inc. is seeking marketing approval of mavacamten for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM) (b) (4) [2]
- This NDA is based on the results of a single phase 3 study, Study MYK-461-005 (EXPLORER-HCM). An End of Phase 2 meeting was held in September 2017 during which the Division provided feedback on the proposed pivotal phase 3 study design and general agreement that a single trial may support an NDA submission.[3]
- Mavacamten received Orphan Designation in April 2016, and Breakthrough Therapy Designation in July 2020.

2.2 Previous COA Reviews

- C20204122_IND 121904_Patel dated May 8, 2020 (DARRTS Reference ID: 4605743)
- C2020005_IND 121904_Patel dated March 23, 2020 (DARRTS Reference ID: 4539961)
- C2019390_IND 121904_Dashiell-Aje dated December 29, 2019 (DARRTS Reference ID: 4539966)
- C2019175_IND 121904_Dashiell-Aje dated December 29, 2019 (DARRTS Reference ID: 4539965)
- C2018349_IND 121904_Dashiell-Aje dated December 29, 2019 (DARRTS Reference ID: 4539964)
- C2018027_IND 121904_Dashiell-Aje dated December 29, 2019 (DARRTS Reference ID: 4539961)
- C2017210_IND 121904_Dashiell-Aje dated December 29, 2019 (DARRTS Reference ID: 4539960)

[1] Fit-for-purpose: A conclusion that the level of validation associated with a tool is sufficient to support its context of use. (Source: BEST (Biomarkers, Endpoints and Other Tools) Resource; https://www.ncbi.nlm.nih.gov/books/NBK338448/)
[2] NDA received January 28, 2021_SN 0001(1)
[3] RPM Filing Review dated March 29, 2021 (DARRTS Reference ID: 4769685)

2.3 Disease Background

Hypertrophic cardiomyopathy (HCM) is thickening of the myocardium, making it more difficult to pump blood. HCM is classified as oHCM or non-obstructive HCM (nHCM) which is defined by whether there is LVOT obstruction. Common symptoms of oHCM include shortness of breath (SoB), angina, and diminished exercise tolerance.

2.4 Investigational Product

Mavacamten (i.e., MYK-461) is a novel reversible inhibitor of cardiac myosin that targets the mechanism of hypercontractility in HCM. Mavacamten immediate-release capsules are administered orally once daily.

3 CLINICAL OUTCOME ASSESSMENT REVIEW

The Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ) produces three domain scores and one total score. Only the SoB domain score is proposed as a secondary endpoint in the EXPLORER-HCM study. Thus, this review is limited to the SoB domain of the HCMSQ (HCMSQ-SB).

The 23-item Kansas City Cardiomyopathy Questionnaire (KCCQ-23) produces domain, total symptom, and clinical symptom scores. Only the clinical symptom score (CSS) is proposed as a secondary endpoint in the EXPLORER-HCM study. Thus, this review is limited to the KCCQ-23 CSS.

3.1 Context of use

3.1.1 Clinical Trial Population

Approximately 251 adult subjects (aged ≥ 18 years) with symptomatic oHCM were randomized into the EXPLORER-HCM study (n=123 subjects in the mavacamten arm; n=128 subjects in the placebo arm).

Approximately 59 adult subjects (aged ≥ 18 years) with symptomatic nHCM were randomized into Study MYK-461-006 (MAVERICK-HCM; n=19 subjects in the mavacamten 200ng/mL arm; n=21 subjects in the mavacamten 500 ng/mL arm; n=19 subjects in the placebo arm). The applicant did not propose this study to contribute to the efficacy profile for this NDA. However, data from the MAVERICK-HCM study contributed to the psychometric evaluation of the HCMSQ-SB and KCCQ-23 CSS.

Both the EXPLORER-HCM and MAVERICK-HCM studies required subjects to have New York Heart Association Functional Class (NYHA FC) II or III symptoms at Screening. A complete list of the inclusion and exclusion criteria is described in the EXPLORER-HCM and MAVERICK-HCM study protocols. The NYHA FC definitions are in Appendix 5.

Reviewer's comment(s):
At Baseline (defined as the last available value before the first administration of study drug), the majority of subjects reported moderate HCM symptom severity on the Patient Global Impression of Severity (PGIS) scale. The majority of subjects at Baseline were classified as NYHA FC II.

3.1.2 Clinical Trial Design

EXPLORER-HCM was a randomized, double-blind, placebo-controlled, 30-week, phase 3 clinical study to evaluate mavacamten in adult subjects with symptomatic oHCM. Patient Reported Outcome (PRO) data was collected according to the assessment schedule shown in Table 1. Double-blind treatment ended (ET) at Week 30 and subjects returned to the site at Week 38 for an end of study (EOS) visit as part of the post-treatment follow-up.

Table 1. Schedule of PRO Data Collection in EXPLORER-HCM

PRO Assessment[a]	Screening Day -35 to Day -1	Day 1	Week 4 (±7 d)	Week 6 (±7 d)	Week 10 (±7 d) (home)	Week 12 (±7 d)	Week 14 (±7 d)	Week 18 (±7 d)	Week 22 (±7 d)	Week 26 (±7 d)	Week 30/ EOT (±7 d)	Week 38/ EOS (±7 d)
HCMSQ	X[b]	←	———	→	X[c]		X[c]	X[c]	X[c]	X[c]	X[c]	X[c]
PGIS[d]	X[d]			X	X		X	X	X	X	X	X
PGIC				X	X		X	X	X	X	X	X
WPAI-SHP		X		X		X		X			X	X
EQ-5D-5L		X		X		X		X			X	X
KCCQ-23		X		X		X		X			X	X

Abbreviations: d, day; EOS, end of study; EOT, end of treatment; EQ-5D-5L, EuroQol five dimensions 5-level questionnaire; home, PRO assessments completed at home; HCMSQ, Hypertrophic Cardiomyopathy Symptom Questionnaire; KCCQ-23, 23-item Kansas City Cardiomyopathy Questionnaire; PGIC, Patient Global Impression of Change questionnaire; PGIS, Patient Global Impression of Severity questionnaire; PRO, patient-reported outcomes; WPAI-SHP, Work Productivity and Activity Impairment questionnaire.

NOTE: Missed PRO assessments by patients outside of study visits are not considered protocol deviations.

[a] The PRO assessments that are completed at visits, with the exception of Screening, should be completed prior to any other study procedure taking place, where possible, and prior to any meaningful discussion about the study or study treatment with investigative site staff.

[b] Participants will receive a handheld electronic device and training at Screening. During Screening they will complete the HCMSQ daily for a minimum of 7 days and every day for the first 6 weeks after treatment initiation.

[c] Participants will complete the HCMSQ on the handheld electronic device daily for a consecutive 7-day (1-week) period prior to the Week 10, 14, 18, 22, 26, 30 (EOT), and 38 (EOS) time points.

[d] During Screening, participants will complete the PGIS on the handheld electronic device immediately following completion of the 1st and 7th day of the HCMSQ assessment. If the Screening periods is >7 days, the PGIS should also be completed immediately following completion of the 14th, 21st, 28th, and 35th day of the HCMSQ.

PRO assessments were completed on an electronic device provided to each participant during the Screening period. Data from these PRO assessments were not made available to the investigators and other site personnel throughout the study.

In the EXPLORER-HCM study, the investigator assessed NYHA FC at every study visit.

The MAVERICK-HCM study was a randomized, double-blind, placebo-controlled, concentration guided, exploratory 16-week phase 2 clinical study of mavacamten in adult subjects with symptomatic nHCM. PRO data was collected according to the assessment schedule shown in Table 2.

Table 2. Schedule of PRO Data Collection in MAVERICK-HCM

Assessment[a]	Screening[b] Day -28 to Day -1	Day 1	Week 2[c] (telephone call)	Week 4[c]	Week 6[c]	Week 8[c]	Week 10 (telephone call)[c]	Week 12[c]	Week 14 (telephone call)[c]	Week 16[c]/ET	Week 24[c]/EOS
PRO Assessments											
KCCQ, EQ-5D		X								X	X
HCMSQ[u]	X[v]	←	—	—	→		X[w]		X[w]	X[w]	X[w]
PGIS[u]	X[x]				X		X		X	X	X
PGIC[u]					X		X		X	X	X

Abbreviations: EQ-5D, EuroQol five dimensions questionnaire; HCMSQ, Hypertrophic Cardiomyopathy Symptom Questionnaire; KCCQ, Kansas City Cardiomyopathy Questionnaire; PGIC, Patient Global Impression of Change questionnaire; PGIS, Patient Global Impression of Severity questionnaire; PRO, patient-reported outcomes

[a] Preferred order of assessments is symptom questionnaires before other assessments (i.e., electrocardiogram (ECG), vital signs, transthoracic echocardiography, transthoracic echocardiogram (TTE), pre-exercise blood draws; exercise test; and post-exercise blood draws).

[b] Screening may require more than 1 visit to accommodate all of the study procedures.

[c] All post−Day 1 study visits have a window of ± 7 days. At Weeks 2, 10, and 14, participants will be contacted by telephone to collect AE and concomitant medication data.

[u] The HCMSQ, PGIS, and PGIC will be completed via either a sponsor-provided handheld electronic device or an app on the patient's smartphone.

[v] Participants will complete the HCMSQ daily for a minimum of 7 days during screening and for the first 6 weeks after initiation of study drug.

[w] Participants will complete the HCMSQ daily for a consecutive 7-day (1-week) period prior to the Week 10, 14, 16 (end of treatment), and 24 (end of study) time points. The PGIS and PGIC will immediately follow the HCMSQ on Day 7 of these weeks.

[x] During Screening, participants will complete the PGIS immediately following completion of the 1st and 7th day of the HCMSQ assessment. If the screening period is > 7 days, the PGIS should also be completed immediately following completion of the 14th, 21st, and 28th days of the HCMSQ.

3.1.3 Endpoint Position, Definition, and Assessment Schedule

Table 3 describes the primary and PRO secondary endpoints for Study EXPLORER-HCM.

Table 3. Endpoint Position, Definition, and Assessment Schedule for Study EXPLORER-HCM

Endpoint Position	Assessment	Endpoint Definition	Assessment Frequency
Primary	Cardiopulmonary exercise testing (CPET), peak oxygen consumption (pVO_2), and NYHA FC	Clinical response at Week 30 defined as achieving: 1. Improvement of at least 1.5 mL/kg/min in pVO_2 as determined by the CPET and a reduction of one or more class in NYHA FC, OR; 2. Improvement of 3.0 mL/kg/min or more in pVO2 with no worsening in NYHA FC	☒ **Other:** pVO_2/CPET: Screening and EOT NYHA FC: Screening, Day 1, and Weeks 4, 6, 8, 12, 14, 18, 22, 26, 30/EOT, and 38/EOS
Secondary ☒Multiplicity adjusted	KCCQ-23 CSS (PRO)	Change from baseline to Week 30 in patient-reported health-related quality of life	☒ **Other**: Day 1 and Weeks 6, 12, 18, 30/EOT, and 38/EOS
Secondary ☒Multiplicity adjusted	HCMSQ (PRO)	Change from baseline to Week 30 in patient-reported severity of HCM symptoms as assessed by the HCMSQ-SB	☒ **Other**: Daily from screening through Week 6, then at Weeks 10, 14, 18, 22, 26, 30/EOT, and 38/EOS

PRO= Patient-reported outcome

3.1.4 Targeted Clinical Outcome Assessment-Related Labeling Claim(s)

The applicant submitted the following PRO-related labeling claims in the proposed draft label:

Secondary endpoints
The treatment effects of [TRADENAME] on LVOT obstruction, functional capacity, and health status were assessed by change from baseline through Week 30 in post-exercise LVOT peak gradient, change in pVO2, proportion of patients with improvement in NYHA class, Kansas City Cardiomyopathy Questionnaire-23 (KCCQ-23) Clinical Summary Score (CSS), and Hypertrophic Cardiomyopathy Symptom Questionnaire (HCMSQ) Shortness of Breath (SoB) domain score. At Week 30, patients receiving [TRADENAME] had greater improvement compared to placebo group across all secondary endpoints (b) (4)

Table 6: Change from Baseline to Week 30 in Post-Exercise LVOT (b) (4) Gradient (b) (4) pVO_2, and (b) (4) NYHA Class (b) (4)

	[TRADENAME] N = 123	Placebo N = 128	Treatment difference (95% CI)	p-value
Mean (SD) (b) (4) (b) (4) post-exercise LVOT (b) (4) gradient (b) (4) (b) (4)	-47 (40) mmHg	-10 (30) mmHg	-35 (-43, -28)	<0.0001

Mean (SD) (b) (4) (b) (4) pVO_2	1.4 (b) (4) mL/kg/min	(b) (4) (3) mL/kg/min	1.4 (0.6, (b) (4)	<0.0006
Number (%) (b) (4) (b) (4) Improve (b) (4) NYHA Class ≥ 1 (b) (4) (b) (4)	80 (65%)	40 (31%)	34 (22, 45)	<0.0001

Table 7: Change from Baseline to Week 30 in KCCQ-23 CSS and HCMSQ SoB Domain

	Baseline		(b) (4)	Change from baseline to Week 30		p-value
	[TRADENAME]	Placebo		[TRADENAME]	Placebo	[TRADENAME] vs. Placebo
KCCQ-23 CSS† (b) (4)	n=99 71 (16)	n=97 71 (19)		(b) (4) 14 (14)	4 (14)	<0.0001
HCMSQ SoB Domain‡ (b) (4)	n=108 5 (3)	n=109 5 (3)		(b) (4) -3 (3)	-1 (2)	<0.0001

† The KCCQ-23 CSS is (b) (4) scores of the KCCQ-23. The Clinical Summary Score (CSS) ranges from 0 to 100, with higher scores representing (b) (4)

‡ The HCMSQ SoB domain score measures frequency and severity of shortness of breath. The HCMSQ Shortness of Breath (SoB) domain score ranges from 0 to 18, with lower scores representing less shortness of breath.

(b) (4)

Figure 1: KCCQ-23 Clinical Summary Score: Mean Change from Baseline Over Time

Figure 2: KCCQ-23 Clinical Summary Score: Cumulative Distribution of Change from Baseline to Week 30

Figure 3: HCMSQ Shortness of Breath Domain: Mean Change from Baseline Over Time

Figure 4: HMCSQ Shortness of Breath Domain: Cumulative Distribution of Change from Baseline to Week 30

An information request (IR) was sent to the applicant on September 9, 2021, requesting the following:

Submit anchor-based eCDF and PDF curves for the change from baseline to Week 6 in KCCQ-23 CSS and HCMSQ-SoB domain scores using the PGIS, PGIC, and NYHA FC as anchors. Include curves reflecting the amount of change (e.g., +1-point change, +2-point change, 0-point change, -1-point change, -2-point change) and the sample size and median score for each eCDF and PDF anchor curve in each figure's legend. Use the raw score change for the analyses. If any of these figures are included in a previous submission, please indicate where they are located.

The eCDF curves in the applicant's response[4] are in Appendices 6.7-6.10.

Reviewer's comment(s):
The applicant's anchor-based analysis supports labeling claims for change from Baseline to Week 30 for the HCMSQ-SB score and the KCCQ-23 CSS. (b) (4)

HCMSQ-SB
In the EXPLORER-HCM study, the mean HCMSQ-SB score at Baseline was 4.86 (Standard Deviation (SD): 2.479) in the mavacamten arm and 4.5 (SD: 3.423) in the placebo arm. The mean change from Baseline at Week 30 in the HCMSQ-SB score was -2.82 (SD: 2.678) in the mavacamten arm and -0.85 (SD: 2.412) in the placebo arm. The difference between the treatment arms was -1.80 (95% CI -2.401, -1.197 p<0.0001).

The HCMSQ has not previously been described in FDA-approved labeling.

KCCQ-23 CSS
In the EXPLORER-HCM study, the mean KCCQ-23 CSS at Baseline was 71.1 (SD: 16.33) in the mavacamten arm and 70.6 (SD: 19.08) in the placebo arm. The mean change from Baseline at Week 30 in KCCQ-23 CSS was 13.6 (SD: 14.42) in the mavacamten arm and 4.2 (SD: 13.68) in the placebo arm. The difference between the treatment arms was 9.1 (95% CI 5.46-12.66; p<0.0001).

The KCCQ Overall Score has been described in FDA-approved labeling for NDA 211996 (Vyndaqel (tafamidis meglumine)[5]. Additionally, the KCCQ-23 Total Symptom Score (TSS), Physical Limitations Score (PLS) and CSS has been qualified under CDER's Clinical Outcome Assessment (COA) Qualification Program to support drug development in adults aged 18 years and older with a diagnosis of heart failure. However, sponsors that use the KCCQ measure in their drug development programs should provide evidence to support thresholds for clinically meaningful within-patient changes in the KCCQ-23 TSS, PLS, and CSS as needed, within the clinical trial context.[6]

[4] Applicant's submission SN 0035(36) received July 26, 2021
[5] Vyndaqel is indicated for the treatment of the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization
[6] FDA Qualification Statement for the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score and its Component Scores. Available at: https://www.fda.gov/media/136862/download. Accessed: August 10, 2021.

Missing data
Approximately 30% of KCCQ-23 CSS and/or HCMSQ-SB data were missing (either the baseline value or the 30-week value). The percentage of patients with missing baseline data was 21.9% for the KCCQ-23 CSS and 13.5% for the HCMSQ-SB. An IR was sent to the applicant requesting clarification on the reason(s) for the missing baseline data. The applicant clarified[7] that the missing baseline data was due to mismanagement of the eCOA device where subject status was not changed to "In Treatment" to trigger the Day 1 PROs per protocol. Per internal discussion with the review team, the missing data is considered missing at random and therefore this review is based on the available clinical data.

3.2 Clinical Outcome Assessment(s)

3.2.1 Clinical Outcome Assessment Description(s)

HCMSQ
The HCMSQ is an 11-item PRO measure assessing severity and frequency of HCM symptoms (i.e., tiredness/fatigue, heart palpitations, chest pain, dizziness, syncope/fainting and shortness of breath). In the EXPLORER-HCM study, the HCMSQ was completed on a handheld electronic device. Per the study protocol, reminder alarms on the electronic device and clinic reminders from the site staff were used to ensure completion of the HCMSQ on schedule. The HCMSQ in in Appendix 1.

KCCQ-23
The KCCQ-23 is a 23-item PRO measure assessing the impact of patients' cardiovascular disease or its treatment on 6 distinct domains (i.e., symptoms/signs, physical limitations, quality of life, social limitations, self-efficacy, and symptom stability) using a 2-week recall.[8] The KCCQ-23 is in Appendix 2.

PGIC
The PGIC is a single-item measure asking respondents to rate their overall change in symptom severity over time (since started taking the study medication) on a 7-point verbal rating scale (VRS). The PGIC is in Appendix 3.

PGIS
The PGIS is a single-item measure asking respondents to rate their overall symptom severity in the past week on a 5-point VRS. The PGIS is in Appendix 4.

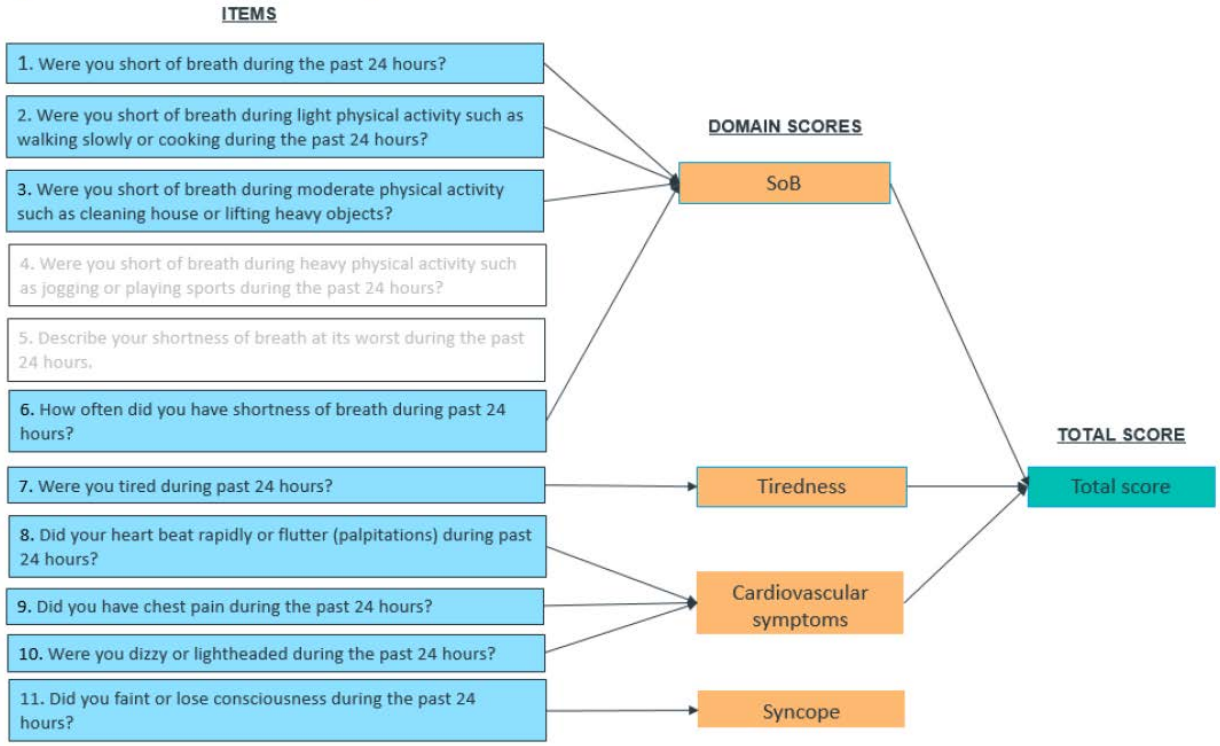
NYHA FC
The NYHA FC assigns participants to 1 of 4 categories based on the participant's heart failure symptoms. The NYHA FC is in Appendix 5.

[7] Applicant's submission SN 0028(28) received June 21, 2021)
[8] Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol. 2000;35:1245-1255.

3.2.2 Conceptual Frameworks

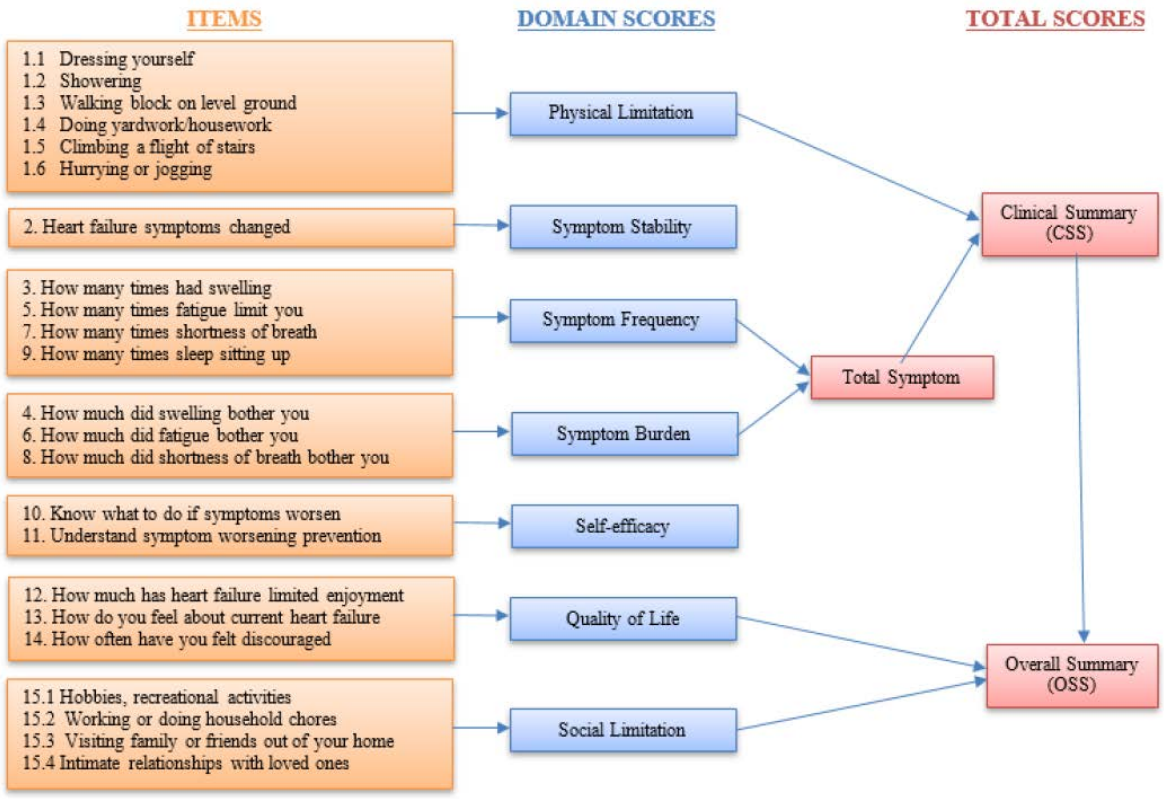
HCMSQ

Figure 1. HCMSQ Conceptual Framework



KCCQ-23

Figure 2. KCCQ-23 Conceptual Framework Based on Established Scoring Algorithm



3.2.3 Scoring Algorithm

HCMSQ-SB

Weekly item scores are derived by averaging item scores over a 7-day period. The HCMSQ-SB score is calculated as the sum of the item scores for items 1-3 and item 6. Item-level responses are scored as shown in Table 4.

Table 4. HCMSQ-SB Item Response Scores

Item	Question	Response Options
1	Were you short of breath during the past 24 hours?	0 = Not at all 1 = Mildly 2 = Moderately 3 = Severely 4 = Very Severely
2	Were you short of breath during light physical activity such as walking slowly or cooking during the past 24 hours?	. = I did not attempt to do the activity 0 = Not at all 1 = Mildly 2 = Moderately 3 = Severely 4 = Very Severely 5 = Too short of breath to do the activity
3	Were you short of breath during moderate physical activity such as cleaning house or lifting heavy objects?	. = I did not attempt to do the activity 0 = Not at all 1 = Mildly 2 = Moderately 3 = Severely 4 = Very Severely 5 = Too short of breath to do the activity
6	How often did you have shortness of breath during past 24 hours?	0 = Never 1 = Seldom 2 = Sometimes 3 = Often 4 = Almost Always

For item 2, if the "I did not attempt…" response choice is endorsed, the subscale score is set to missing for that day. For item 3, if the "I did not attempt…" response choice is endorsed, scores are imputed as the mean of items 1, 2, and 6 for that day. The potential HCMSQ-SB score ranges from 0 to 18, where lower scores indicate less SoB.

The final HCMSQ scoring algorithm is based on a series of analyses using pooled baseline data from the EXPLORER-HCM and MAVERICK-HCM trials (n=290), as described below.

- Rasch model analysis: Rasch model analysis was conducted to examine how well the SoB items fit as a SoB domain and to examine the ordering of the responses for the SoB items based on the average trait level (degree of severity) for each response choice. The analysis determined that endorsement of the response option "too short of breath to do the activity" was not an indicator of more severe symptoms
- Mixed Effect Model Repeated Measures (MMRM): An MMRM analysis was conducted to assess if potential bias is introduced to the scores when values for "I did not attempt…" response choice are imputed for items 2 and 3. The analysis found that item 3 can be imputed but doing so for item 2 would introduce bias and therefore should be set to missing if the response option "I did not attempt…" was endorsed.
- Exploratory Factor Analysis (EFA) and Confirmatory Factor Analysis (CFA): Both EFA and CFA were conducted to explore the data structure of the HCMSQ based on pooled EXPLORER-HCM and MAVERICK-HCM data. Pooled data was used because the

sample size from study MAVERICK-HCM was too small for the EFA analysis. Results using the 7-day Baseline pool data found that items 1-3 and 6 loaded highly into one factor (loadings ranged from 0.781-0.9).

- Missing data simulation analysis: A missing data simulation study was conducted and confirmed that HCMSQ-SB scores remain stable when three or fewer days have missing data. Thus, the applicant used a 50% missing data rule which requires more than 50% of the data to be present in order to compute an HCMSQ-SB score.

The HCMSQ items 4 and 5 also ask about SoB but do not contribute to the HCMSQ-SB score. These items were omitted from the HCMSQ-SB scoring algorithm as described in Table 5.

Table 5. Rationale for omitting items 4 and 5 from the HCMSQ-SB scoring algorithm

Item 4	Item 5
Descriptive analysis showed that 77% of entries endorsed the "I did not attempt…" response option.	Exit interviews with 17 oHCM subjects and 5 nHCM subjects found that only 5 patients ordered the response options as intended, raising concerns about the content validity of this item.
The Rasch analysis found a misfit between item response and a person's SoB severity.	

The scoring algorithm was confirmed by sensitivity analyses that tested various imputations and data structures, taking into account the underlying pathophysiology of HCM. Additionally, alternative scoring approaches were explored (e.g., Severity of SoB based on items 1-5, Frequency of SoB (FSB) based on item 6). The selected scoring algorithm was found to be the most appropriate as it assesses both severity and frequency of SoB, is consistent with how patients spoke about their experience of SoB during concept elicitation (CE) interviews, and offers similar levels of sensitivity to the algorithm for FSB.

KCCQ-23 CSS

The KCCQ-23 CSS is derived from 13 item scores that comprise the PLS (i.e., Items 1a-f) and TSS (i.e., items 3-9) domains. Item response scores are in Table 6. The KCCQ-23 CSS ranges from 0-100 where lower scores represent more severe symptoms and/or limitations and scores of 100 indicate no symptoms and/or no limitations.

Table 6. KCCQ-23 CSS Item Response Scores

Domain	Item(s)	Item Code/Algorithm
Physical Limitation	1a-f	Extremely limited = 1 Quite a bit limited = 2 Moderately limited = 3 Slightly limited = 4 Not at all limited = 5 Limited for other reasons or did not do = . **Algorithm:** If at least 3 questions are not missing then: Physical Limitation = 100 * [(mean of questions 1a-f answered) – 1]/4

Symptom Frequency	3, 5, 7, 9	*Question 3* Every morning = 1 3 or more times a week but not every day = 2 1-2 times a week = 3 Less than once a week = 4 Never over the past weeks = 5 *Questions 5 & 7* All of the time = 1 Several times a day = 2 At least once a day = 3 3 or more times a week but not every day = 4 1-2 times a week = 5 Less than once a week = 6 Never over the past 2 week = 7 *Question 9* Every night = 1 3 or more times a week but not every day = 2 1-2 times a week = 3 Less than once a week = 4 Never over the past 2 weeks = 5 **Algorithm**: If at least 2 questions are not missing then S3 = [question 3 – 1]/4 S5 = [question 5 – 1]/6 S7 = [question 7 – 1]/6 S9 = [question 9 – 1]/4 Symptom Frequency = 100 * (mean of S3, S5, S7, S9)
Symptom Burden	4, 6, 8	Extremely bothersome = 1 Quite a bit bothersome = 2 Moderately bothersome = 3 Slightly bothersome = 4 Not at all bothersome = 5 I've had no swelling/fatigue/shortness of breath = 5 **Algorithm:** If at least 1 question is not missing then: Symptom Burden = 100 * [(mean of questions 4, 6, 8) – 1]/4
Total Symptom Burden		**Algorithm:** Mean of available summary scores: Symptom frequency Symptom burden
Clinical Summary		**Algorithm:** Mean of the following available summary scores: Physical Limitation Total Symptom

3.2.4 Content Validity

The applicant submitted a PRO evidence dossier to support their PRO-based labeling claims. The dossier contained copies of the instruments as they were used in the clinical trial, described how the PROs were developed/selected based on literature, documentation of expert input, qualitative input from patients, and included the results of quantitative analyses to support the PRO measures' measurement properties and interpretation of clinically meaningful within patient change.

Identification of the core symptoms of HCM

Core symptoms of HCM were identified based on several sources, shown in Table 7 (only includes symptoms reported by the majority from each source). Symptoms assessed by the HCSMSQ-SB and/or the KCCQ-23 CSS are highlighted in blue. Refer to section 5.1.2 Conceptual Framework(s) for more detail.

Table 7. Core symptoms and impacts of HCM

	Patient web survey[a] (n=444)	Literature and Guidelines[b]	Clinician interviews [c] (n=3)	CE interviews[d] (n=17)	EL-PFDD Meeting[e]
angina/chest pain	þ*	þ[9,10,12]	þ#	þ#	þ
arrhythmias/ heart palpitations	þ	þ[12,11]	þ#	þ#	þ
depression	--	þ[12,16]	--	þ	--
dizziness/ lightheadedness/ presyncope	þ#	þ[12]	þ#	þ#	þ
dyspnea/ shortness of breath	þ#	þ[9,12]	þ#	þ#	þ
fatigue	þ#	þ[12,13]	þ	þ#	þ
limitations to physical function/ activities	þ	þ[11,14,15]	þ	þ#	--
syncope	þ*	þ[9,11,12,16]	þ#	þ	þ

* : Reported by < 50% of patients
#: Top symptoms reported

a. An 80-question survey was developed and distributed via email to members of the Hypertrophic Cardiomyopathy Association (HCMA). Responses were collected and analyzed using an online platform. Among all respondents, 58% reported suffering from oHCM.
b. A targeted review of the scientific literature, national/international guidelines, and patient advocacy websites was conducted to identify key signs, symptoms, and impacts of HCM, and to understand if there are any differences between oHCM and nHCM. A secondary goal was to review cardiac-specific and generic PRO measures that may be appropriate for assessing symptoms and impacts of HCM.
c. One-on-one semi-structured interviews were conducted with 3 content-area clinical experts from the US (n=1) and Europe (n=2). The qualitative data obtained from these interviews were used to confirm which of the cardinal symptoms of HCM are most relevant from a clinical perspective and how patients talk about these symptoms. The clinicians reported that symptoms are often non-specific, overlap with one another, can vary day to day, and show similarities with side effects of treatment or symptoms of a comorbidity. In their assessment of HCM patients, the clinicians endorsed all the core symptoms and impacts identified in the literature.
d. Five rounds of concept elicitation interviews were conducted with a total of 17 subjects with oHCM from the US (n=12) and Europe (n=5). Eligible patients were aged 18-75 years and preference was given to patients who could self-report that their NYHA FC was >1.
e. Externally led Patient Focused Drug Development Meeting conducted on June 26, 2020 by the HCMA. The most troubling symptoms reported included shortness of breath, exercise intolerance, arrhythmias and palpitations, chest pain, chronic and acute fatigue, brain fog, sudden cardiac arrest, sudden cardiac death, and emotional distress and depression.[13]

Content validity of the HCMSQ-SB

The HCMSQ is a novel instrument that was developed and refined using an iterative process. Its content validity is supported by 5 rounds of combined concept elicitation/cognitive interviews conducted in the U.K., France, Italy, and the U.S., with 33 patients with HCM (17 patients with oHCM). The majority of patients with oHCM were male (n=9). In rounds 1-4 (n=11 patients with oHCM), the mean age of oHCM patients interviewed was 47.6 years (standard deviation:

[9] Bois JP, Adams JC, Kumar G, Ommen SR, Nishimura RA, Klarich KW. Relation between Temperature Extremes and Symptom Exacerbation in Patients with Hypertrophic Cardiomyopathy. Am J Cardiol. Mar 15 2016;117(6):961-965
[10] Fortunato de Cano S, Nicolas Cano M, de Ribamar Costa J, Jr., et al. Long-term clinical follow up of patients undergoing percutaneous alcohol septal reduction for symptomatic obstructive hypertrophic cardiomyopathy. Catheter Cardiovasc Interv. Nov 15 2016;88(6):953-960
[11] Sweeting J, Ingles J, Timperio A, Patterson J, Ball K, Semsarian C. Physical activity in hypertrophic cardiomyopathy: prevalence of inactivity and perceived barriers. Open Heart. 2016;3(2):e000484.
[12] Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA Guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2011;58:e212-260.
[13] Hypertrophic Cardiomyopathy Association. The Voice of the Patient Report for Hypertrophic Cardiomyopathy (HCM); Proceedings from an Externally Led Public Patient-Focused Drug Development Meeting. Meeting held June 26, 2020. Report dated January 9, 2021.
[14] Minto C, Bauce B, Calore C, et al. Is Internet use associated with anxiety in patients with and at risk for cardiomyopathy? Am Heart J. Jul 2015;170(1):87-95, 95 e81-84.
[15] Luiten RC, Ormond K, Post L, Asif IM, Wheeler MT, Caleshu C. Exercise restrictions trigger psychological difficulty in active and athletic adults with hypertrophic cardiomyopathy. Open Heart. 2016;3(2):e000488.
[16] Magnusson P, Morner S, Gadler F, Karlsson J. Health-related quality of life in hypertrophic cardiomyopathy patients with implantable defibrillators. Health Qual Life Outcomes. Apr 14 2016;14:62.

17.36; range: 26-74). In round 5 (n=6 patients with oHCM), the majority of oHCM patients interviewed were aged 51-65 years (n=4).

The final version of the HCMSQ reflects patient input on the most appropriate response scale and heterogeneity in patients' experience of SoB. The majority of patients interviewed reported that the HCMSQ instructions and item stems were clear, easy to understand, relevant to their oHCM experience, and used language frequently used by patients with oHCM. Additionally, the majority of patients reported that the "past 24 hours" recall period was appropriate. Usability testing for the handheld electronic device was conducted with a total of 10 HCM patients (4 patients with oHCM) and found that there were no difficulties with language, format, and ability to respond using the electronic device.

Content validity of the KCCQ-23 CSS

The applicant conducted 2 rounds of cognitive interviews with a total of 26 patients with oHCM to explore the content validity of the KCCQ-23 in the oHCM population. The majority of patients interviewed were aged 36-50 years (n=14 (54%)), female (n=16 (62%)), had a college/university degree or higher (n=18 (69%)), and were employed full-time (n=16 (61%)). All 26 patients interviewed reported that the KCCQ items were relevant to patients with oHCM. All patients noticed that the instrument asked about heart failure and 42% (n=11) of patients did not feel they had heart failure. Of these patients, 10 reported that they would have answered the questions the same if the term "heart failure" was replaced with "oHCM". The only item that participants stated they would have changed their response due to terminology is item 13, which is not included in the KCCQ-23 CSS.

Reviewer's comment(s):
The evidence submitted by the applicant supports the content validity of the HCMSQ-SB and the KCCQ-23 CSS in the proposed context of use.

Both the KCCQ and HCMSQ were translated into the following languages using the ISPOR task force principles: Arabic (Israel), Czech, Danish, Dutch (Belgium, Netherlands), English (U.S., U.K.), French (Belgium, France), German (Belgium, Germany), Hebrew, Italian (Italy), Polish, Portuguese (Portugal), Russian (Israel), and Spanish (U.S., Spain).

During the IND phase, the Agency communicated the following to the sponsor:

- *Assess the most common symptoms reported for oHCM, but dyspnea can be the basis for a claim.*[17]
- (b) (4) [18]
- (b) (4)
  We recommend using the KCCQ-CSS or TSS as they include concepts that are more responsive to treatment (e.g., core disease symptoms, physical function).[19]

[17] IND 121904 Meeting Minutes dated August 8, 2016 (DARRTS Reference ID: 3969132)
[18] IND 121904 Meeting Minutes dated October 18. 2017 (DARRTS Reference ID: 4168832)
[19] IND 121904 Meeting Minutes dated March 24, 2020 (DARRTS Reference ID: 4580283)

The KCCQ-23 TSS, PLS, and CSS have been Qualified by CDER's COA Qualification Program indicating that there is adequate evidence of content validity and cross-sectional measurement properties (i.e., internal consistency reliability, test-retest reliability, convergent validity, and known-groups validity) to support these measures in adult heart failure patients.[20]

3.2.5 Other Measurement Properties

To date, the applicant submitted the quantitative analysis synopsis, full quantitative analysis plan, and quantitative summary report to support reliability, construct validity, and ability to detect change and the scoring algorithm for the HCMSQ-SB score and the KCCQ-23 CSS in the proposed context of use. Two psychometric analyses were performed:

1. A cross-sectional psychometric analysis conducted using baseline data from the MAVERICK-HCM and EXPLORER-HCM studies.[21]
2. A longitudinal psychometric analysis using data from the MAVERICK-HCM and EXPLORER-HCM studies.[21,22]

Cross-sectional Psychometric Analysis

The objectives of the cross-sectional psychometric analysis[21] were to examine the psychometric properties (e.g., reliability and validity) of the HCMSQ and KCCQ-23 using baseline MAVERICK-HCM and EXPLORER-HCM data to support that these measures are fit-for-purpose for both the nHCM and oHCM populations.

A total of 48 subjects were included in the cross-sectional psychometric analysis from study MAVERICK-HCM. The majority of subjects were female (n=27 (56.3%)), White (n=30 (62.5%)), had baseline NYHA FC II (n=38, 79.2%), and Mild baseline HCM Severity (n=95 (60.9%)) as defined by the PGIS. The mean age was 52.94 years (standard deviation 16.63 years). The mean (variance) HCMSQ-SB score was 3.6 (6.0), ranging from 0 to 8 (calculated as the sum of items 1 – 5, with a possible range of 0 – 23).

A total of 217 subjects were included in the cross-sectional psychometric analysis from study EXPLORER-HCM. The majority of subjects were male (n=149 (68.7%)), White (n=197 (90.8%)), had baseline NYHA FC II (n=183, 84.3%), and had "Moderate" baseline HCM symptom Severity (n=349 (43%)) as defined by the PGIS. The mean age was 58.47 years (standard deviation 11.93 years). The mean (variance) HCMSQ-SB score was 5.1 (9.3), ranging from 0 to 15.4.

The results of the quantitative analyses are summarized in Table 8.

Table 8. Results of the cross-sectional psychometric analysis for the HCMSQ-SB and KCCQ-23 CS

	HCMSQ-SB	**KCCQ-23 CS**
Item characteristics	Study MAVERICK-HCM Floor effects[a] were present for all 4 items of the HCMSQ-SB based on the	Study MAVERICK-HCM Floor effects were observed for items 1.1-1.5, 3, 4, and 9. Ceiling effects were

[20] FDA. COA Qualification Statement dated April 9, 2020. Available at: https://www.fda.gov/media/136862/download. Accessed August 16, 2021.
[21] IND 121904 SN 0142(152) received January 15, 2020, containing the cross-sectional psychometric analysis report
[22] NDA 214998 SN 001(1) received January 28, 2021, containing the PRO Evidence Dossier

	percentage of entries with each response choice and percentage of subjects who endorsed the response choice at least once. Ceiling effects[b] were not observed. The majority of subjects responded, "I did not do the activity" (item 3), "Not at All" (items 2 and 6), or "Mildly" (item 1). <u>Study EXPLORER-HCM</u> Floor effects were observed for items 1, 2, and 6 based on the percentage of entries with each response choice and for all HCSQ-SB items based on the percentage of patients who endorsed the response choice at least once. The majority of subjects responded, "Not at All" (items 2 and 3), or "Mildly" (items 1 and 6).	observed for item 1.6. The majority of subjects responded, "Not at all" (items 1.1-1.5), "Extremely limited (item 1.6), "Never" (items 3, 5, 7, 9), "I've had no swelling" (item 4), "Quite a bit (item 6), and "Slightly" (item 8). <u>Study EXPLORER-HCM</u> Floor effects were observed for items 1.1-1.3, 3, 4, and 9. Ceiling effects were not observed for any of the items. The majority of subjects responded, "Not at all" (items 1.1-1.3), "Slightly" (items 1.4 and 1.5) "Moderately (item 1.6 and 8), "Never" (items 3 and 9), "I've had no swelling" (item 4), 3 or more times/week (item 5), "Slightly" (item 6), and At least once/day (item 7)
	---	An exploratory regression analysis using pooled data from the 2 studies indicated that there were no differences in KCCQ-23 domain and total scores at Baseline between the two analysis populations conditioning on age, symptom severity as measured by PGIS, and NYHA FC.
Internal consistency	<u>Study MAVERICK-HCM</u> Cronbach's alpha coefficient = 0.924 When items 1-3 and 6 were removed, the Cronbach alpha coefficient ranged from 0.873 (items 3 and 6) to 0.957 (item 2)) <u>Study EXPLORER-HCM</u> Cronbach's alpha coefficient = 0.961 When items 1-3 and 6 were removed, the Cronbach alpha coefficient ranged from 0.936 (items 3) to 0.961 (item 2))	<u>Study MAVERICK-HCM</u> Cronbach's alpha coefficient = 0.922 <u>Study EXPLORER-HCM</u> Cronbach's alpha coefficient = 0.905
Construct validity: item-to-item correlations[c,d]	Item-to-item correlation analyses were conducted using day 7 of the 7-day Baseline period[c] and the mean weekly scores during Baseline[f]. <u>MAVERICK-HCM</u> - Correlation coefficients for daily scores ranged from 0.485 to 0.648 - Correlation coefficients for weekly scores ranged from 0.499-0.880 <u>EXPLORER-HCM</u> - Correlation coefficients for daily scores ranged from 0.619 to 0.719 - Correlation coefficients for weekly scores ranged from 0.763 to 0.912	<u>MAVERICK-HCM</u> Low Spearman correlation coefficients (<0.3) using pairwise deletion were observed between: º Items 3 and 7 º Items 3 and 9 º Items 4 and 6 º Items 4 and 8 <u>EXPLORER-HCM</u> Low Spearman correlation coefficients using pairwise deletion were observed between: º Items 1a and 1f º Items 1b and 1f º Items 3 and 5 º Items 3 and 7

Construct validity: item-scale correlations[e]	MAVERICK-HCM Pearson correlation coefficients for items 1, 2, 3, and 6 with the HCMSQ-SB score ranged from 0.768 to 0.95. EXPLORER-HCM Pearson correlation coefficients for items 1, 2, 3, and 6 with the HCMSQ-SB score at baseline ranged from 0.938 to 0.954.	MAVERICK-HCM Pearson correlation coefficients for items 1a-1f and 3-9 with the KCCQ-23 CSS ranged from 0.514-0.878. EXPLORER-HCM Pearson correlation coefficients for items 1a-1f and 3-9 with the KCCQ-23 CSS ranged from 0.467-0.813.
Convergent validity:	MAVERICK-HCM HCMSQ-SB and KCCQ-23 CSS: -0.716 HCMSQ-SB and EQ-5D-5L VAS: -0.565 KCCQ-23 CSS and EQ-5D-5L VAS: 0.652 EXPLORER-HCM HCMSQ-SB and KCCQ-23 CSS: -0.703 HCMSQ-SB and EQ-5D-5L: -0.441 KCCQ-23 CSS and EQ-5D-5L: 0.607	
Known groups validity	MAVERICK-HCM ANOVA results demonstrated the HCMSQ-SB was able to differentiate between groups as defined by the PGIS (p=0.0101) but not between groups as defined by NYHA FC (p=0.3167) EXPLORER-HCM ANOVA results demonstrated the HCMSQ-SB was able to differentiate between groups as defined by the PGIS (p<0.0001) and NYHA FC (p<0.0001)	MAVERICK-HCM ANOVA results demonstrated the KCCQ-23 CSS was able to differentiate between groups as defined by the PGIS (p=0.0207) but not between groups as defined by NYHA FC (p=0.2133) EXPLORER-HCM ANOVA results demonstrated the KCCQ-23 CSS was able to differentiate between groups as defined by the PGIS (p<0.0001) and NYHA FC (p<0.0001)
Differential Item Functioning (DIF)	Based on the pooled baseline data from the MAVERICK-HCM and EXPLORER-HCM studies, all p-values for all HCMSQ-SB items were greater than 0.01 indicating that the items did not differ systematically between the MAVERICK-HCM and EXPLORER-HCM populations.	Based on the pooled baseline data from the MAVERICK-HCM and EXPLORER-HCM studies, all p-values for all KCCQ-23 items were greater than 0.01 indicating that the items did not differ systematically between the MAVERICK-HCM and EXPLORER-HCM populations.

a. Floor effects were defined as >25% of responses with the response choice indicating the lowest degree of severity
b. Ceiling effects were defined as >25% of responses with the response indicating the highest degree of severity
c. Correlation analyses used the Cramer's V correlations.
d. Moderate and strong correlations were defined as r > 0.30.
e. Item-scale correlations were considered adequate if the Pearson coefficient values were at least 0.40.
f. Assessed by Spearman Correlations

Regarding the low item-to-item correlations, the applicant stated the following:

- MAVERICK-HCM
  These negligible to low correlations indicate that these items may have little associations with items pertaining to limitations due to shortness of breath and heart failure, and fatigue. However, this finding may be due to the small sample size and the lack of variation observed for these items (72% reported no swelling in feet, ankles, or legs [item 3], 59% reported that they did not have any swelling and therefore was not bothersome [item 4], 80% reported that they did not have to sleep sitting up [item 9])

- EXPLORER-HCM
  These negligible to low correlations indicate that these items may have little associations with items pertaining to limitations due to shortness of breath and fatigue. However, this may be due to the lack of variation observed for most of these items (68% reported not having trouble dressing (item 1a), 79% reported not having trouble showering/bathing (item 1b), 73% reported no swelling in feet, ankles, or legs [item 3], 64% reported that they did not have any swelling and therefore was not bothersome [item 4], 73% reported that they did not have to sleep sitting up [item 9])

Longitudinal Psychometric Analysis

The objectives of the longitudinal psychometric analyses included the following:

- Using MAVERICK-HCM study data:
  - Assess test-retest reliability validity for Baseline to Week 6 HCMSQ-SB and KCCQ-23 CSS for stable patients as defined by the PGIS and PGIC
  - Assess sensitivity to change by comparing mean change from Baseline to Week 16 HCMSQ-SB and KCCQ-23 CS scores across Week 16 PGIS categories (Improved vs. Stable/Worsened) using one-way ANOVA
- Using EXPLORER-HCM study data:
  - Assess test-retest reliability for the HCMSQ-SB and KCCQ-23 CS scores at Week 30 and Week 38 for stable patients as defined by the PGIS and PGIC
  - Assess convergent validity by calculating Spearman correlation coefficients among change from Baseline to Week 30 HCMSQ domain/total scores with change from Baseline to Week 30 KCCQ-23 and EQ-5D-5L VAS scores.
  - Assess known-groups validity by comparing mean change HCMSQ domain/total scores from Baseline to Week 30 across groups defined by change in NYHA FC, change in PGIS ratings, change in pVO_2 scores, and change in LVOT scores.
  - Assess sensitivity to change by comparing mean change from Baseline to Week 30 and Baseline to Week 18 HCMSQ scores across Week 30 and Week 18 PGIC and PGIS collapsed categories (Improved vs. Stable/Worsened) using one-way ANOVA and Fisher's least significance difference test
  - Assess meaningful change from Baseline to Week 30 in HCMSQ and KCCQ-23 scores using anchor-based methods

The results of the longitudinal psychometric analysis are described in Table 9.

Table 9. Results of the longitudinal psychometric analyses for the HCMSQ-SB and KCCQ-23 CS

	HCMSQ-SB Score	KCCQ-23 CSS
Test-Retest Reliability	Study MAVERICK-HCM Item 1: Intraclass correlation coefficient (ICC) > 0.7 for both the PGIS and PGIC - Item 2: ICC 0.6-0.63 for both the PGIS and PGIC - Item 3: ICC=0.723 for the PGIS. Could not assess for the PGIC due to sample size (n=4) - Item 6: ICC > 0.7 for both the PGIS and PGIC Study EXPLORER-HCM All item and domain scores had ICC > 0.7 using data from Baseline and Week 6, Week 6 and Week 18, and Week 18 and 30 based on stable PGIS and PGIC ratings.	Study MAVERICK-HCM Could not be assessed due to sample size (n=3). Study EXPLORER-HCM Based on the PGIC and PGIS, Moderate-Strong test-retest reliability (ICC>0.6) was observed for the PL, SF, SB, and CS domains using data from Baseline and Week 6, Week 6 and Week 18, and Week 18 and 30.
Convergent validity[a]	EXPLORER-HCM Moderate change from baseline to Week 30 Spearman correlation coefficients were observed between HCMSQ-SB and KCCQ-23 CS scores (-0.659), HCMSQ-SB score, and EQ-5D-5L VAS (-0.393) and KCCQ-23 CSS and EQ-5D-5L VAS (0.525).	
Known-groups validity	EXPLORER-HCM The results of ANOVA using HCMSQ-SB change from Baseline to Week 30 scores by change from Baseline to Week 30 PGIS ratings, pVO_2, and NYHA FC status demonstrated statistically significant differences ($p<0.05$) in the expected direction. This was not observed by change from Baseline to Week 30 LVOT scores.	EXPLORER-HCM The results of ANOVA using KCCQ-23 CSS change from Baseline to Week 30 scores by change from Baseline to Week 30 PGIS ratings, NYHA FC status, and pVO_2 demonstrated statistically significant differences in the expected direction. This was not observed by change from Baseline to Week 30 LVOT scores.
Sensitivity to change	MAVERICK-HCM Mean change scores for the HCMSQ-SB were statistically significant for both the PGIS (p=0.025) and the PGIC (p=0.009) EXPLORER-HCM Mean change scores for the HCMSQ-SB were statistically significant for both the PGIS ($p<0.001$) and the PGIC ($p<0.001$) at Week 30 and Week 18	MAVERICK-HCM Mean change scores for the KCCQ-23 CS were statistically significant for both the PGIS (p=0.008) but not for the PGIC (p=0.1858) EXPLORER-HCM Mean change scores for the KCCQ-23 CSS were statistically significant for both the PGIS ($p<0.001$) and the PGIC ($p<0.001$) at Week 30 and Week 18

a. Change from Baseline to Week 30 Spearman Correlations between HCMSQ-SB, KCCQ-23 CS, and EQ-5D-5L VAS scores

Refer to Section 3.2.6. Interpretation of Meaningful Within-Patient Score Changes for the results and discussion of the assessment of meaningful change in HCMSQ-SB and KCCQ-23 CS scores.

Reviewer's comment(s):
The applicant appropriately pre-specified the quantitative analysis plans, including hypothesized relationships among variables to be tested, estimates for reliability and validity, and thresholds to interpret the analyses. The results of the quantitative analyses support the measurement properties of the HCMSQ-SB score and the KCCQ-23 CSS in the proposed context of use.

3.2.6 Interpretation of Meaningful Within-Patient Score Changes

Clinically meaningful change thresholds for the HCMSQ-SB and KCCQ-23 CS scores were derived using distribution-based and anchor-based methods supplemented by empirical cumulative distribution function (eCDF) and probability density function (PDF) curves based on MAVERICK-HCM and EXPLORER-HCM data. The proposed responder threshold estimates for the HCMSQ-SB score and KCCQ-23 CSS are shown in the applicant's tables below.

Table 26: Responder Estimates for HCMSQ SoB using Anchor and Distribution-based Methods

		MAVERICK-HCM	EXPLORER-HCM
Anchor-based approaches (primary)	PGIC anchor (improved to w16/w30)	-2.01 (n=10)	-2.57 (n=136)
	PGIS anchor (improved to w16/w30)	-2.35 (n=8)	-3.40 (n=90)
Distribution-based approaches (supportive)	0.5 SD baseline	1.08	1.45
	1 SEM baseline	0.94	1.15

HCMSQ: SoB = Shortness of breath; SD = standard deviation; SEM = standard error of the mean; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity

Table 25: Responder Estimates for KCCQ-23 CSS using Anchor and Distribution-based Methods

		MAVERICK-HCM	EXPLORER-HCM
Anchor-based approaches (primary)	PGIC anchor (improved to w16/w30)	---	13.98 (n=143)
	PGIS anchor (improved to w16/w30)	17.71 (n=7)	16.82 (n=91)
Distribution-based approaches (supportive)	0.5 SD baseline	9.60	8.84
	1 SEM baseline	5.39	5.30

KCCQ-23: CSS = Clinical Summary Score; SD = standard deviation; SEM = standard error of the mean; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity
Note: Anchor used in the MAVERICK-HCM study was improvement from baseline to Week 16, while anchor used in the EXPLORER-HCM study was improvement from baseline to Week 30

The eCDF curves based on the PGIS and PGIC anchor scales based on study EXPLORER-HCM and study MAVERICK-HCM data are shown in Appendices 6.1-6.4 and 7.1 – 7.4, respectively. Based on these analyses and, in addition, literature for the KCCQ-23 CSS[23], the applicant

[23] Spertus J, Peterson E, Conard MW, et al., "Monitoring clinical changes in patients with heart failure: a comparison of methods," Am Heart J. 2005;150:707-15

proposed the following ranges to reflect improvement in the HCMSQ-SB and KCCQ-23 CS scores:

Table 10. Proposed responder definition estimates for the HCMSQ-SB and the KCCQ-23 CS scores

	HCMSQ-SB	**KCCQ-23 CSS**
Proposed responder definition estimate in scores (range)[1,2,3]	-2.5 (-2 to -3)	10 (5-15)

[1] Improvement based on the PGIC was defined by the "improved" PGIC responses (i.e , very much improved, much improved, minimally improved). Improvement based on the PGIS was defined as subjects that improved by at least 1 category on the PGIS from baseline.
[2] The proposed responder thresholds are based on data from the MAVERICK-HCM study, the EXPLORER-HCM study, and the literature.

The amount of change (i.e., 2-category improvement, 1-category improvement, no change, 1-category worsening, and 2-category worsening) from baseline to Week 30 in HCMSQ-SB and KCCQ-23 CS scores in Study EXPLORER-HCM demonstrated that patients that reported more severe HCM symptoms over a 7-day period assessed by the PGIS at baseline reported a greater improvement in HCMSQ-SB and KCCQ-23 CS scores (Appendices 8.1 and 8.3).

An IR was sent to the applicant on July 19, 2021 stating the following:

> **For the EXPLORER-HCM study, create and submit** [tables] **corresponding to the data used for the primary and pre-specified secondary endpoints (KCCQ-23 CSS and HCMSQ-SOB Domain).**
>
> **Using NYHA Class as an anchor submit anchor-based eCDF and PDF curves of the severity change scores from baseline to week 30 for the pre-specified secondary endpoints assessed by the KCCQ-23 CSS and HCMSQ-SOB Domain in the EXPLORER-HCM study for all patients by NYHA class change (e.g., +1-point change, +2-point change, 0-point change, -1 point change, -2 point change). Use the raw score change for the analyses.**
>
> **Include the sample size and median score for each eCDF and PDF anchor curve in each figure's legend. In addition, provide and justify which NYHA class change category represents clinically meaningful within-patient change. If any of these figures are included in a previous submission, please indicate where they are located.**

The eCDF curves in the applicant's response[24] are in Appendices 6.5, 6.6, 8.2 and 8.4.

Reviewer's comment(s):
Based on triangulation of the eCDF curves for interpretation of meaningful change in HCMSQ-SB scores and the results of the distribution-based analysis, the proposed responder definition estimate of -2.5-points in HCMSQ-SB scores appears reasonable. The eCDF curves demonstrated separation between the "no change" and improvement groups. Reviewer

[24] Applicant's submission SN 0044(44) received July 15, 2021

interpretation of the eCDF curves for a threshold of clinically meaningful within patient change in HCMSQ-SB scores are in Table 11.

***Table 11**. Interpretation of thresholds for meaningful change in HCMSQ-SB scores*

	Anchor: PGIS	*Anchor: PGIC*	*Anchor: NYHA FC*
Range of meaningful change threshold for HCMSQ-SB scores, EXPLORER-HCM (change from baseline to Week 30)	*-3 to -5 (n=197)*	*-1.3 to -2 (n=215)*	*-2.57 to -3.34 (n=171)*
Range of meaningful change threshold for HCMSQ-SB scores, MAVERICK-HCM (change from baseline to Week 16)	*-1.35 (n=6)*	*-1.3 (n=10)*	---

[*] *Only the anchor-based analyses using the change in PGIS and PGIC ratings were pre-specified.*
[#] *Results using EXPLORER-HCM data were presented as uncollapsed categories, allowing a range for the meaningful change threshold to be derived. Results using MAVERICK-HCM data were presented as collapsed categories (i.e., Improved, Stable, Deteriorated) and thus only a single threshold is shown.*

Based on the eCDF curves for interpretation of meaningful change in KCCQ-23 CSS, literature evidence, and the results of the distribution-based analysis, the proposed responder definition estimate of 10-points in the KCCQ-23 CSS appears reasonable. The eCDF curves demonstrated separation between the "no change" and improvement groups. Reviewer interpretation of the eCDF curves for a threshold of clinically meaningful within patient change in HCMSQ-SB scores are in Table 12.

***Table 12**. Interpretation of thresholds for meaningful change in KCCQ-23 CSS*

	Anchor: PGIS	*Anchor: PGIC*	*Anchor: NYHA FC*
Range of meaningful change threshold for KCCQ-23 CS scores, EXPLORER-HCM (change from baseline to Week 30)	*14 to 21(n=209)*	*8 to 11 (n=225)*	*10.94 to 22.4 (n=180)*
Meaningful change threshold for KCCQ-23 CS scores, MAVERICK-HCM (change from baseline to Week 16)	*8.5 (n=7)*	*7 (n=11)*	---

[*] *Only the anchor-based analyses using the change in PGIS and PGIC ratings were pre-specified.*
[#] *Results using EXPLORER-HCM data was presented as uncollapsed categories, allowing a range for the meaningful change threshold to be derived. Results using MAVERICK-HCM data was presented as collapsed categories (i.e., Improved, Stable, Deteriorated) and thus only a single threshold is shown.*

The PGIS and PGIC are not ideal anchor scales to interpret meaningful change in HCMSQ-SB and KCCQ-23 CS scores given that they are not specific (i.e., assess overall HCM symptoms) and use a different recall period. Additionally, the PGIS item stem asks about HCM symptoms over the "past week" but the first response option uses the term, "today". However, the PGIS scale demonstrated moderate correlations with the KCCQ-23 CSS (Baseline correlation coefficient= -0.496 in the MAVERICK-HCM study and -0.626 in the EXPLORER-HCM study)

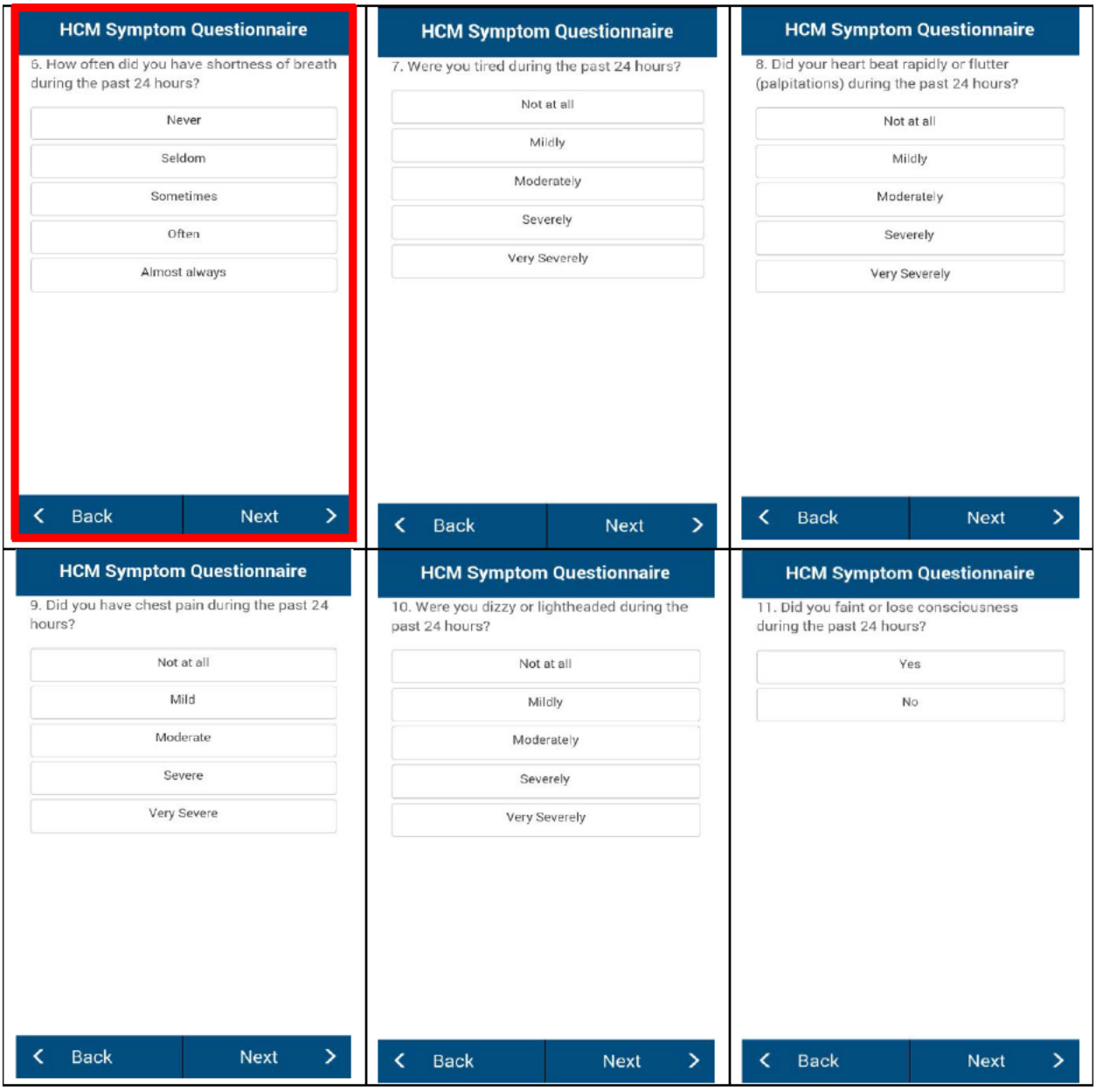
and with the HCMSQ-SB scores (Baseline correlation coefficient = 0.513 in the MAVERICK-HCM study and 0.691 in the EXPLORER-HCM study). Given the heterogeneity of HCM symptoms, the PGIS and PGIC anchor scales are considered informative for interpreting clinically meaningful within patient change in HCMSQ-SB and KCCQ-23 CS scores.

Similar to the anchor-based analyses based on the PGIS and PGIC anchor scales, analyses using the NYHA FC as an anchor demonstrated separation between eCDF curves for the proposed thresholds of clinically meaningful within patient change in HCMSQ-SB and KCCQ CS scores and that patients with a more severe NYHA FC at baseline reported a greater improvement in HCMSQ-SB and KCCQ-23 CS scores.

4 APPENDICES

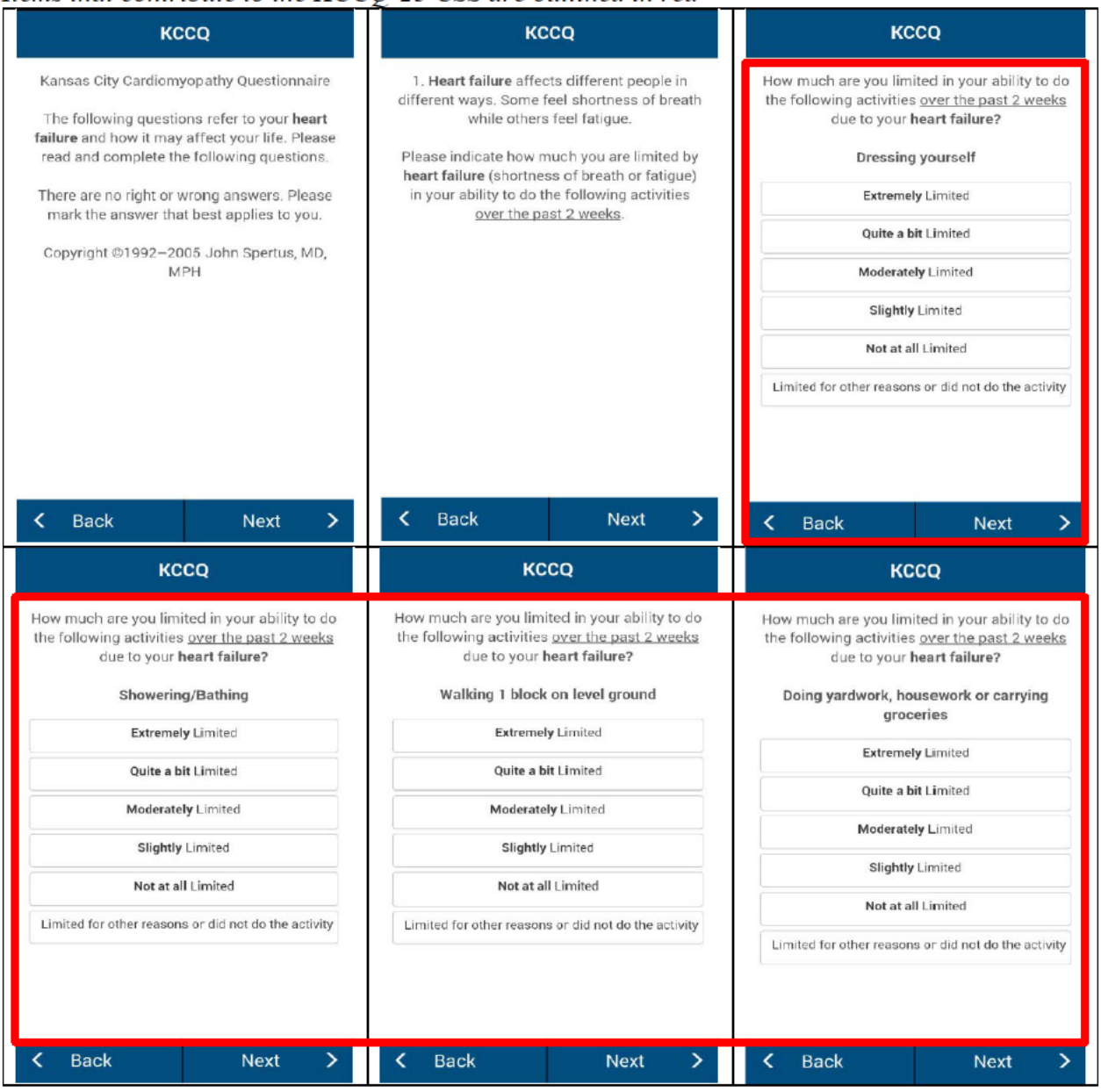
Appendix 1. Hypertrophic Cardiomyopathy Symptom Questionnaire

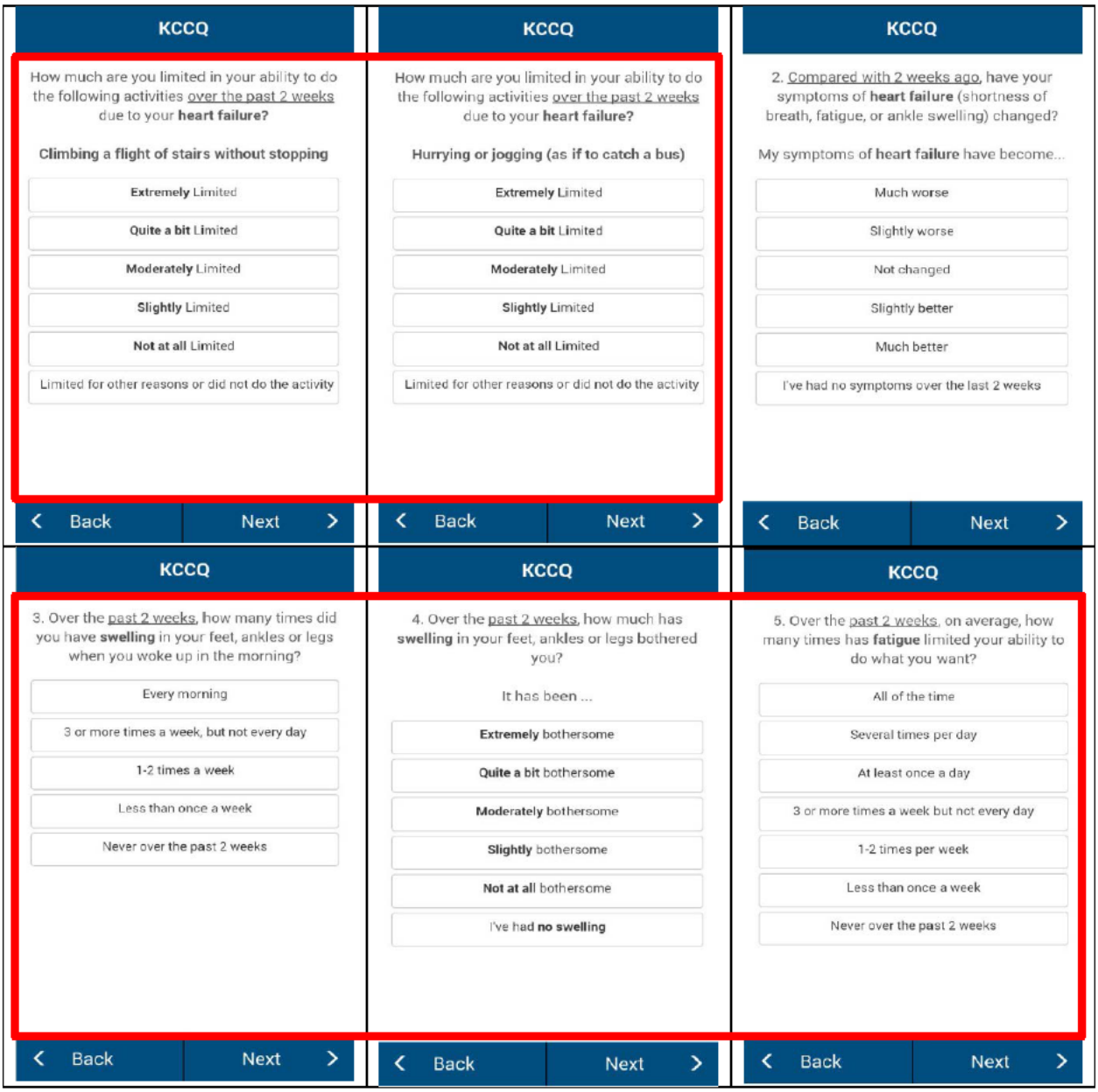
Items that contribute to the HCMSQ-SB score are outlined in red.

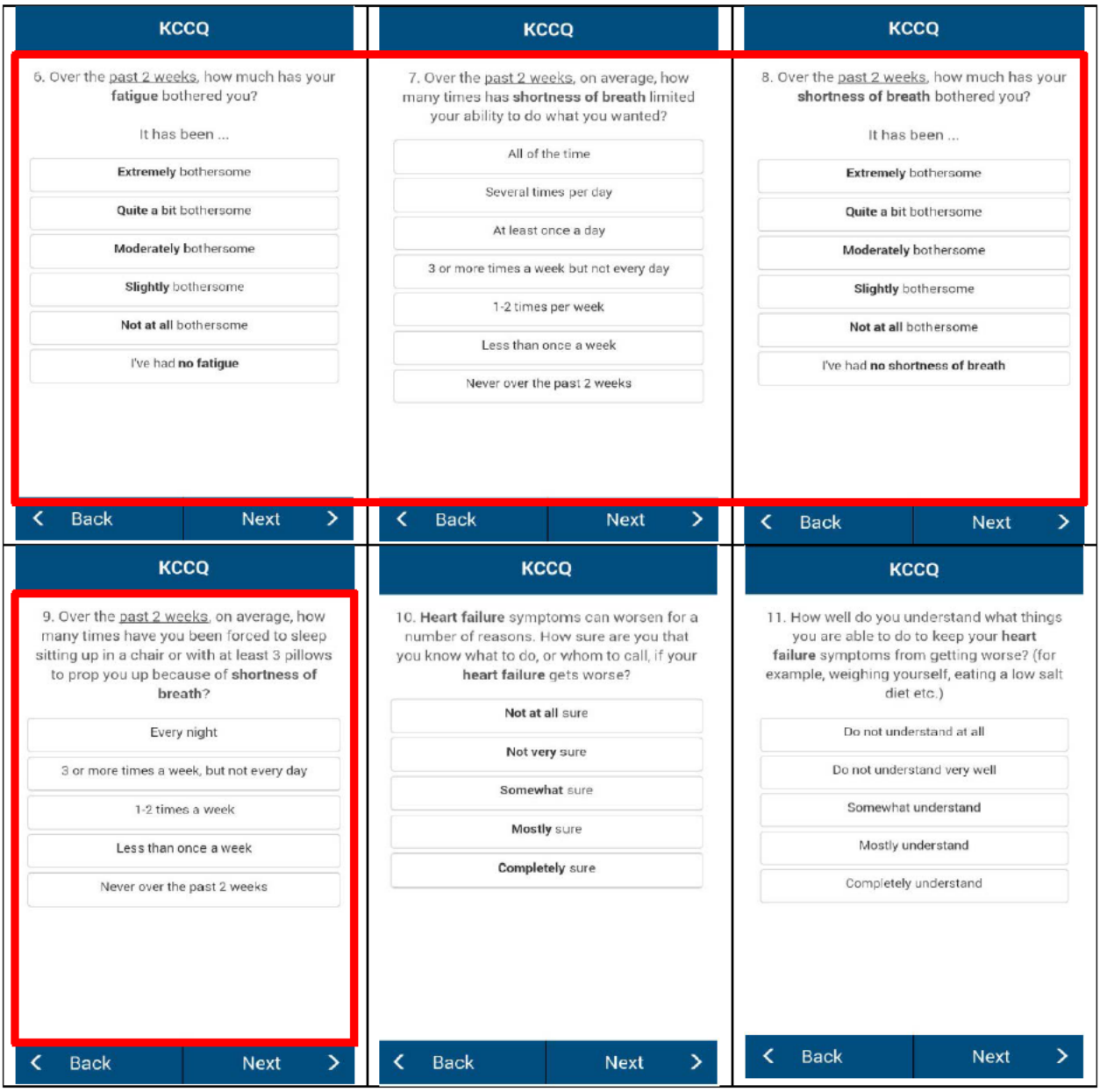

HCM Symptom Questionnaire
5. How often did you have shortness of breath during the past 24 hours?
Never
Seldom
Sometimes
Often
Almost always
Back
Next
HCM Symptom Questionnaire
7. Were you tired during the past 24 hours?
Not at all
Mildly
Moderately
Severely
Very Severely
Back
Next
HCM Symptom Questionnaire
8. Did your heart beat rapidly or flutter (palpitations) during the past 24 hours?
Not at all
Mildly
Moderately
Severely
Very Severely
Back
Next
HCM Symptom Questionnaire
9. Did you have chest pain during the past 24 hours?
Not at all
Mild
Moderate
Severe
Very Severe
Back
Next
HCM Symptom Questionnaire
10. Were you dizzy or lightheaded during the past 24 hours?
Not at all
Mildly
Moderately
Severely
Very Severely
Back
Next
HCM Symptom Questionnaire
11. Did you faint or lose consciousness during the past 24 hours?
Yes
No
Back
Next

Appendix 2. 23-item Kansas City Cardiomyopathy Questionnaire

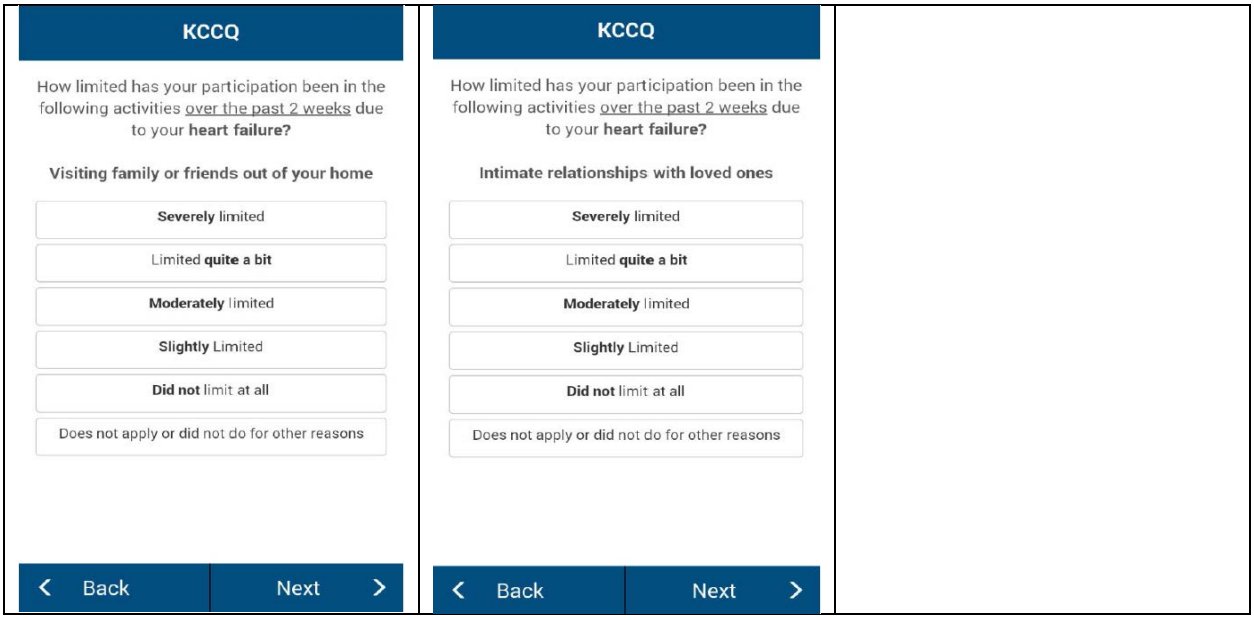
Items that contribute to the KCCQ-23 CSS are outlined in red




KCCQ
How much are you limited in your ability to do the following activities over the past 2 weeks due to your heart failure?
Climbing a flight of stairs without stopping
Extremely Limited
Quite a bit Limited
Moderately Limited
Slightly Limited
Not at all Limited
Limited for other reasons or did not do the activity
Back
Next
KCCQ
How much are you limited in your ability to do the following activities over the past 2 weeks due to your heart failure?
Hurrying or jogging (as if to catch a bus)
Extremely Limited
Quite a bit Limited
Moderately Limited
Slightly Limited
Not at all Limited
Limited for other reasons or did not do the activity
Back
Next
KCCQ
2. Compared with 2 weeks ago, have your symptoms of heart failure (shortness of breath, fatigue, or ankle swelling) changed?
My symptoms of heart failure have become...
Much worse
Slightly worse
Not changed
Slightly better
Much better
I've had no symptoms over the last 2 weeks
Back
Next
KCCQ
3. Over the past 2 weeks, how many times did you have swelling in your feet, ankles or legs when you woke up in the morning?
Every morning
3 or more times a week, but not every day
1-2 times a week
Less than once a week
Never over the past 2 weeks
Back
Next
KCCQ
4. Over the past 2 weeks, how much has swelling in your feet, ankles or legs bothered you?
It has been ...
Extremely bothersome
Quite a bit bothersome
Moderately bothersome
Slightly bothersome
Not at all bothersome
I've had no swelling
Back
Next
KCCQ
5. Over the past 2 weeks, on average, how many times has fatigue limited your ability to do what you want?
All of the time
Several times per day
At least once a day
3 or more times a week but not every day
1-2 times per week
Less than once a week
Never over the past 2 weeks
Back
Next


KCCQ
6. Over the past 2 weeks, how much has your fatigue bothered you?
It has been ...
Extremely bothersome
Quite a bit bothersome
Moderately bothersome
Slightly bothersome
Not at all bothersome
I've had no fatigue
Back
Next
KCCQ
7. Over the past 2 weeks, on average, how many times has shortness of breath limited your ability to do what you wanted?
All of the time
Several times per day
At least once a day
3 or more times a week but not every day
1-2 times per week
Less than once a week
Never over the past 2 weeks
Back
Next
KCCQ
8. Over the past 2 weeks, how much has your shortness of breath bothered you?
It has been ...
Extremely bothersome
Quite a bit bothersome
Moderately bothersome
Slightly bothersome
Not at all bothersome
I've had no shortness of breath
Back
Next
KCCQ
9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of shortness of breath?
Every night
3 or more times a week, but not every day
1-2 times a week
Less than once a week
Never over the past 2 weeks
Back
Next
KCCQ
10. Heart failure symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your heart failure gets worse?
Not at all sure
Not very sure
Somewhat sure
Mostly sure
Completely sure
Back
Next
KCCQ
11. How well do you understand what things you are able to do to keep your heart failure symptoms from getting worse? (for example, weighing yourself, eating a low salt diet etc.)
Do not understand at all
Do not understand very well
Somewhat understand
Mostly understand
Completely understand
Back
Next


KCCQ
12. Over the past 2 weeks, how much has your heart failure limited your enjoyment of life?
It has extremely limited my enjoyment of life
It has limited my enjoyment of life quite a bit
It has moderately limited my enjoyment of life
It has slightly limited my enjoyment of life
It has not limited my enjoyment of life at all
Back
Next
KCCQ
13. If you had to spend the rest of your life with your heart failure the way it is right now, how would you feel about this?
Not at all satisfied
Mostly dissatisfied
Somewhat satisfied
Mostly satisfied
Completely satisfied
Back
Next
KCCQ
14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your heart failure?
I felt that way all of the time
I felt that way most of the time
I occasionally felt that way
I rarely felt that way
I never felt that way
Back
Next
KCCQ
15. How much does your heart failure affect your lifestyle?
Please indicate how your heart failure may have limited your participation in the following activities over the past 2 weeks.
Back
Next
KCCQ
How limited has your participation been in the following activities over the past 2 weeks due to your heart failure?
Hobbies, recreational activities
Severely limited
Limited quite a bit
Moderately limited
Slightly Limited
Did not limit at all
Does not apply or did not do for other reasons
Back
Next
KCCQ
How limited has your participation been in the following activities over the past 2 weeks due to your heart failure?
Working or doing household chores
Severely limited
Limited quite a bit
Moderately limited
Slightly Limited
Did not limit at all
Does not apply or did not do for other reasons
Back
Next


KCCQ
How limited has your participation been in the following activities over the past 2 weeks due to your heart failure?
Visiting family or friends out of your home
Severely limited
Limited quite a bit
Moderately limited
Slightly Limited
Did not limit at all
Does not apply or did not do for other reasons
Back
Next
KCCQ
How limited has your participation been in the following activities over the past 2 weeks due to your heart failure?
Intimate relationships with loved ones
Severely limited
Limited quite a bit
Moderately limited
Slightly Limited
Did not limit at all
Does not apply or did not do for other reasons
Back
Next

Appendix 3. Patient Global Impression of Change

The Patient Global Impression of Change (PGIC) item:

Overall, how would you rate the change in your HCM symptoms since you started this study?

- Very Much Improved
- Much Improved
- Minimally Improved
- No Change
- Minimally Worse
- Much Worse
- Very Much Worse

Appendix 4. Patient Global Impression of Severity

The Patient Global Impression of Severity (PGIS) item:

Overall, how would you rate the severity of your HCM symptoms over the past week?

- No symptoms today
- Mild
- Moderate
- Severe
- Very severe

Appendix 5. New York Heart Association Functional Classification of Heart Failure

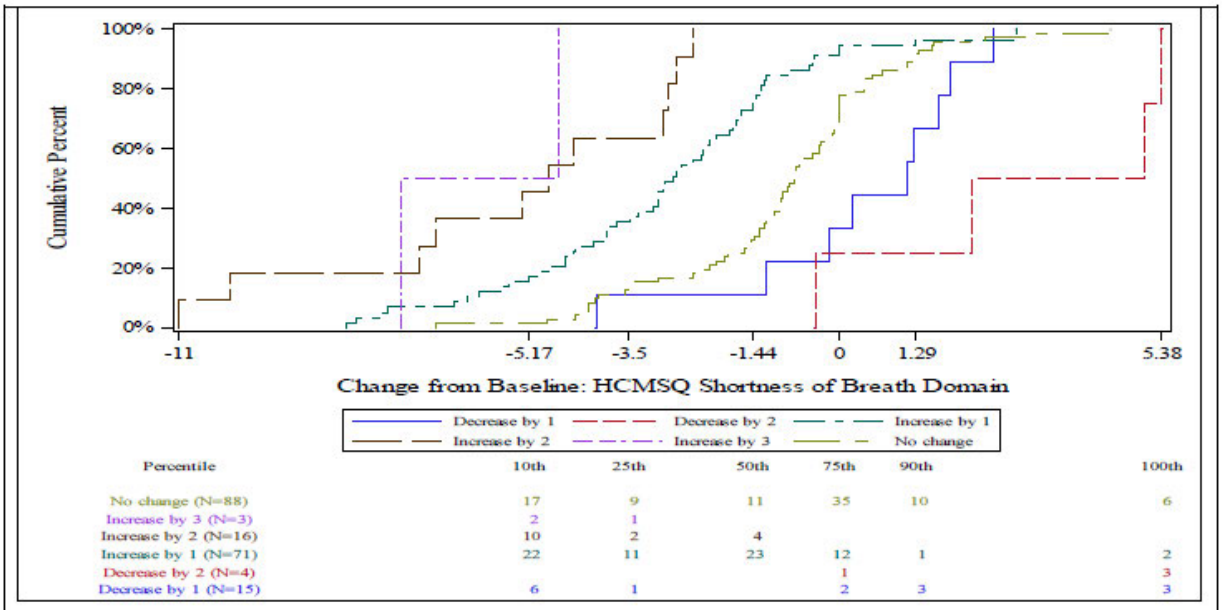
Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Source: American Heart Association. Classes of Heart Failure. Available at: https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure. Accessed August 2, 2021

Appendix 6. CDF Curves based on the EXPLORER-HCM study data

Appendix 6.1. eCDF Curves for Change from Baseline to Week 30 in HCMSQ-SB scores based on PGIS Rating

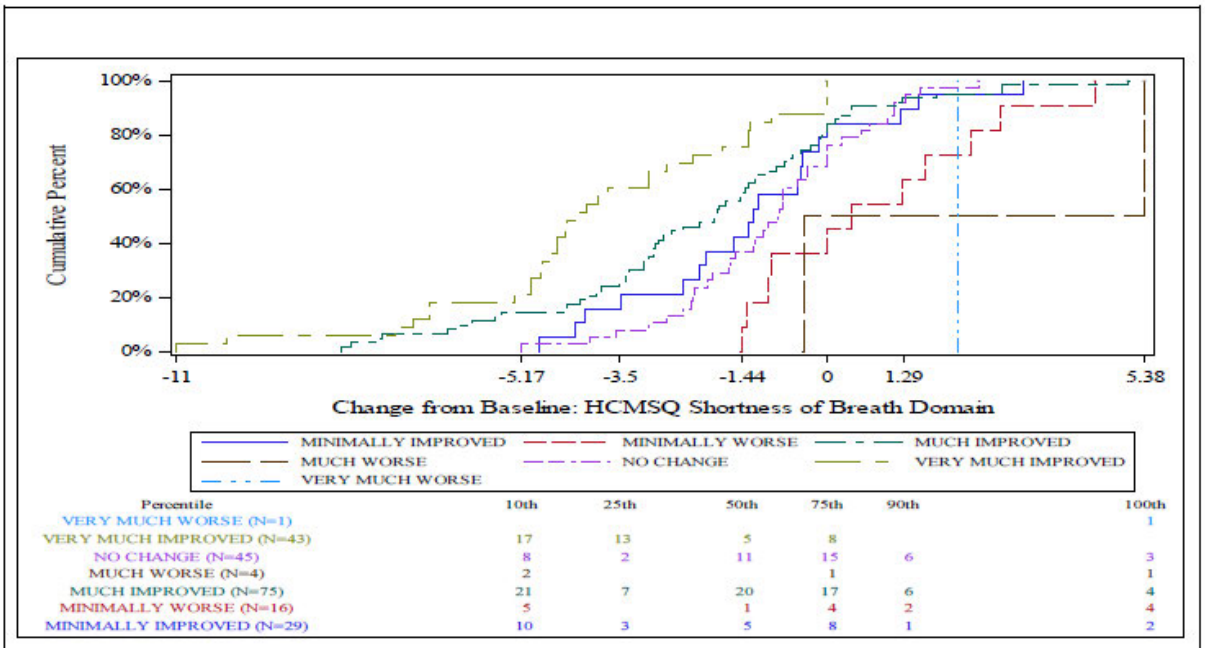
Figure 4. CDF Curves from Baseline to Week 30 for HCMSQ Shortness of Breath using Uncollapsed Categories of PGIS



Percentile	10th	25th	50th	75th	90th	100th
No change (N=88)	17	9	11	35	10	6
Increase by 3 (N=3)	2	1				
Increase by 2 (N=16)	10	2	4			
Increase by 1 (N=71)	22	11	23	12	1	2
Decrease by 2 (N=4)				1		3
Decrease by 1 (N=15)	6	1		2	3	3

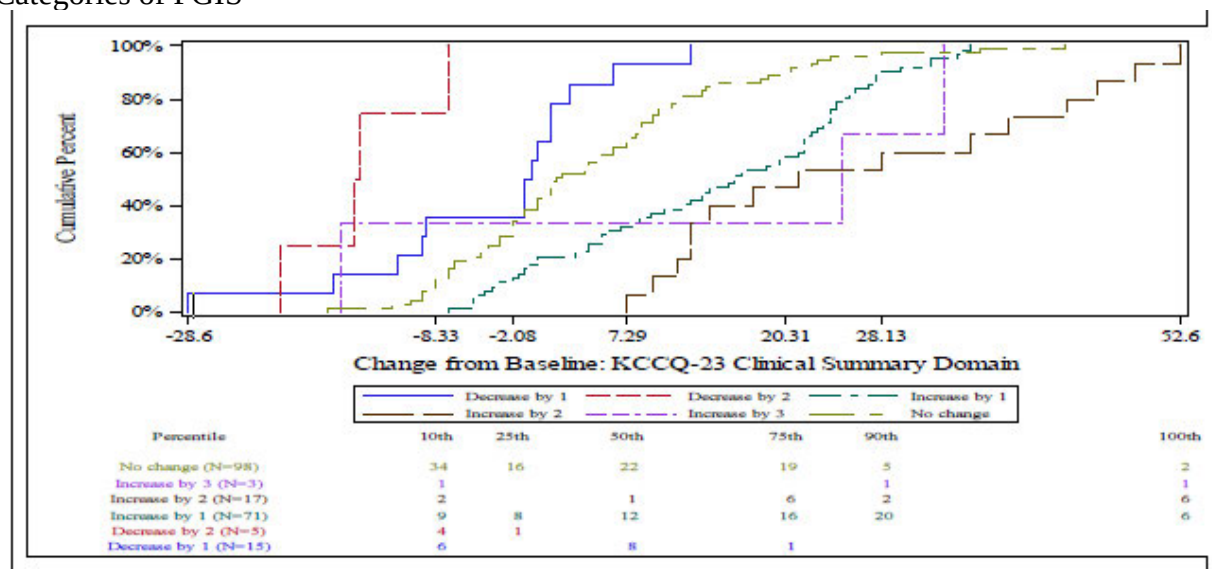
Appendix 6.2. eCDF Curves for Change from Baseline to Week 30 in HCMSQ-SB scores based on PGIC Rating

Figure 5. CDF Curves from Baseline to Week 30 for HCMSQ Shortness of Breath using Uncollapsed Categories of PGIC



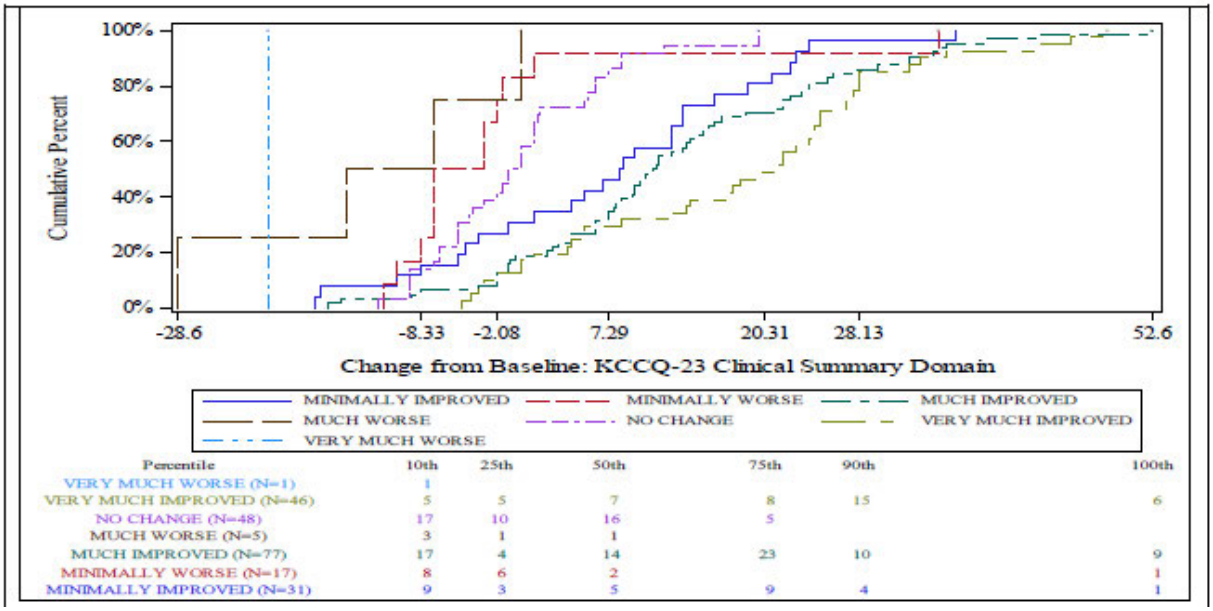
Appendix 6.3. eCDF Curves for Change from Baseline to Week 30 in KCCQ-23 CSS scores based on PGIS Rating

Figure 6. CDF Curves from Baseline to Week 30 for KCCQ-23 CSS using Un-collapsed Categories of PGIS



Appendix 6.4. eCDF Curves for Change from Baseline to Week 30 in KCCQ-23 CSS based on PGIC Rating

Figure 7. CDF Curves from Baseline to Week 30 for KCCQ-23 CSS using Un-collapsed Categories of PGIC

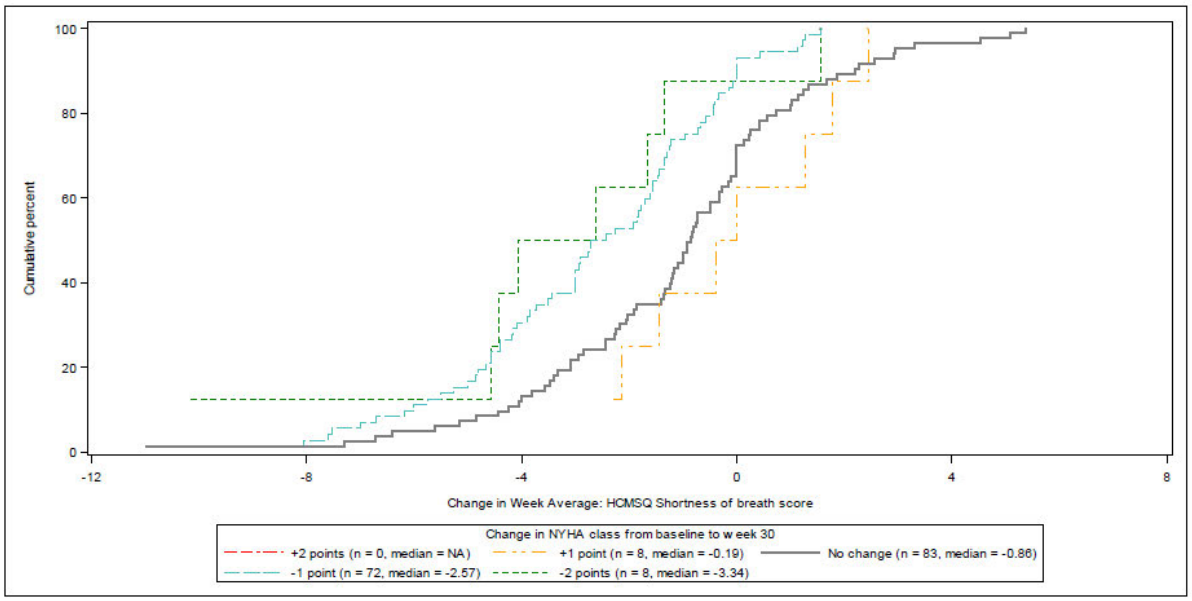


Percentile	10th	25th	50th	75th	90th	100th
VERY MUCH WORSE (N=1)	1					
VERY MUCH IMPROVED (N=46)	5	5	7	8	15	6
NO CHANGE (N=48)	17	10	16	5		
MUCH WORSE (N=5)	3	1	1			
MUCH IMPROVED (N=77)	17	4	14	23	10	9
MINIMALLY WORSE (N=17)	8	6	2			1
MINIMALLY IMPROVED (N=31)	9	3	5	9	4	1

Appendix 6.5. eCDF Curves for Change from Baseline to Week 30 in HCMSQ-SB scores based on NYHA FC Rating

Figure 2: CDF and PDF Curves in HCMSQ-SoB by NYHA Functional Class Change

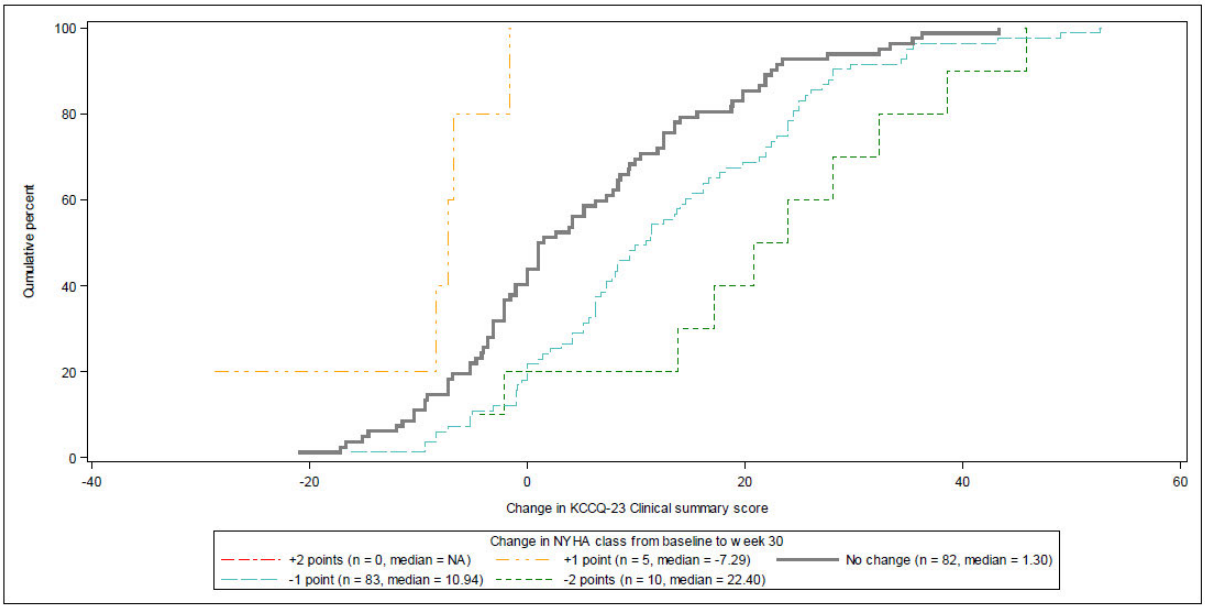
(1) Cumulative distribution function of change in HCMSQ Shortness of Breath score by NYHA functional class change



Appendix 6.6. eCDF Curves for Change from Baseline to Week 30 in KCCQ-23 CSS based on NYHA FC Rating

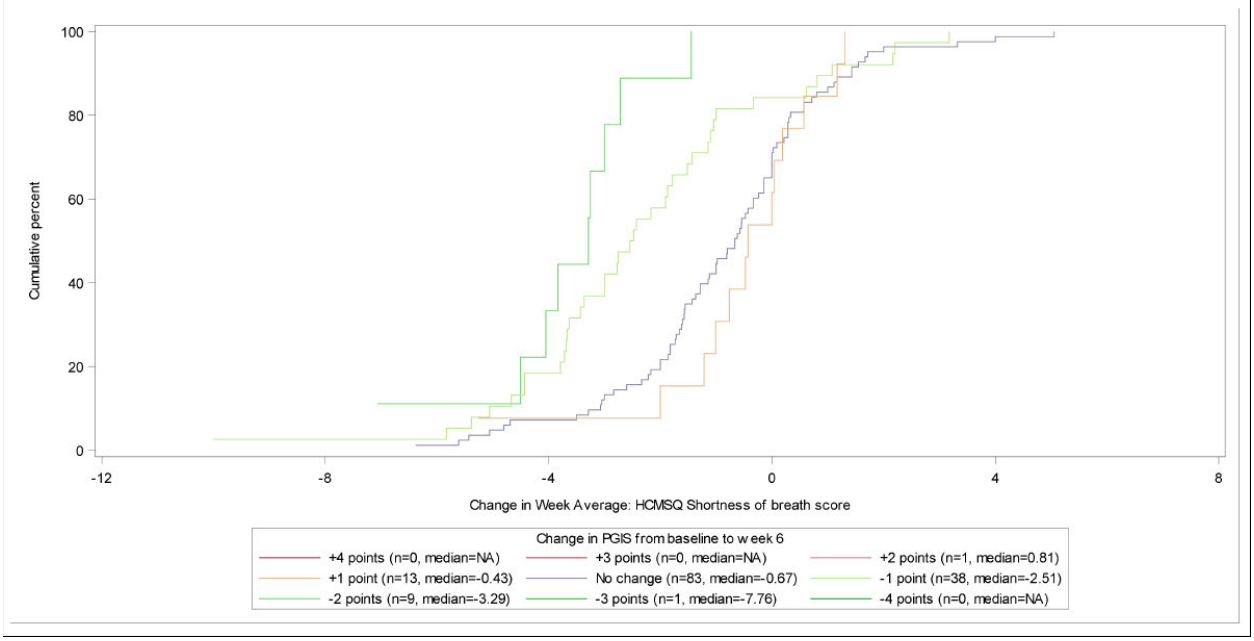
Figure 1: CDF and PDF Curves in KCCQ-23 CSS by NYHA Functional Class Change

(1) Cumulative distribution function of change in KCCQ-23 Clinical Summary Score by NYHA functional class change



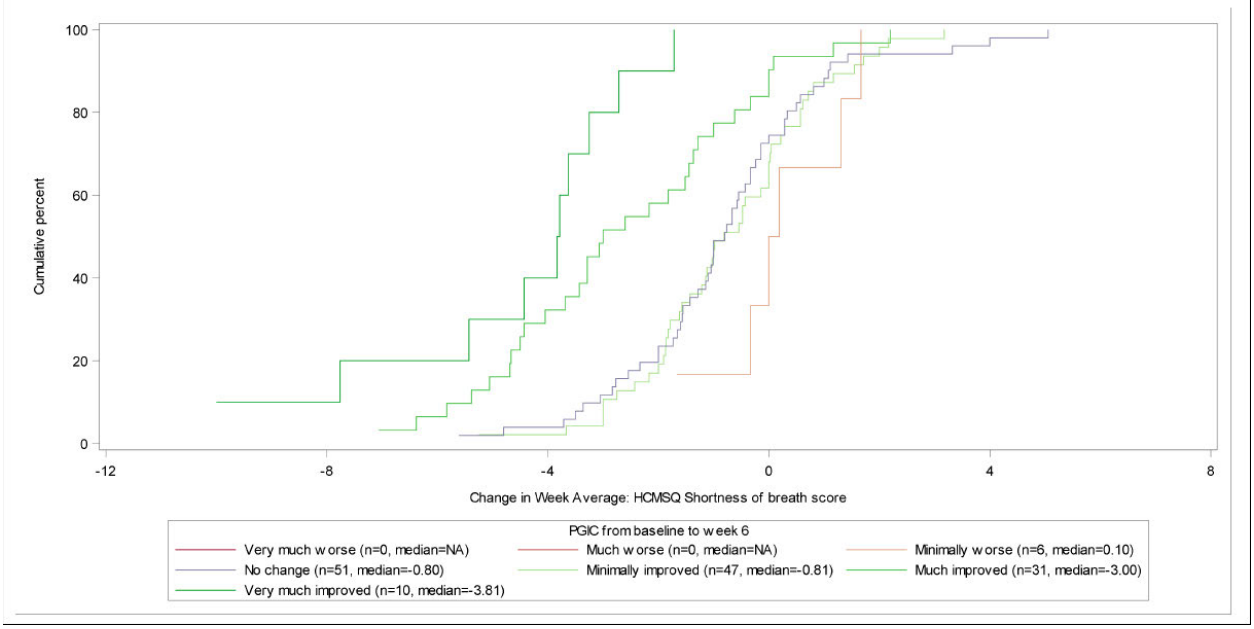
Appendix 6.7. eCDF Curves for Change from Baseline to Week 6 in HCMSQ-SB scores based on PGIS Rating

Figure 7: eCDF for Change from Baseline to Week 6 in HCMSQ-SoB by PGIS Change



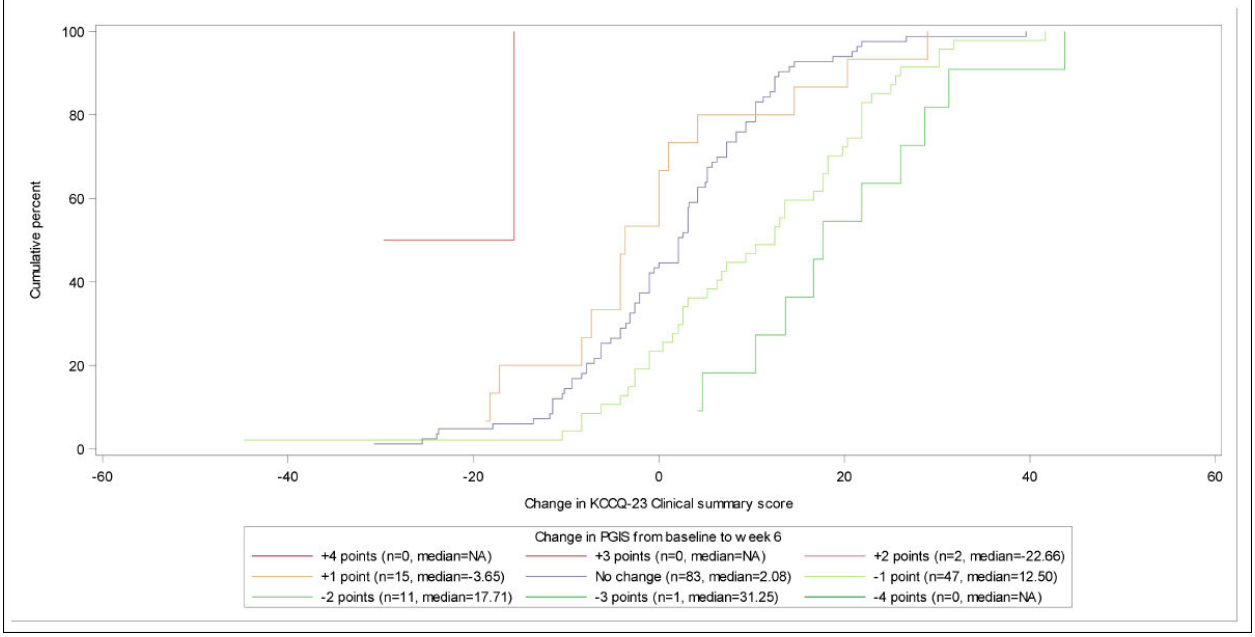
Appendix 6.8. eCDF Curves for Change from Baseline to Week 6 in HCMSQ-SB scores based on PGIC Rating

Figure 9: eCDF for Change from Baseline to Week 6 in HCMSQ-SoB by PGIC



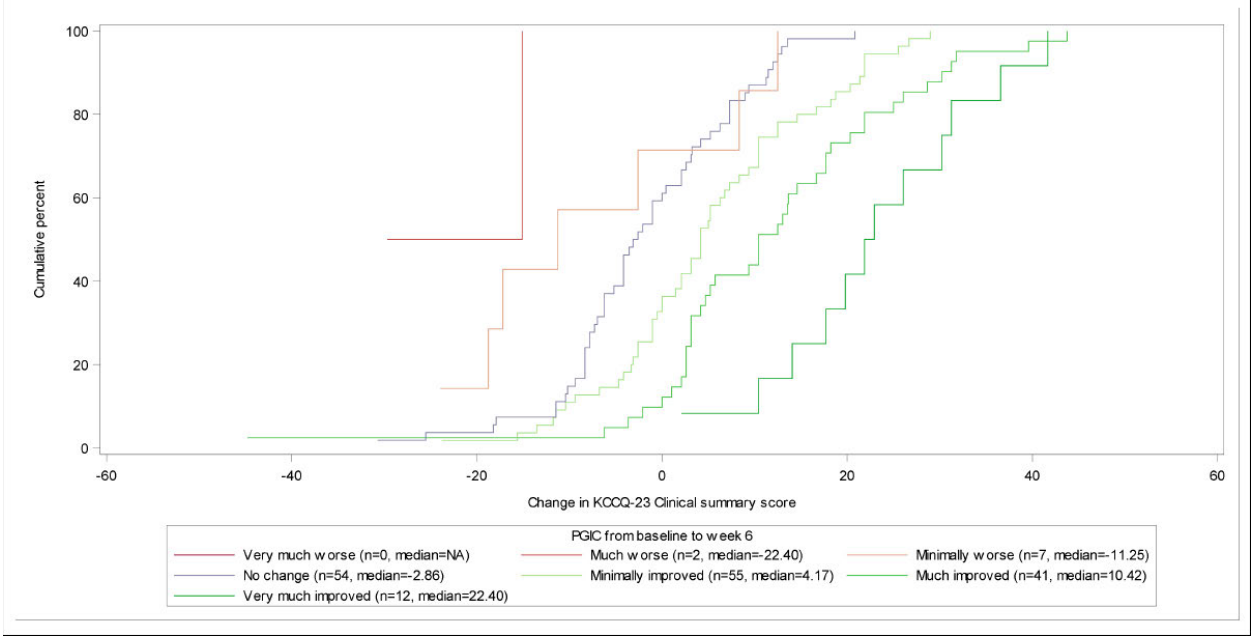
Appendix 6.9. eCDF Curves for Change from Baseline to Week 6 in KCCQ-23 CSS based on PGIS Rating

Figure 1: eCDF for Change from Baseline to Week 6 in KCCQ-23 CSS by PGIS Change



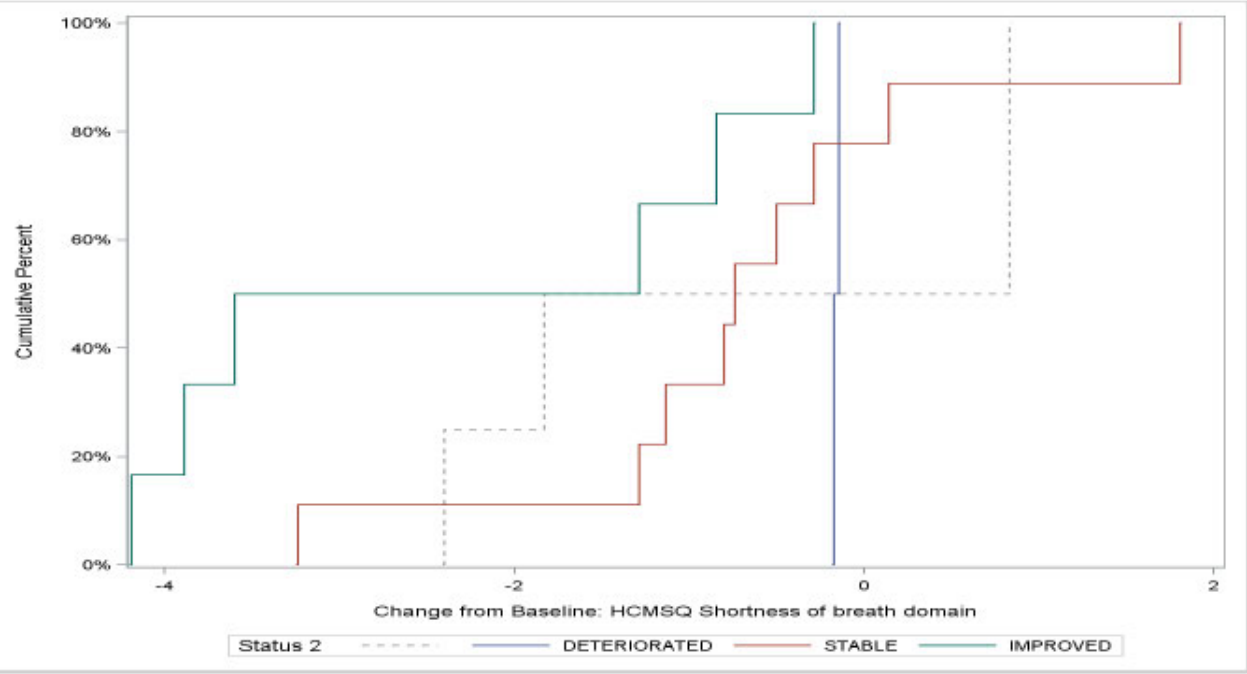
Appendix 6.10. eCDF Curves for Change from Baseline to Week 6 in KCCQ-23 CSS based on PGIC Rating

Figure 3: eCDF for Change from Baseline to Week 6 in KCCQ-23 CSS by PGIC

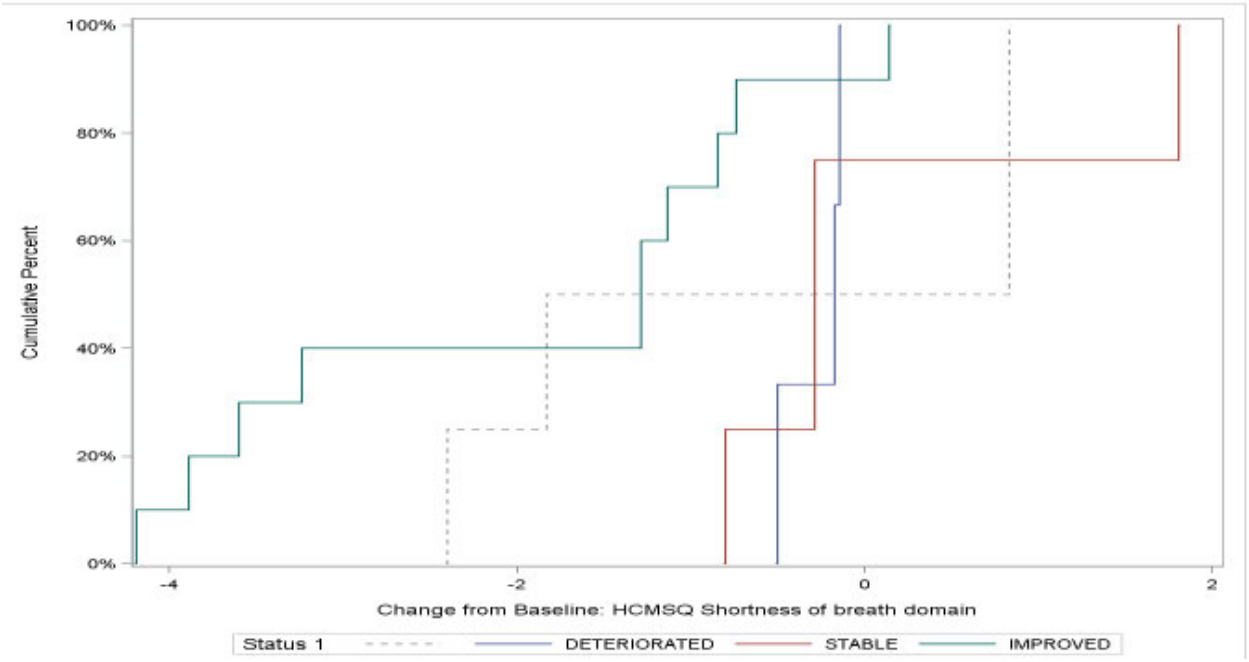


Appendix 7. CDF Curves based on the MAVERICK-HCM study data

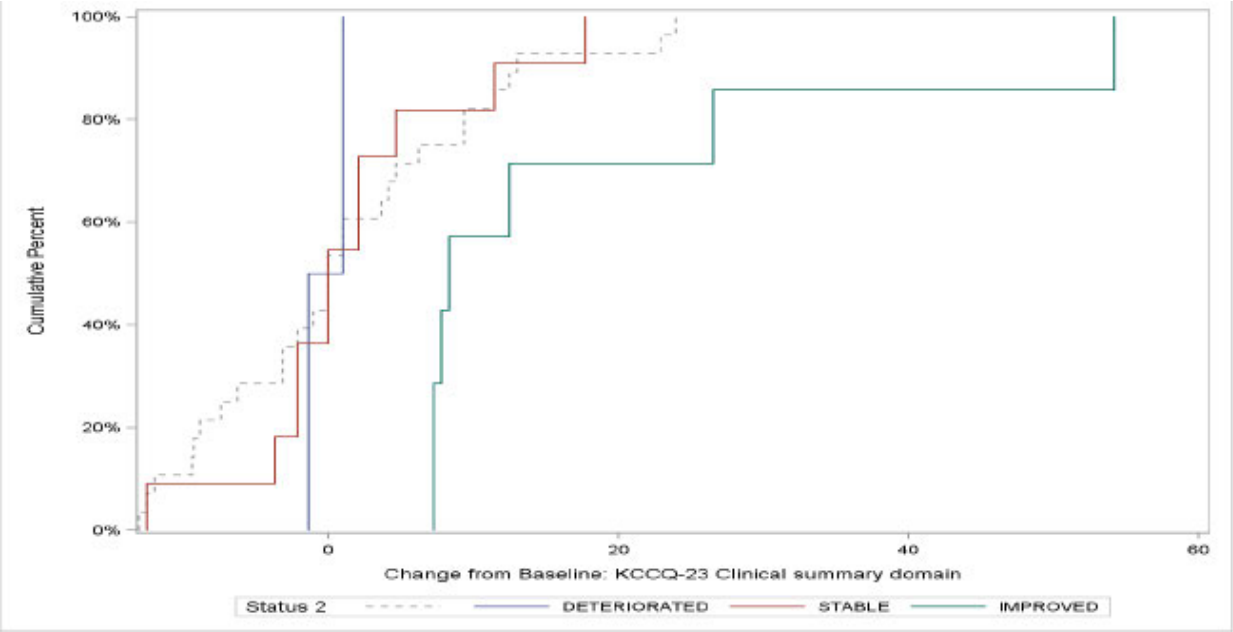
Appendix 7.1. CDF Curves for HCMSQ-SB change scores based on change in PGIS ratings at Week 16



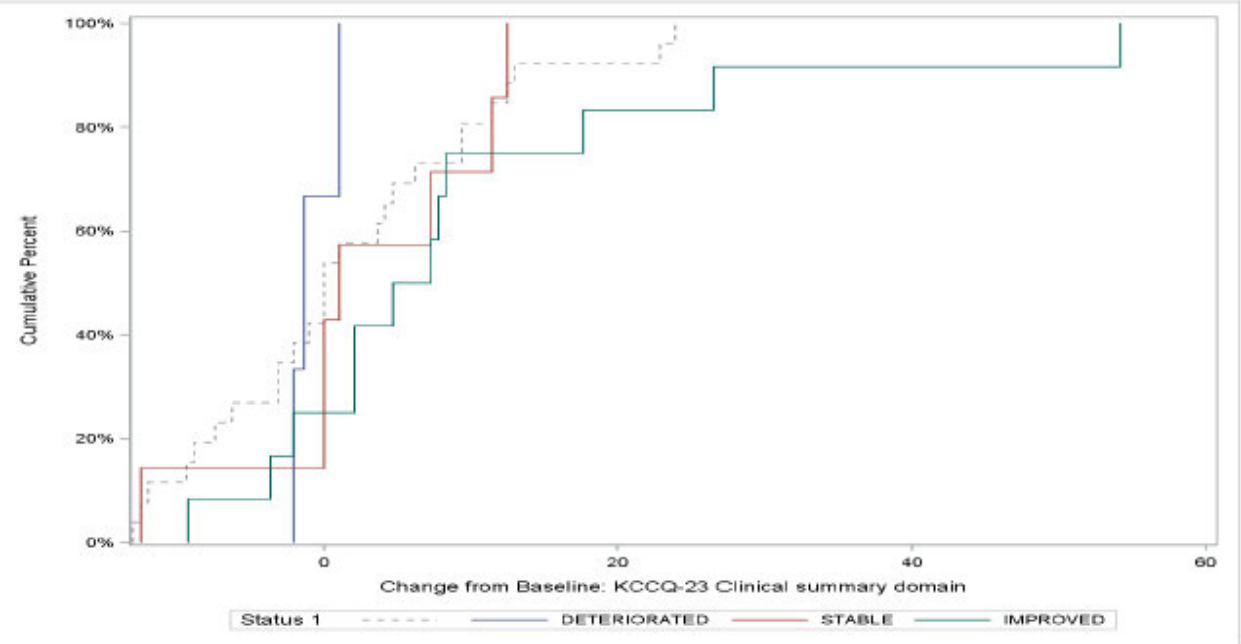
Appendix 7.2. CDF Curves for HCMSQ-SB change scores based on change in PGIC ratings at Week 16



Appendix 7.3. CDF Curves for KCCQ-23 CS change scores based on change in PGIS ratings at Week 16



Appendix 7.4. CDF Curves for KCCQ-23 CS change scores based on change in PGIC ratings at Week 16



Appendix 8. Tables showing change from baseline to Week 30 in PRO endpoints by baseline PGIS rating based on the EXPLORER-HCM study

Appendix 8.1 Baseline to Week 30 HCMSQ-SB by Baseline PGIS Status

Table 37. Baseline to Week 30 HCMSQ Shortness of Breath Domain by Baseline PGIS Status

PGIS Category Change	Change Score Percentile	Baseline PGIS Category				
		Mild	Moderate	Severe	Very Severe	Total
		n = 17	n = 35	n = 6	n = 1	n = 59
PGIS 1-category change	10th Percentile	-5.00	-6.40	-7.52	-1.37	-6.19
	25th Percentile	-4.43	-4.10	-6.19	-1.37	-4.43
	50th Percentile	-3.00	-2.76	-2.76	-1.37	-2.76
	75th Percentile	-1.43	-1.62	0.00	-1.37	-1.43
	90th Percentile	-0.50	-0.40	2.95	-1.37	-0.40
			n = 8	n = 5		n = 13
PGIS 2-category change	10th Percentile	---	-10.14	-11.00	---	-10.14
	25th Percentile	---	-6.86	-7.29	---	-7.00
	50th Percentile	---	-5.05	-4.67	---	-4.83
	75th Percentile	---	-2.82	-4.42	---	-2.93
	90th Percentile	---	-2.43	-2.86	---	-2.71

PGIS = Patient Global Impression of Severity
Source: Table 8.2

Appendix 8.2 Baseline to Week 30 HCMSQ-SB by Baseline NYHA FC

Table 6: Subjects who achieved a 1-category improvement in NYHA Class

		Baseline NYHA Class		
		II	III	IV
Change of HCMSQ-SoB from baseline to Week 30	**N**	54	18	0
	10th Percentile	-5.50	-7.52	
	25th Percentile	-4.17	-4.86	
	Median (50th percentile)	-2.57	-2.49	
	75th Percentile	-0.67	-1.56	
	90th Percentile	0.00	1.14	

Table 7: Subjects who achieved a 2-category improvement in NYHA Class

		Baseline NYHA Class	
		III	IV
Change of HCMSQ-SoB from baseline to Week 30	**N**	8	0
	10th Percentile	-10.14	
	25th Percentile	-4.49	
	Median (50th percentile)	-3.34	
	75th Percentile	-1.50	
	90th Percentile	1.56	

Table 8: Subjects who achieved no change in NYHA Class

		Baseline NYHA Class			
		I	II	III	IV
Change of HCMSQ-SoB from baseline to Week 30	**N**	0	65	18	0
	10th Percentile		-4.43	-4.25	
	25th Percentile		-2.43	-2.86	
	Median (50th percentile)		-0.93	-0.63	
	75th Percentile		0.00	2.29	
	90th Percentile		1.14	4.53	

Table 9: Subjects who achieved a 1-category worsening in NYHA Class

		Baseline NYHA Class		
		I	II	III
Change of HCMSQ-SoB from baseline to Week 30	**N**	0	8	0
	10th Percentile		-2.29	
	25th Percentile		-1.79	
	Median (50th percentile)		-0.19	
	75th Percentile		1.53	
	90th Percentile		2.44	

Table 10: Subjects who achieved a 2-category worsening in NYHA Class

		Baseline NYHA Class	
		I	II
Change of HCMSQ-SoB from baseline to Week 30	**N**	0	0
	10th Percentile		
	25th Percentile		
	Median (50th percentile)		
	75th Percentile		
	90th Percentile		

Appendix 8.3 Baseline to Week 30 KCCQ-23 CSS by Baseline PGIS Status

Table 41. Baseline to Week 30 KCCQ-23 CSS by Baseline PGIS Status

PGIS Category Change	Change Score Percentile	Baseline PGIS Category				
		Mild	Moderate	Severe	Very Severe	Total
		n = 18	n = 37	n = 6	n = 1	n = 62
PGIS 1-category change	10th Percentile	3.13	-5.21	-1.56	-3.13	-3.13
	25th Percentile	5.21	-0.00	12.50	-3.13	4.17
	50th Percentile	11.41	18.75	22.14	-3.13	16.15
	75th Percentile	21.88	25.00	23.96	-3.13	23.96
	90th Percentile	27.08	32.29	32.29	-3.13	28.13
			n = 10	n = 8		n = 18
PGIS 2-category change	10th Percentile	---	8.33	-16.15	---	7.29
	25th Percentile	---	11.46	13.28	---	12.50
	50th Percentile	---	19.53	29.17	---	23.18
	75th Percentile	---	35.42	40.94	---	38.54
	90th Percentile	---	47.40	52.60	---	48.96

PGIS = Patient Global Impression of Severity
Source: Table 8.2

Appendix 8.4. Baseline to Week 30 KCCQ-23 CSS by Baseline NYHA FC

Table 1: Subjects who achieved a 1-category improvement in NYHA Class

		Baseline NYHA Class		
		II	III	IV
Change of KCCQ-23 CSS from baseline to Week 30	N	58	25	0
	10th Percentile	-5.21	-1.04	
	25th Percentile	2.08	6.77	
	Median (50th percentile)	8.33	16.15	
	75th Percentile	19.79	26.04	
	90th Percentile	27.08	34.90	

Table 2: Subjects who achieved a 2-category improvement in NYHA Class

		Baseline NYHA Class	
		III	IV
Change of KCCQ-23 CSS from baseline to Week 30	N	10	0
	10th Percentile	-3.23	
	25th Percentile	13.85	
	Median (50th percentile)	22.40	
	75th Percentile	32.29	
	90th Percentile	42.19	

Table 3: Subjects who achieved no change in NYHA Class

		Baseline NYHA Class			
		I	II	III	IV
Change of KCCQ-23 CSS from baseline to Week 30	N	0	66	16	0
	10th Percentile		-9.17	-14.58	
	25th Percentile		-3.13	-9.90	
	Median (50th percentile)		2.08	-0.52	
	75th Percentile		12.50	16.46	
	90th Percentile		21.88	33.33	

Table 4: Subjects who achieved a 1-category worsening in NYHA Class

		Baseline NYHA Class		
		I	II	III
Change of KCCQ-23 CSS from baseline to Week 30	N	0	5	0
	10th Percentile		-28.65	
	25th Percentile		-8.33	
	Median (50th percentile)		-7.29	
	75th Percentile		-6.77	
	90th Percentile		-1.56	

Table 5: Subjects who achieved a 2-category worsening in NYHA Class

		Baseline NYHA Class	
		I	II
Change of KCCQ-23 CSS from baseline to Week 30	N	0	0
	10th Percentile		
	25th Percentile		
	Median (50th percentile)		
	75th Percentile		
	90th Percentile		

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/s/

SUSAN M PRETKO
09/30/2021 10:14:17 AM

DAVID S REASNER
09/30/2021 04:58:17 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Disease, Pediatrics, Urology, and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
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Division of Pediatrics and Maternal Health Memorandum

Date: July 28, 2021 **Date Consulted:** June 3, 2021

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Lynne Yao, MD, DPMH Director

To: Alexis Childers, Regulatory Project Manager (RPM)
Division of Cardiology and Nephrology (DCN)

Drug: Camzyos (mavacamten)

NDA: 214998

Proposed Indication: Treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in adults to improve functional capacity, (b) (4) and symptoms.

Applicant: MyoKardia Inc.

Subject: Postmarketing Requirement (PMR) for a descriptive pregnancy safety study

Materials Reviewed:

- NDA 214998 submitted on January 28, 2021.
- DPMH Consult Memo for Mavacamten IND 121904 by Anissa Davis-Williams, RN, BSN, MPH, RPM, dated December 8, 2020. DARRTS Reference ID: 4714273.
- DCN Preliminary Type C Meeting Comments, by Brian Proctor, RAC, dated December 7, 2020. DARRTS Reference ID: 4712938.

- Type C Meeting Background Materials for Mavacamten IND 121904, submitted on October 26, 2020.

Consult Question: "DPMH guidance is requested to assist in developing a postmarketing study assessing pregnancy exposure to mavacamten."

INTRODUCTION

On January 28, 2021, the applicant, MyoKardia Inc., submitted a new NDA (214998) for a new molecular entity (NME), Camzyos (mavacamten). On June 3, 2021, the Division of Cardiology and Nephrology (DCN) consulted the Division of Pediatric and Maternal Health (DPMH) to assist in developing a postmarketing study to assess pregnancy exposure to mavacamten based on concerns for teratogenic effects observed in animal reproduction studies. DCN did not request DPMH to provide Pregnancy and Lactation Labeling Rule (PLLR) labeling recommendations.

REGULATORY HISTORY

- Camzyos (mavacamten) is a first in class cardiac myosin inhibitor with the proposed indication for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in adults to improve functional capacity, (b) (4) and symptoms.
- On April 27, 2016, Orphan designation was granted.
- On July 22, 2020, Breakthrough Therapy was granted.
- On September 30, 2020, the applicant requested a Type C meeting to discuss plans for their proposed postapproval pregnancy safety to evaluate the teratogenic potential of mavacamten in females of childbearing potential in order to inform future labeling.
- On December 7, 2020, DCN sent the applicant preliminary meeting comments from DPMH and the Division of Epidemiology (DEPI-2) which stated the proposal to conduct a pregnancy safety study for mavacamten seems reasonable, pending NDA review.[1]
- On December 10, 2020, the applicant withdrew the meeting request.

BACKGROUND

Drug Characteristics

- *Mechanism of action:* cardiac myosin inhibitor
  - (b) (4)
- *Half-life:* terminal half-life is 6-9 days in CYP 2C19 normal metabolizers (NM). Mean half-life is prolonged in CYP 2C19 poor metabolizers (PM) compared to NM (23 days versus 6-9 days, respectively). (b) (4)
- *Molecular weight:* 273.33 g/mol
- *Plasma protein binding:* 97-98%

[1] DCN Preliminary Type C Meeting Comments, by Brian Proctor, RAC, dated December 7, 2020. DARRTS Reference ID: 4712938.

Proposed labeling:

- *Dosage forms and strengths:* 2.5 mg, 5 mg, 10 mg, 15 mg.
- *Dosage and Administration:* the recommended starting dose is 5 mg orally once daily. (b) (4)

[redacted]

(b) (4)

Condition: Hypertrophic Cardiomyopathy (HCM) Pregnancy[2,3]

- *HCM:* chronic, progressive disease of the cardiomyocyte, defined by left ventricular (LV) hypertrophy, with a diverse clinical presentation and course. There are two common types of HCM: obstructive hypertrophic cardiomyopathy (oHCM) and nonobstructive hypertrophic cardiomyopathy. In a general population of young adults, the prevalence of HCM is approximately 1 per 500.
    - In the subset of patients with oHCM, the presence of LVOT obstruction is an important prognostic factor associated with an increased risk of disease progression, congestive heart failure, stroke, and death.
    - Patients with oHCM experience exertional dyspnea, fatigue, chest pain, and limited exercise capacity, which worsen over time in the absence of effective treatment.
    - Mortality in HCM patients is significantly higher than the U.S. general population. Mortality in young HCM patients (20-29 years of age) is elevated > 4-fold, and in older patients (50-69 years of age) > 3-fold.

- *HCM and pregnancy:* pregnancy places a significant burden on the cardiovascular system (such as marked increases in circulating blood volume, stroke volume, and heart rate)which may lead to heart failure, arrhythmias, and, rarely, maternal mortality in women with a pre-existent cardiomyopathy.
    - A systemic review of 11 observational studies which included 9 patient cohorts (a total of 237 women with HCM and 408 pregnancies), demonstrated that most pregnancies in women with HCM are uneventful.[2] Nevertheless, pregnancy in women with HCM carries maternal and fetal risks. The maternal mortality rate was 0.5% and any complication or worsening of symptoms occurred in 29% of the patients. Fetal mortality caused by spontaneous abortion (15%), therapeutic abortion (5%), and stillbirth (2%), was comparable with that in the general population. However, the observed risk of premature birth (26%) was increased.

[2] Schinkel, Arend F.L. MD, PhD. Pregnancy in Women with Hypertrophic Cardiomyopathy. Cardiology in Review. September/October 2014-Volume 22-Issue 5-p 217-222.
[3] Pieper, PG, et al. Pregnancy in Women with Hypertrophic Cardiomyopathy. Neth Heart J (2013) 21:14-18.

REVIEW

PREGNANCY

Nonclinical Experience[4]

When mavacamten was administered orally to pregnant rats ((b) (4) mg/kg/day) during the period of organogenesis, decreased mean fetal body weight, and increases in post implantation loss and fetal malformations (visceral and skeletal) were observed in the high dose group (1.5 mg/kg/day). Visceral malformations (heart malformation in fetuses, including one total situs inversus) and increased incidences of skeletal malformations (mainly fused sternebrae) were observed. Plasma exposure (AUC) at the no effect dose (b) (4) for embryo-fetal development in rats (b) (4)

When mavacamten was administered orally to pregnant rabbits ((b) (4) mg/kg/day) during the period of organogenesis, fetal malformations (visceral and skeletal) were increased at doses of 1.2 mg/kg/day and higher. Visceral findings consisted of malformations of the great vessels (dilatation of pulmonary trunk and/or aortic arch) (b) (4) Skeletal malformations consisted of higher incidences of fused sternebrae (b) (4) Plasma exposure (AUC) at the no effect dose (b) (4) (b) (4) for embryo-fetal development in rabbits is (b) (4) in humans at the MRHD.

In a pre/postnatal development study, mavacamten was administered orally to pregnant rats ((b) (4) mg/kg/day) from gestation Day 6 to lactation/post-partum Day 20. No adverse effects were observed in the dams or offspring exposed daily from before birth (in utero) through lactation. 1.5 mg/kg/day (the highest dosage level tested) was considered to be the no-observed-adverse-effect level (NOAEL). (b) (4)

Reviewer's Comment: DPMH discussed the applicant's proposed labeling above and mavacamten reproductive toxicity findings with the Nonclinical Review Team. The nonclinical review and labeling edits are currently pending.[5] *The Nonclinical Review Team provided the exposure multiples listed in the table below and concluded mavacamten has a high probability of being a teratogen when administered during gestation as evidenced in both rat and rabbit embryo-fetal development studies.*

Species	Dose mg/kg/ day	Effects	Parameter	PK data-Tox study		Multiple, Animal/human[1]	
				Cmax	AUC	Cmax	AUC
Embryo-fetal Development Toxicity							
Rat[2]	1.5	Teratogenic potential		1080	16500	1.12	0.98
	0.75	Developmental	**NOAEL**	356	5690	0.40	0.34
Rabbit[2]	1.2	Teratogenic potential		1100	16500	1.14	0.98
	0.6	Maternal and developmental	**NOAEL**	516	7160	0.54	0.42

Male and female combined C_{max} (ng/ml) and AUC_{0-24} (h*ng/mL) values
1: Based on EXPLORER-HCM study at a dose of 15 mg MYK-461/day for 10 days. Mean Cmax: 962 ng/ml, AUC0-24 16,891 h*ng/mL used for calculating exposure multiples (per sponsor email).
2. Exposure data in reproductive toxicity were based on gestation day 12.

[4] Mavacamten Proposed Labeling, NDA 214988.
[5] DPMH Personal Communication with Gowra Jagadeesh, PhD, Nonclinical Review Team, dated 6/17/21 and 7/28/21.

Applicant's Review of Published Literature
The applicant did not perform a literature search related to mavacamten use and pregnancy.

DPMH's Review of Published Literature
PubMed, Embase, Micromedex[6], TERIS[7], Reprotox[8], and Briggs[9] were searched using "mavacamten" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," and "miscarriage." No relevant articles were identified.

Clinical Trials
Pregnant women were excluded from clinical trials during the development program for mavacamten. As of the 120-day Safety Update, the applicant stated there are no clinical safety data for embryo-fetal toxicity because no pregnancies have been reported for female subjects or female partners of male subjects treated with mavacamten.

Applicant's Rationale for a Postapproval Pregnancy Safety[10]
Based on the reproductive toxicology findings, the applicant proposes a postapproval pregnancy safety study for mavacamten to evaluate the teratogenic potential in clinical use. The applicant's rationale for conducting a pregnancy safety study instead of a pregnancy exposure registry, is due to anticipated low pregnancy exposure (b) (4)

Table 1: Assumptions to Calculate the Annual Sample Size of Pregnant Women Exposed to Mavacamten

Total US population in 2019: ~328 million
US Female population*: ~166 million (50.8% of total US population)
US Female population 18 to 44*: ~60 million (36.5% of US Female population)
US Female population 18 to 44 with HCM: ~120,000 (based on a prevalence of 0.2% among adults)
US Female population 18 to 44 with HCM pregnant**: ~1400
(b) (4)

* US Census 2010 (Howden, Meyer, & U.S. Census Bureau, 2011).
** Birth rate of 11.6 per 1,000 population (L. A. Martin, Hamilton, Osterman, & Driscoll, 2019).
(b) (4)

Table from applicant's Type C Meeting Background Materials for Mavacamten IND 121904 (page 19).

LACTATION
Nonclinical Experience
There are no available data on the presence of mavacamten in animal milk. Refer to the Nonclinical Review by Gowra Jagadeesh, PhD.

Applicant's Review of Published Literature
The applicant did not perform a literature search related to mavacamten use and lactation.

[6] Truven Health Analytics information, http://www micromedexsolutions.com.Accessed 6/23/21.
[7] TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 6/23/21.
[8] Reprotox® Website: www.Reprotox.org. REPROTOX® system Accessed 6/23/21.
[9] Briggs, GG. Freeman, RK. & Yaffe, SJ. (2017). Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.
[10] Type C Meeting Background Materials for Mavacamten IND 121904, submitted on October 26, 2020.

DPMH's Review of Published Literature

PubMed, Embase, Micromedex[6], TERIS[7], Reprotox[8], and Briggs[9], *Medications and Mother's Milk*[11], and LactMed[12] were searched using "mavacamten" AND "breastfeeding" or "lactation." No relevant articles were identified.

Clinical Trials

Lactating women were excluded from clinical trials during the development program for mavacamten. The applicant stated there were no reported cases of exposure in lactation.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Mavacamten was not found to be genotoxic in a reverse mutation bacterial test (Ames test), a human in vitro lymphocyte clastogenicity assay, or a rat in vivo micronucleus assay. There was no evidence of carcinogenicity seen in a 6-month rasH2 transgenic mouse study at mavacamten doses of up to 2.0 mg/kg/day in males and 3.0 mg/kg/day in females, which resulted in exposures that were 1.8- and 3.2-fold higher in males and females, respectively, compared to the MRHD.

In reproductive toxicity studies, there was no evidence of effects of mavacamten on mating and fertility in male or female rats at doses up to 1.2 mg/kg/day, or in the viability and fertility of offspring of dams dosed up to 1.5 mg/kg/day. Plasma exposure (AUC) of mavacamten at the highest dose tested was less than in humans at the MRHD. For more details, refer to the Nonclinical Review by Gowra Jagadeesh, PhD.

Applicant's Review of Published Literature

The applicant did not perform a literature search related to mavacamten use and fertility.

DPMH's Review of Published Literature

PubMed, Embase, Reprotox[8] were searched using, "mavacamten" AND "fertility," "infertility," "contraception," and "oral contraceptives." No relevant articles were identified.

DISCUSSION AND CONCLUSIONS

Pregnancy

Pregnant women were excluded from clinical trials with mavacamten and no inadvertent cases of exposure during pregnancy have been reported. DPMH discussed the available data from animal studies with the nonclinical team, who concluded mavacamten has a high probability of being a teratogen when administered during gestation as evidenced in both rat and rabbit embryo-fetal development studies.[13] In embryo-fetal development studies in rats, mavacamten increased post-implantation loss, lowered mean fetal body weight, slightly reduced fetal skeletal ossification, induced heart malformation (total situs inversus), and increased incidences of skeletal malformations when compared to controls. In rabbits, increased incidences of cleft palate, great vessel malformations (dilatation of pulmonary trunk and/or aortic arch), and fused sternebrae in

[11] Hale, Thomas (2017) Medications and Mothers' Milk. Amarillo, Texas. Hale Publishing.

[12] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. LactMed is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare providers and nursing women. LactMed provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 6/23/21

[13] Personal Communication with Gowra Jagadeesh, PhD, Nonclinical Review Team, dated 6/17/21.

fetuses were observed at the same doses that caused maternal toxicity. Exposure of the fetus, placenta and amniotic fluid to mavacamten was demonstrated in pregnant rats.

Based on the lack of available human pregnancy data and the findings from animal studies which may indicate a potential safety concern for teratogenicity, DPMH recommends issuing a postmarketing requirement (PMR) for a descriptive pregnancy safety study. DPMH agrees with the applicant's proposed labeling which does not include a pregnancy contraindication but does include a Warning and Precaution for Embryo-fetal Toxicity and recommends the use of contraception in females of reproductive potential during treatment and for 4 months after the final dose because of the concerns for teratogenicity as observed in animal studies. Because pregnancy exposure is likely to be rare, DPMH does not recommend issuing a pregnancy registry for mavacamten. Instead, the descriptive pregnancy safety study PMR should be designed to capture all prospective and retrospectively reported cases of inadvertent exposure to mavacamten during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes should be assessed through at least the first year.

Lactation

Lactating women were excluded from clinical trials with mavacamten and no inadvertent cases of exposure during lactation have been reported. There are no available data on the presence of mavacamten in human or animal milk, the effects on the breastfed infant, or the effects on milk production. There are no available data to inform the risks related to the use of mavacamten during lactation. Because exposure during lactation is likely to be rare, DPMH does not recommend issuing a clinical lactation study. Instead, capturing infant outcomes related to exposure during lactation has been incorporated into the descriptive pregnancy safety study PMR.

Females and Males of Reproductive Potential

There are no available data on the effects of mavacamten on female or male fertility. DPMH discussed the available data from animal studies with the Nonclinical Team, who concluded mavacamten did not cause transgenerational reproductive effects or adversely affect fertility of male or female rats when repeatedly dosed. Mavacamten was not mutagenic or genotoxic in vivo and in vitro assays.[13] (b) (4)

RECOMMENDATIONS

DPMH recommends issuing a PMR for a descriptive pregnancy safety study with suggested language below:

> Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to mavacamten during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life.

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/

KRISTIE W BAISDEN
07/28/2021 02:49:08 PM

TAMARA N JOHNSON
07/28/2021 03:46:08 PM

LYNNE P YAO
08/20/2021 08:00:50 AM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 214998
Submission Number	001
Submission Date	1/28/2021
Date Consult Received	2/21/2021
Drug Name	Mavacamten (MYK-461)
Indication	Symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in adults to improve functional capacity, (b) (4) and symptoms
Therapeutic dose	Initiation of treatment: 5 mg once daily (QD) Titration of treatment: based on LVEF and VLVOT Dose range: 2.5–15 mg QD
Clinical Division	DCN

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult dated 2/21/2021 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review under IND 121904 dated 9/12/2017 and 10/7/2019 in DARRTS;
- Proposed label (Submission 0001);
- Summary of clinical pharmacology (Submission 0001);
- Clinical study report: 002, 003, 004, 005, 006, 007, 008, 010, 014 (Submission 0001);
- QT evaluation report submission checklist (including Highlights of Clinical Pharmacology and Cardiac Safety table) (Submission 0001); and
- Concentration-QT Modeling report and SAP (Submission 0001).

1 SUMMARY

In healthy volunteers, mavacamten concentration-dependent QT prolongation was detected with repeated dosing over the dose range of 2–25 mg daily doses. At the upper limit of the target concentration range in pivotal Phase 3 study MYK-461-005 (i.e. 700 ng/mL), the predicted mean QTc effect is 4.6 msec (90% CI: -0.2 to 9.4 msec). However, no significant QTc prolongation was detected in patients with obstructive hypertrophic cardiomyopathy or non-obstructive hypertrophic cardiomyopathy (oHCM and nHCM) over the therapeutic concentration range. In nonclinical safety pharmacology studies, data suggests that mavacamten does not directly interact with hERG channels but QTc prolongation was observed in dogs. There is no evidence for hERG trafficking inhibition. The mechanism for QTc prolongation is unknown.

The effect of mavacamten on the QTc interval was evaluated in multiple clinical trials in healthy volunteers and in HCM patients. The highest dose tested in healthy volunteers

was 25 mg QD, which covers the target concentration range in the pivotal Phase 3 study (<700 ng/mL). The data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that mavacamten is associated with significant QTc prolonging effect in HCM patients, but a concentration-dependent QT prolonging effect was observed in healthy volunteers after repeat dosing (refer to section 4.5) – see Table 1 for overall results in the primary studies. The findings of this analysis are further supported by the by time analysis (section 4.3) and categorical analysis (section 4.4).

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

Study ID	Population	Treatment	Concentration (ng/mL)	ΔΔQTcF (msec)	90% CI (msec)
MYK-461-003	Healthy volunteers	1 mg BID	75.8	-0.77	(-5.3 to 3.7)
		3 mg BID	178.6	0.1	(-4.3 to 4.5)
		12.5 mg QD	482.4	2.7	(-1.8 to 7.2)
		18.5 mg QD	1033.3	7.4	(1.8 to 13.0)
		25 mg QD	1194.0	8.8	(2.7 to 14.8)
MYK-461-005	oHCM	5 mg QD with titration up to 15 mg QD	407.5	-8.4	(-11.4 to -5.4)
MYK-461-006	nHCM		392.1	-8.2	(-11.2 to -5.2)
Sponsor's reported $C_{max,ss}$	oHCM		452.0	-9.0	(-12.2 to -5.9)

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

- In vitro data suggested that mavacamten do not acutely or chronically interact with hERG current. However, mavacamten-induced QT prolongation was observed in dogs following both single (delayed effect) and multiple dosing.
- In clinical trials, concentration-dependent increase in QTc interval was observed in healthy volunteer MAD study 003 (up to 25 mg QD) but not in the healthy volunteer SAD study 002 (up to 48 mg) or in patients with hypertrophic cardiomyopathy in studies 005 and 006 (up to 15 mg QD).
- The underlying mechanism for the observed QT prolongation in dogs and the exposure-response relationships in healthy volunteers with repeated dosing is not known. The sponsor postulates that the *"findings in healthy hearts are attributed to an adaptive response to the cardiac mechanical/functional changes (marked mechanical LV depression) occurring in response to myosin inhibition in hearts with normal physiology and LV contractility."*
- PK/ECG sampling schedules in studies MYK-461-005 and MYK-461-006 may not capture QT effect around maximum drug exposure at steady state. However, considering a consistent pattern of lower ΔQTcF with increasing concentration in studies 004, 005, and 006 in a wide dose/exposure range (i.e. up to 15 and 20 mg QD in study 004), we do not expect QT prolonging effect in the clinically relevant exposure range (<1000 ng/mL) in the HCM patient population.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN 001 (link) from the IRT. Our changes are highlighted (addition, ~~deletion~~) as suggestions only and we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In healthy volunteers receiving multiple doses of [TRADENAME], a concentration-dependent increase in the QTc interval was observed at doses up to 25 mg QD. No acute QTc changes have been observed at similar exposures during single dose studies. The mechanism of the QT prolongation effect is not known.

A meta-analysis across clinical studies in HCM patients does not suggest clinically relevant increases in the QTc interval in the therapeutic exposure range. In HCM, the QT interval may be intrinsically prolonged due to the underlying disease, in association with ventricular pacing, or in association with drugs with potential for QT prolongation commonly used in HCM population. (b) (4)

[redacted]

coadministration of [TRADENAME] with QT prolonging drugs or in patients with potassium channel variants resulting in a long QT interval.

(b) (4)

[redacted]

(b) (4)

Reviewer's comment:

- *We propose to report the findings in healthy volunteers before reporting the findings in patients.*
- *Two multiple dose studies in healthy volunteers showed a trend of higher QTc with increasing mavacamten exposure (studies 003 and 010; study 003 was included in the primary exposure-response analysis in healthy volunteers). The single dose study in healthy volunteers (study 002) did not provide higher exposure as compared to multiple dose study that showed concentration-dependent increases in the QTc interval (study 003).*
- *The mechanism for QTc prolongation in dogs and in healthy volunteer is not known. Considering the elevated baseline QTc, the magnitude of the observed QT shortening effect in HCM patients does not appear of particular concern. We propose to report a lack of QT prolonging effect* (b) (4)
- *We do not recommend* (b) (4) *in labeling.*

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Mavacamten (MYK-461) is a cardiac myosin inhibitor indicated for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in adults to improve functional capacity, (b) (4) and symptoms.

Previously the sponsor requested to waive a thorough QT study in healthy volunteers (HV) because such a study is unlikely to provide additional insight into drug effect as compared to data from study MYK-461-003 (i.e. a multiple ascending dose study in HV). The IRT agreed with the sponsor's request because available data suggested that MYK-461 was a QTc prolonger and the sponsor was recommended to collect ECGs in future trials to ensure patient safety (IRT review under IND 121904 dated 09/12/2017 in DARRTS). Because safety ECGs collected in the ongoing studies are not designed to characterize drug effect on the QTc interval, the IRT also agreed with the sponsor's proposal to waive the submission of ECG waveforms and to analyzed ECG data in patients in the integrated summary of safety (IRT review under IND 121904 dated 10/07/2019 in DARRTS).

In the current submission, the sponsor provided a concentration-QTc analysis report of mavacamten based on clinical studies MYK-461-002 to MYK-461-008, MYK-461-010, and MYK-461-014. The sponsor's summary of data included in the analysis is provided below (all patient studies employed dose titration based on PK or PD findings):

ID	Population/Design/ Dose	# Subjects (Active/Placebo)	ECG sampling schedule
(b) (6)	HV, SAD, solution formulation, 1-48 mg	36/12	pre-dose; and 1 h and Days 2, 3, 4, 5, 7, 10, and 28 post-dose

(b) (6)			
	HV, MAD, 1-25 mg QD x28 days	50/10	pre-dose on Day 1; 1 h post-dose on Days 1, 4, 7, 10, 13, 16, 19, 22, 25, and 28 (EOT); Days 35, 49, and 63
	HV, DDI, 25 mg QD on Days 1 and 2, 15 mg QD on Days 3-17	13/0	Days 1 and 15 (pre-dose, 1, 2, 4, 8, 12, and 24 h post-dose), Days 2-14, 16, 17 (EOT), 18, and 52 (pre-dose)
	HV, food effect, 15 mg single dose	24/0	Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 48, 72 h, and on Day 4 post-dose and in each of 3 dosing periods
	oHCM patients; initial dose: 2, 10, or 15 mg QD	21/0	Day 1, Weeks 1-8, 12 (EOT), and 16 (EOS)
	oHCM patients; initial dose: 5 mg QD	~125/125	Day 1, Weeks 4, 6, 12, 18, 22, 26, 30 (EOT), and 38 (EOS)
	nHCM patients	~39/20	Day 1, Weeks 4, 8, 12, 16 (EOT), and 24, (EOT)
	oHCM patients; initial dose: 5 mg QD	90/0	Day 1, Weeks 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96, and 104 (EOT)
	oHCM patients; initial dose: 5 mg QD	13/0	Day 1, Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 104 (EOT), and 116 (EOS)

Source: Table 1 in the sponsor's concentration-QTc modeling report.

Reviewer's comment:

- *In contrary to the sponsor's summary of study features, dense ECG data in study 002 was collected at predose, 0.25, 0.5, 1, 1.5, 2, 4, 8, 12, and 22.5 hours postdose (study 002 protocol), and only sparse ECG data were collected in each study period in study 014 (i.e. predose and 2 hours postdose) (study 014 protocol). In study 002, doses ≥6 mg is that achieved after 8 aliquots administered 15 minutes apart.*
- *Study subjects in study 010 also received a single dose of 35 μg ethinyl estradiol + 1 mg norethindrone on Day 15.*
- *Dose titration criteria in the patient studies are not identical and are not the same as what is proposed in the submitted label. For example, study 005 involved titration based on both PK and PD outcomes (i.e. up-titration maybe triggered by concentration <350 ng/mL and down-titration maybe triggered by concentration >700 ng/mL) while study 006 involved a titration scheme that aimed at 200 ng/mL or 500 ng/mL in two active treatment groups. In the long term extension studies 007-008, concentrations >1000 ng/mL will trigger temporary discontinuation. The proposed dosing regimen in the product label does not rely on PK measurement.*

According to the sponsor, mavacamten shows linear PK in the dose range of 2.5–15 mg. Tmax is 1 or 4 hours in the fasted and fed conditions, respectively. The primary route of elimination is by oxidative metabolism and <3% parent drug was excreted in urine unchanged. Only minor metabolites (≤4% of parent AUC) were detected in systemic circulation. Mavacamten has a long terminal half-life (6-9 days in normal CYP2C19 metabolizers) relative to the dosing interval. The sponsor's population PK analysis does not suggest significant impact on PK by age, sex, or race. AUC and Cmax decreased by approximately 13% and 50%, respectively, after a high fat meal. Verapamil 240 mg and CYP2C19 poor metabolizer genotype increases Cmax by 52% after a single dose of mavacamten, which represent the highest exposure scenario evaluated so far (i.e. mild/moderate hepatic impairment, age, sex, race, and omeprazole 20 mg). The sponsor's population PK analysis suggested a significant decrease (reduction by approximately 3-fold) in clearance in subjects with CYP2C19 poor metabolizer genotype.

Reviewer's comment: *In the pivotal Phase 3 study 005, the sponsor's reported a median Cmax at Week 30 visit was 452 ng/mL. The data was collected within 1-2 hours postdose. Time-matched ECG data were not available at this time point.*

3.1.2 Nonclinical Safety Pharmacology Assessments

In the current submission, the sponsor provided raw data from Study NC-14-0061. FDA's independent analysis of the submitted electrophysiology data demonstrated that mavacamten and metabolite MYK-1078 don't acutely and chronically interact with hERG channel at therapeutic exposure (refer to Appendix 5).

In conclusion, mavacamten-induced QTc prolongations in the in vivo studies cannot be explained by hERG inhibition. The mechanisms of mavacamten-induced QT prolongations in dogs remain unknown.

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for mavacamten was based on exposure-response analysis. Please see section 3.2.3 for additional details.

Reviewer's comment: *FDA reviewers evaluated QTcF, ΔQTcF, HR, PR and QRS for two healthy volunteer studies (studies 002 and 003) and two patient studies (studies 005 and 006). Sponsor's descriptive statistics for different studies are not directly comparable with the reviewer's analysis results. Please see section 4.3 for additional details.*

3.2.1.1 Assay Sensitivity

The sponsor did not propose any analyses to establish assay sensitivity to support a lack of QT prolongation effect in the patient population.

3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted by the sponsor.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., > 500 msec).

Reviewer's comment: *FDA reviewer included all nine studies in the categorical analysis. Results provided by the sponsor are similar to FDA reviewer's analysis. FDA reviewer could not locate categorical analysis of other intervals (HR, PR and QRS) for all studies. FDA reviewer performed categorical analysis for all intervals. Please see section 4.4 for additional details.*

3.2.3 Exposure-Response Analysis

The sponsor used QTcF as the primary correction method and used QTcB and QTcN for sensitivity analyses.

HVs had lower baseline QTcF (median 399 ms) values than patients with oHCM (442 ms) and nHCM (444 ms). A linear concentration-QTcF model was built to describe the ΔQTcF with mavacamten plasma concentrations. The model estimated one slope of

concentration effect for HV and another for patients with oHCM or nHCM. The model estimated a different intercept of concentration effect (i.e., "placebo" effect) by study, visit, and time post-dose (a non-parametric approach) to account for the heterogeneity of the data. Inter-individual variabilities were described using random effects on the intercept and the linear slope. An additive residual error was used in the model.

Table 5 Summary of Final Model Parameters

Parameters	QTcF Estimate (90% CI)	QTcB Estimate (90% CI)	QTcN Estimate (90% CI)
eo.I, coefficient of the effect of baseline QTcF on the intercept[a]	-0.345 (-0.374, -0.317)	-0.384 (-0.415, -0.354)	-0.373 (-0.403, -0.344)
Slope of linear drug effect in oHCM/nHCM (ms·mL/µg)	-19.3 (-23.9, -14.7)	-9.36 (-14.3, -4.48)	-14.8 (-19.5, -10.2)
Slope of linear drug effect in HV (ms·mL/µg)	8.63 (0.285, 17)	11.6 (2.72, 20.5)	9.96 (1.5, 18.4)
Slope.I, coefficient of the effect of baseline QTcF on the slope of linear drug effect in oHCM/nHCM[a]	-0.931 (-1.07, -0.796)	-0.722 (-0.865, -0.58)	-0.71 (-0.844, -0.576)
ωeo,subject (ms), standard deviation of the random effect of the intercept, η1	8.73 (8.11, 9.39)	9.96 (9.27, 10.7)	9.11 (8.47, 9.8)
ωslope,subject (ms), standard deviation of the random effect of the slope, η2	28.5 (25.3, 32)	29 (25.6, 32.9)	28.5 (25.3, 32.1)
σ (ms), standard deviation of the residual error of ΔQTc, ε	12.3 (12.1, 12.5)	14 (13.8, 14.2)	12.7 (12.5, 12.9)

Source: script\qtc.er.r

[a] Center to median baseline QTcF=442, baseline QTcB=443, and baseline QTcN=443 ms.

Sources: Table 5 in the sponsor's concentration-QT Modeling report

No clinically relevant QTc prolongation after mavacamten treatment was found in patients with oHCM or nHCM. The mean ΔΔQTc after mavacamten treatment was negative in patients with typical baseline QTc. Moderate increase of ΔΔQTc with mavacamten concentration was found in HVs.

Reviewer's comments:

1) *Considering the significant differences in study populations (e.g., disease condition, baseline QTc values) and study design features (e.g. inconsistent use of placebo treatment, large variations in the duration of treatment), the reviewers have concerns with pooling data from 9 clinical trials for the concentration-QTc analysis.*
2) *ECG data in the patient studies were collected with trough PK data only. In studies where dense PK data were collected after repeated daily dosing with oral solid dosage forms (e.g. 003 and 010), the ratio between Cmax and Cmin varies between 1.7- to 1.9- fold across different dose levels. Even though high fat high calorie meal significantly reduces Cmax, because the patient studies do not control meal intake, it is likely that ECG data in the patient population (collected at predose only) do not capture QT effect around maximum drug exposure.*
3) *The reviewers conducted concentration-QTc analysis in healthy volunteers and in patients separately. Reviewer's results are similar to the sponsor's results in that the slope coefficients are significantly different in healthy volunteers and in patients. The*

predicted QTc changes in HCM patients are similar in the reviewer's and the sponsor's analyses.

3.2.4 Safety Analysis Related to QTc Prolongation

Review of AE data in the mavacamten integrated NDA dataset using the SMQ "Torsade de pointes/QT Prolongation" or PT "seizure", including by treatment and mavacamten plasma concentration, does not suggest a safety concern for mavacamten. For mavacamten-treated subjects, the only events identified based on application of the MedDRA SMQ Narrow "Torsade de pointes/QT prolongation" on the Mavacamten NDA integrated dataset were events of ventricular tachycardia.

Table 3: Subject Incidence of Reported AEs in SMQ (Narrow) Torsade de Pointes/QT Prolongation and PT Seizure in Any Treatment Group

	All-Mava combined N = 263 n (%)		oHCM				nHCM			
			RCT-Mava N = 123 n (%)		RCT-Placebo N = 128 n (%)		RCT-Mava N = 39 n (%)		RCT-Placebo N = 19 n (%)	
Preferred Term	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
SMQ (narrow) Torsade de pointes/QT prolongation										
Ventricular tachycardia	10 (3.8)	0	2 (1.6)	0	2 (1.6)	1 (0.8)	1 (2.6)	0	1 (5.3)	0
Electrocardiogram QT prolonged	0	0	0	0	1 (0.8)	0	0	0	0	0
Electrocardiogram QT interval abnormal	0	0	0	0	0	0	0	0	0	0
Long QT syndrome	0	0	0	0	0	0	0	0	0	0
Long QT syndrome congenital	0	0	0	0	0	0	0	0	0	0
Torsade de pointes	0	0	0	0	0	0	0	0	0	0
PT Seizure										
Seizure	0	0	0	0	0	0	0	0	0	0

Abbreviations: AE = adverse event; Mava = mavacamten; nHCM = non-obstructive hypertrophic cardiomyopathy; oHCM = obstructive hypertrophic cardiomyopathy; RCT = randomized controlled trial.
Data presented in this table are treatment emergent.
Safety Population includes all subjects who received at least 1 dose of study drug.
Source: Appendix 5 Table 1.1, Appendix 5 Table 1.2, Appendix 5 Table 1.3

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable as large increases or decreases in heart rate (i.e. |mean| < 10 beats/min) were not observed within the clinical dose range (up to 15 mg QD) (see section 4.3.2). A mean increase in heart rate above 10 beats/min was observed in the 25 mg QD group in study 003 only. The observation is not expected to impact the conclusion of QT assessment in the clinical dose range.

4.2 ECG ASSESSMENTS

4.2.1 Overall

Paper ECGs for study 014 were submitted, while digital ECGs from other eight studies were in as well. Overall ECG acquisition and interpretation appears acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer evaluated the ΔQTcF effect using nonparametric descriptive statistics in two healthy volunteer studies (MYK-461-002, MYK-461-003) and parametric descriptive statistics in two patient studies (MYK-461-005, MYK-461-006). Study MYK-461-002 had one day data and data are presented in hours. Data are presented across days (hour 1) for study MYK-461-003 and by weeks for study MYK-461-005 and study MYK-461-006.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups for study MYK-461-002, MYK-461-003, MYK-461-005, and MYK-461-006. The maximum ΔΔQTcF values by treatment are shown in Table 2.

Figure 1: Median and 90% CI of ΔΔQTcF Time Course (unadjusted CIs) by study.

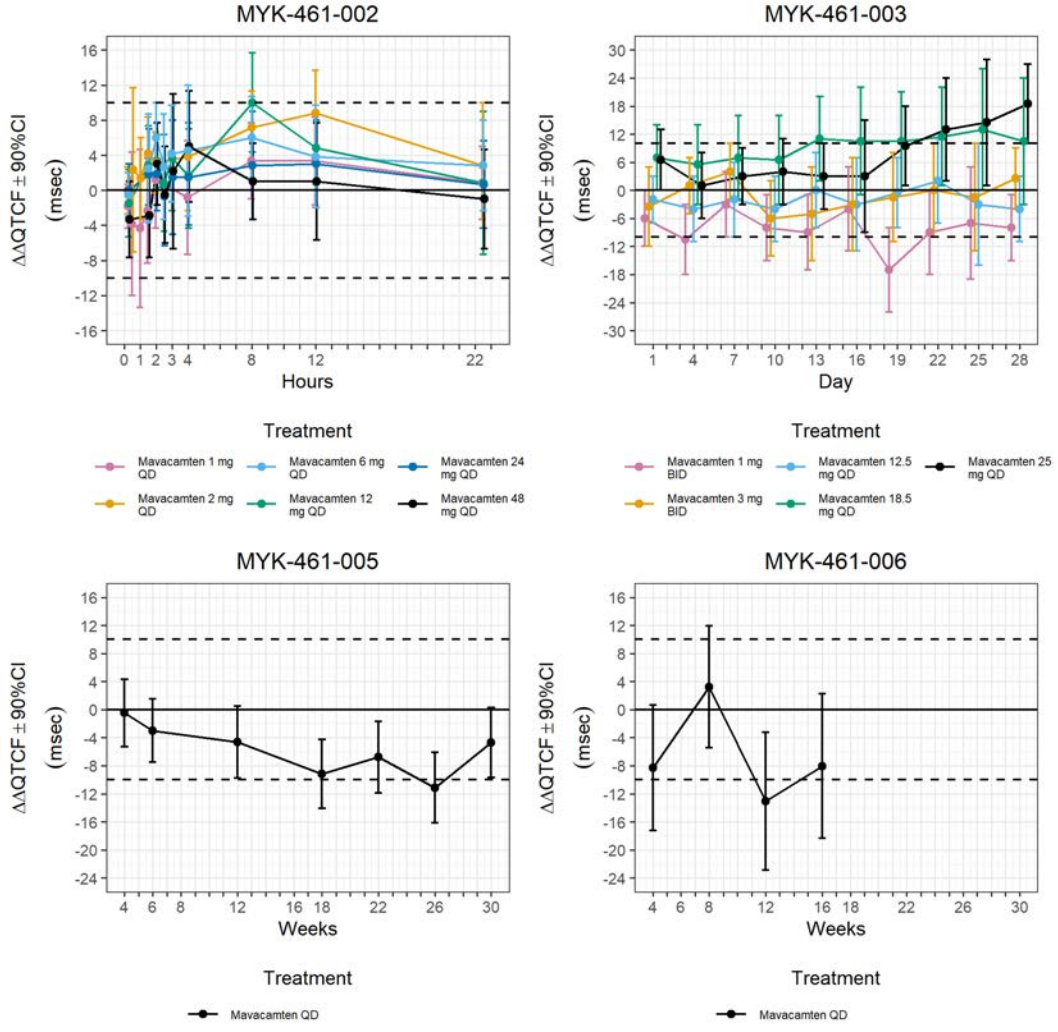


Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTc

Study Identifier	Treatment	Period Day (C)	Nact / Npbo	Time (Hours)	ΔΔQTCF (msec)	90.0% CI (msec)
MYK-461-002	Mavacamten 1 mg QD	1	6 / 12	12.0	3.3	(-1.7 to 8.3)
MYK-461-002	Mavacamten 2 mg QD	1	6 / 12	12.0	8.8	(4.0 to 13.7)
MYK-461-002	Mavacamten 6 mg QD	1	5 / 12	4.0	4.5	(-3.0 to 12.0)
MYK-461-002	Mavacamten 12 mg QD	1	6 / 12	8.0	10.0	(4.3 to 15.7)
MYK-461-002	Mavacamten 24 mg QD	1	6 / 12	8.0	2.8	(-3 3 to 9.0)
MYK-461-002	Mavacamten 48 mg QD	1	6 / 12	4.0	5.0	(-1.3 to 11.3)
MYK-461-003	Mavacamten 1 mg BID	16	10 / 10	1.0	-4.0	(-13.0 to 5.0)
MYK-461-003	Mavacamten 3 mg BID	22	10 / 10	1.0	0.0	(-10 0 to 10.0)
MYK-461-003	Mavacamten 12.5 mg QD	22	10 / 10	1.0	2.0	(-7.0 to 11.0)
MYK-461-003	Mavacamten 18.5 mg QD	28	9 / 4	4.0	20.5	(5.0 to 36.0)
MYK-461-003	Mavacamten 25 mg QD	28	10 / 4	0.5	27.5	(14.0 to 41.0)
MYK-461-005	Mavacamten QD	28	123 / 128	0.0	-0.5	(-5 3 to 4.3)
MYK-461-006	Mavacamten QD	56	38 / 19	0.0	3.2	(-5.4 to 11.9)

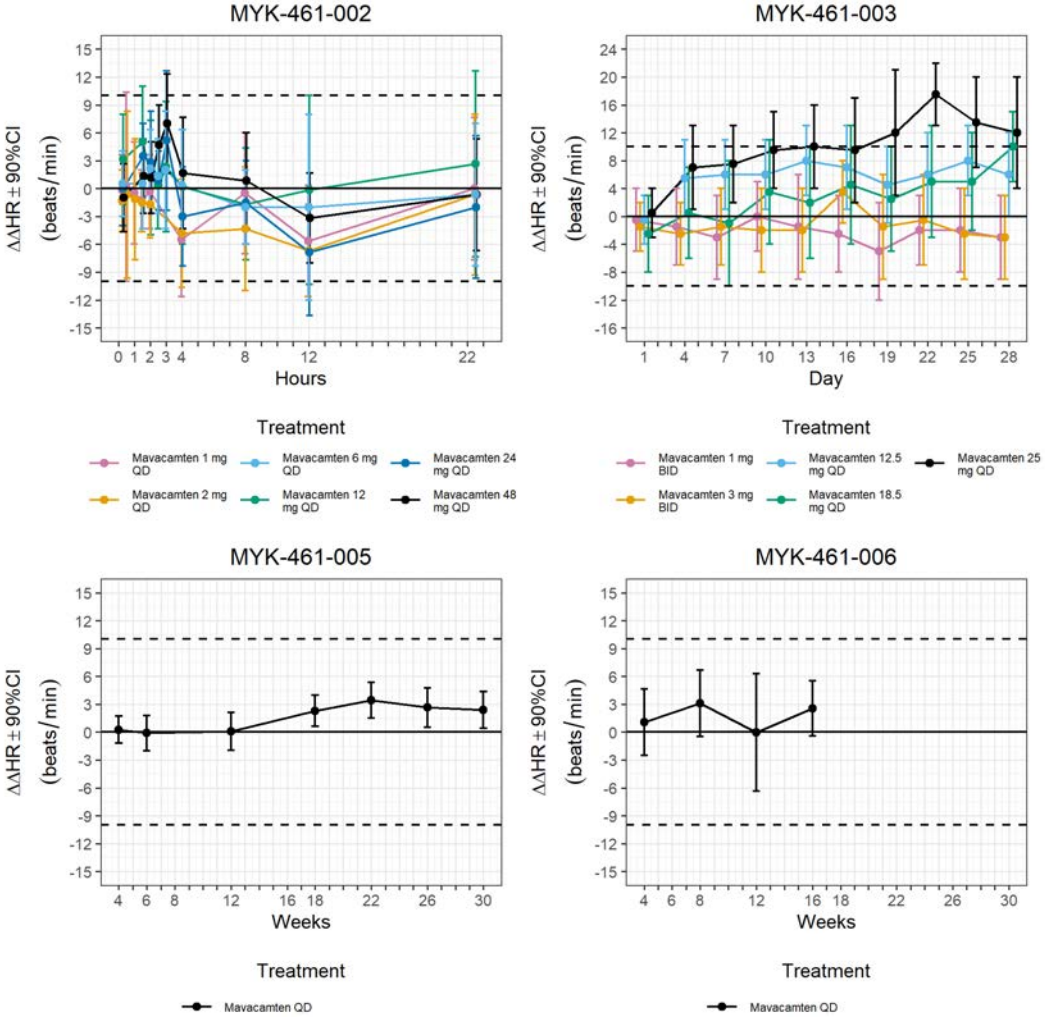
4.3.1.1 Assay sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups for study MYK-461-002, MYK-461-003, MYK-461-005, and MYK-461-006.

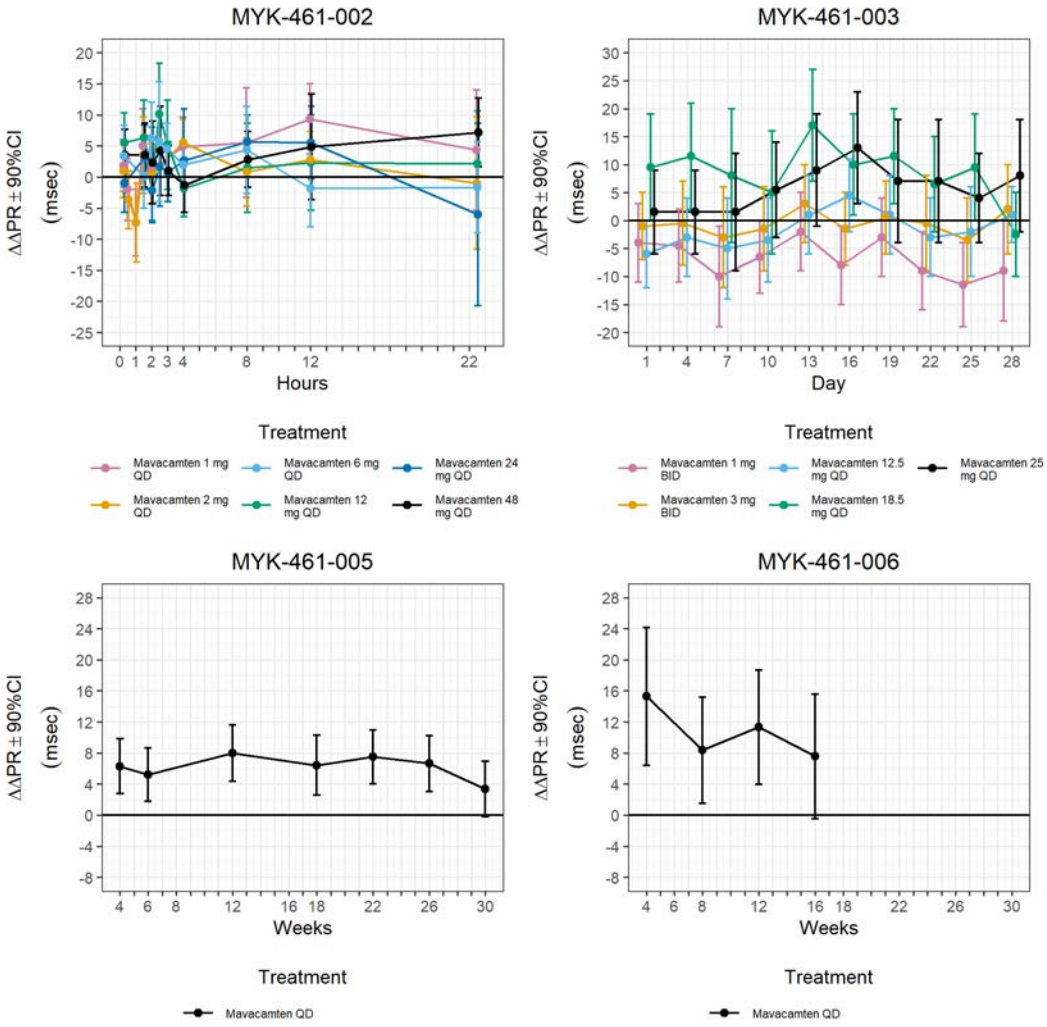
Figure 2: Median and 90% CI ΔΔHR Time Course by study.



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups for study MYK-461-002, MYK-461-003, MYK-461-005, and MYK-461-006.

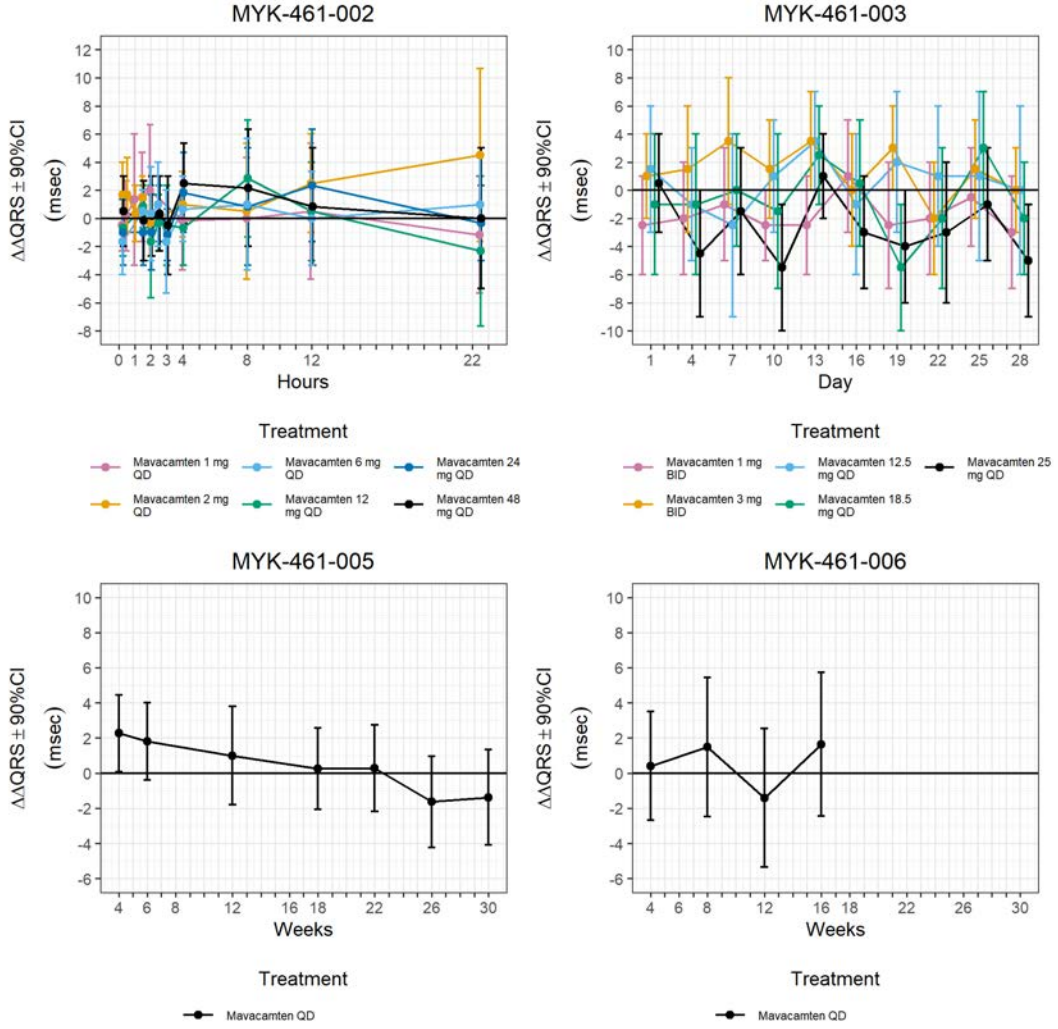
Figure 3: Median and 90% CI of ΔΔPR Time Course by study.



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups for study MYK-461-002, MYK-461-003, MYK-461-005, and MYK-461-006.

Figure 4: Median and 90% CI of ΔΔQRS Time Course by study.



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs. All nine studies are included in the categorical analysis. All the results are presented below for each interval. If a category is omitted in the categorical table that means that no subjects had values in that category. Only studies with outlier values are included in the tables.

4.4.1 QTc

None of the subjects experienced QTcF greater than 500 msec with or without a change from baseline greater than 60 msec in any of the studies.

Table 3 lists the categorical analysis results for ΔQTcF (less than 30 msec, between 30 and 60 and greater than 60 msec). Five subjects treated with mavacamten in two studies experienced ΔQTcF >60 msec.

Table 3: Categorical Analysis for ΔQTcF (maximum)

	Pooled dose	Total (N)		Value <=30 msec		30 msec < Value <=60 msec		Value >60 msec	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
MYK-461-005	Mavacamten	123	941	101 (82.1%)	886 (94.2%)	20 (16.3%)	53 (5.6%)	2 (1.6%)	2 (0.2%)
	Placebo	128	976	108 (84.4%)	924 (94.7%)	17 (13.3%)	47 (4.8%)	3 (2.3%)	5 (0.5%)
MYK-461-007	Mavacamten	167	778	143 (85.6%)	731 (94.0%)	21 (12.6%)	41 (5.3%)	3 (1.8%)	6 (0.8%)

4.4.2 HR

Table 4 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). Seventeen subjects treated with mavacamten in six studies experienced HR >100 beats/min.

Table 4: Categorical Analysis for HR (maximum)

	Pooled dose	Total (N)		Value <=100 beats/min		Value >100 beats/min	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
MYK-461-002	Mavacamten	35	312	33 (94.3%)	310 (99.4%)	2 (5.7%)	2 (0.6%)
	Placebo	12	107	12 (100.0%)	107 (100.0%)	0 (0%)	0 (0%)
MYK-461-003	Mavacamten	50	855	48 (96.0%)	853 (99.8%)	2 (4.0%)	2 (0.2%)
	Placebo	10	174	10 (100.0%)	174 (100.0%)	0 (0%)	0 (0%)
MYK-461-004	Mavacamten	21	201	17 (81.0%)	196 (97.5%)	4 (19.0%)	5 (2.5%)
MYK-461-005	Mavacamten	123	941	119 (96.7%)	937 (99.6%)	4 (3.3%)	4 (0.4%)
	Placebo	128	976	125 (97.7%)	973 (99.7%)	3 (2.3%)	3 (0.3%)
MYK-461-006	Mavacamten	39	198	38 (97.4%)	196 (99.0%)	1 (2.6%)	2 (1.0%)
	Placebo	19	95	18 (94.7%)	94 (98.9%)	1 (5.3%)	1 (1.1%)
MYK-461-007	Mavacamten	167	778	163 (97.6%)	770 (99.0%)	4 (2.4%)	8 (1.0%)

4.4.3 PR

Table 5 lists the categorical analysis results for PR (less than 200 msec; between 200 and 220 msec and above 220 msec with and without 25% increase over baseline). Eight subjects treated with mavacamten in 4 studies experienced PR >220 msec and increase was greater than or equal to 25% from baseline PR values.

Table 5: Categorical Analysis for PR

	Pooled dose	Total (N)		Value <=220 msec		Value >220 msec & <25%		Value >220 msec & >=25%	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
MYK-461-005	Mavacamten	118	882	91 (77.1%)	770 (87.3%)	22 (18.6%)	107 (12.1%)	5 (4.2%)	5 (0.6%)

	Pooled dose	Total (N)		Value <=220 msec		Value >220 msec & <25%		Value >220 msec & >=25%	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
	Placebo	117	883	88 (75.2%)	757 (85.7%)	27 (23.1%)	120 (13.6%)	2 (1.7%)	6 (0.7%)
MYK-461-006	Mavacamten	35	175	29 (82.9%)	155 (88.6%)	5 (14.3%)	19 (10.9%)	1 (2.9%)	1 (0.6%)
	Placebo	15	72	13 (86.7%)	63 (87.5%)	2 (13.3%)	9 (12.5%)	0 (0%)	0 (0%)
MYK-461-007	Mavacamten	153	715	122 (79.7%)	620 (86.7%)	29 (19.0%)	93 (13.0%)	2 (1.3%)	2 (0.3%)
MYK-461-008		12	104	5 (41.7%)	74 (71.2%)	6 (50.0%)	29 (27.9%)	1 (8.3%)	1 (1.0%)

4.4.4 QRS

Table 6 lists the categorical analysis results for QRS (less than 120 msec and above 120 msec with and without 25% increase over baseline). Six subjects treated with mavacamten in three studies experienced QRS >120 msec and the increase was greater than or equal to 25% from baseline QRS values.

Table 6: Categorical Analysis for QRS

	Pooled dose	Total (N)		Value <=120 msec		Value >120 msec & <25%		Value >120 msec & >=25%	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
MYK-461-005	Mavacamten	123	941	92 (74.8%)	777 (82.6%)	27 (22.0%)	156 (16.6%)	4 (3.3%)	8 (0.9%)
	Placebo	128	976	95 (74.2%)	807 (82.7%)	27 (21.1%)	157 (16.1%)	6 (4.7%)	12 (1.2%)
MYK-461-006	Mavacamten	39	198	34 (87.2%)	178 (89.9%)	4 (10.3%)	19 (9.6%)	1 (2.6%)	1 (0.5%)
	Placebo	19	95	13 (68.4%)	66 (69.5%)	6 (31.6%)	29 (30.5%)	0 (0%)	0 (0%)
MYK-461-007	Mavacamten	167	778	131 (78.4%)	661 (85.0%)	35 (21.0%)	113 (14.5%)	1 (0.6%)	4 (0.5%)

4.5 EXPOSURE-RESPONSE ANALYSIS

Because exploratory analysis showed major differences in baseline QTc and exposure-response relationship, the reviewer conducted separate E-R analyses for healthy volunteers and for patients.

4.5.1 QTc – Healthy volunteers

The primary concentration-QTc analysis in healthy volunteers was conducted based on study 003. All subjects with baseline and at a least one post-baseline ECG with time-matched PK were included.

- Study 003 included a placebo control and a wide dose range. The multiple dose part was conducted in the fasting state. It provided the widest exposure range of all submitted clinical trials.
- Study 002 included a placebo control and Holter ECG data. This single dose study had a narrower exposure range as compared to study 003. The study used an oral

solution formulation that were not used in the other submitted clinical trials. PK/ECG data were reviewed in secondary analysis.

- Studies 010 and 014 do not include a placebo control for QTc assessment. In addition, study 014 only included 1 dose level and sparse PK/ECG data while study 010 used concomitant medication during the trial. These studies were not considered in the exposure-response analysis.

Prior to evaluating the relationship between drug concentration and QTc using a linear model, the three key assumptions were evaluated in exploratory analysis: 1) absence of significant changes in heart rate; 2) absence of delay between plasma concentration and ΔΔQTc; and 3) absence of non-linear relationship.

- Figure 5 shows the time course of drug exposure, ΔΔHR, and ΔΔQTc in study 003. A mean increase in HR >10 beats/min after repeated dosing at the highest tested dose (25 mg QD), however, it is not expected to impact the conclusion of QTc assessment for the clinically relevant dose range (2.5 to 15 mg QD).
- The change in HR and QTc appeared to be dose dependent. The sponsor did not collect intensive PK/ECG data to detect potential PK/PD hysteresis within each dosing interval, however, considering the wide exposure range and intensive sampling schedule during the time course of treatment, it is not expected that potential delay between plasma concentration and ΔΔQTc on the time scale of several hours will significantly impact the exposure-response analysis results.
- Figure 6 shows the relationship between drug concentration and ΔQTc. The figures suggests linear relationship in the exposure range up to 1500 ng/mL. There is apparent deviation from linearity in the high exposure range. It is noted that a similar trend of higher ΔQTcF with increasing mavacamten concentration was observed in study 010 (data not shown).

Figure 5: Time course of mavacamten concentration, ΔΔheart rate, and ΔΔQTc in study 003.

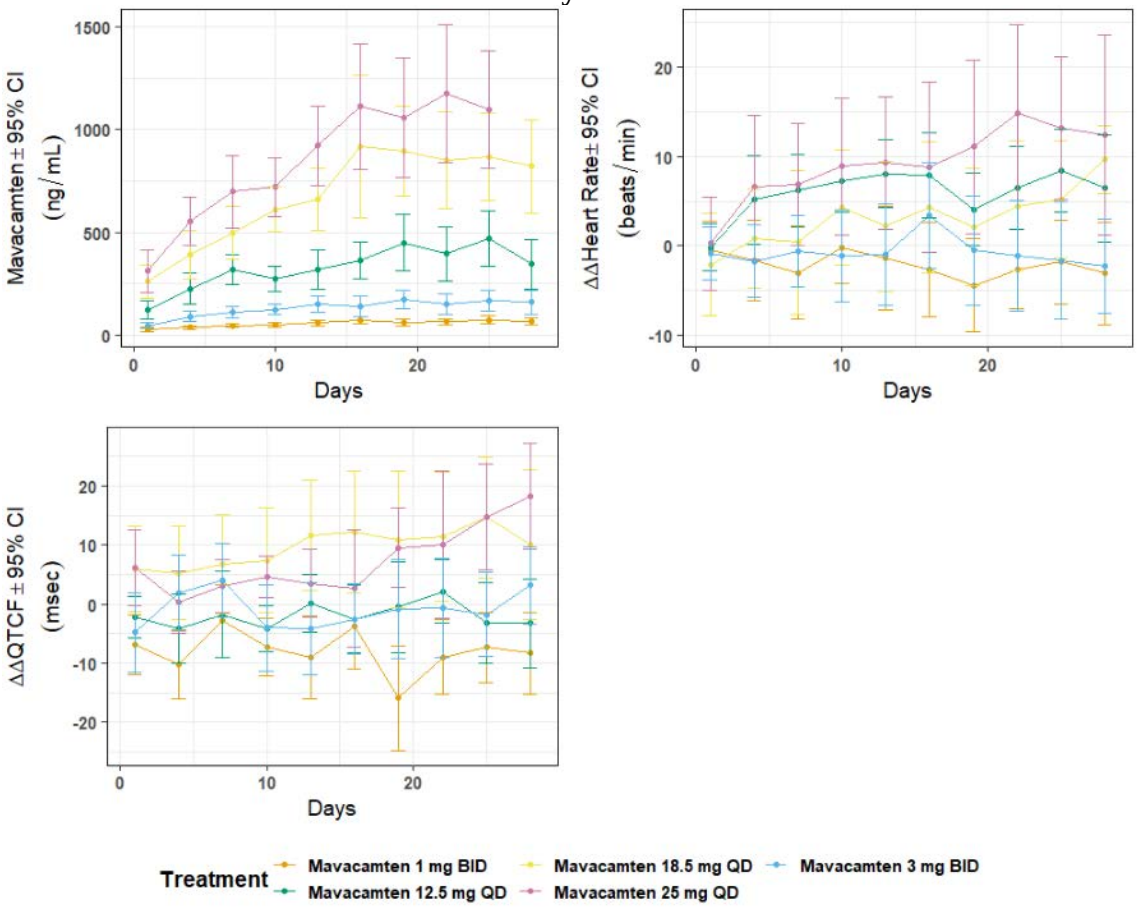
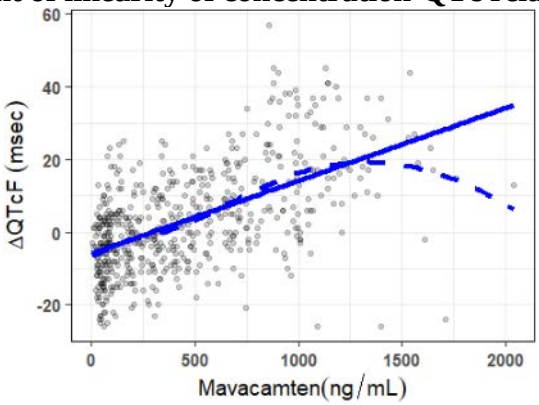


Figure 6: Assessment of linearity of concentration-QTc relationship (study 003)



When the White Paper model was applied to the data (ΔQTcF ~ 1 + concentration + treatment + study day + baseline QTc, with random effect on the intercept and slope), the goodness-of-fit plot is shown in Figure 7. The analysis suggested a positive exposure response relationship between mavacamten concentration and QTc increase. Predictions from the concentration-QTc model are provide in Table 7.

Figure 7: Goodness-of-fit plot for QTc

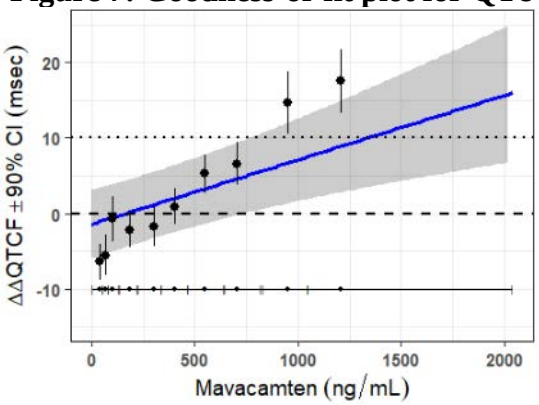


Table 7: Predictions from concentration-QTc model

Actual Treatment	Mavacamten (ng/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
Mavacamten 1 mg BID	75.8	-0.8	(-5.3 to 3.7)
Mavacamten 3 mg BID	178.6	0.1	(-4.3 to 4.5)
Mavacamten 12.5 mg QD	482.4	2.7	(-1.8 to 7.2)
Mavacamten 18.5 mg QD	1033.3	7.4	(1.8 to 13.0)
Mavacamten 25 mg QD	1194.0	8.8	(2.7 to 14.8)

Using the concentration-QTc model developed from study 003, the upper bound of 90% CI of predicted ΔΔQTcF at a geometric mean Cmax of 700 ng/mL is below 10 msec. However, the study does not provide sufficient exposure margin to waive the need of a positive control and to exclude a small mean effect at this exposure level.

In the secondary analysis on study 002, a trend for the dose dependent change in ΔΔQTc was not apparent (Figure 8). The linearity plot did not suggest a trend for positive exposure-response relationship between mavacamten concentration and ΔQTc. The reviewer did not conduct linear mixed effect modeling on the data.

Figure 8: Time course of mavacamten concentration, and ΔΔQTc in study 002.

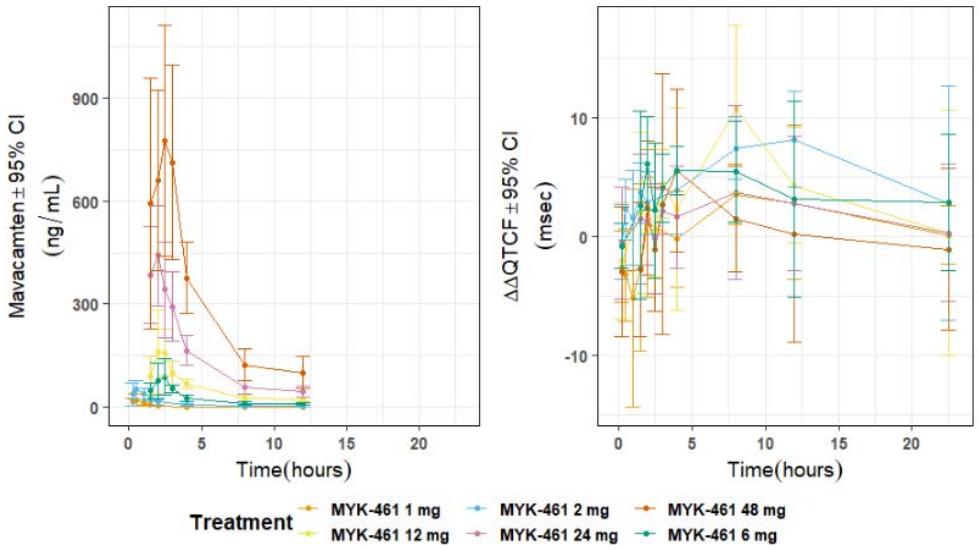
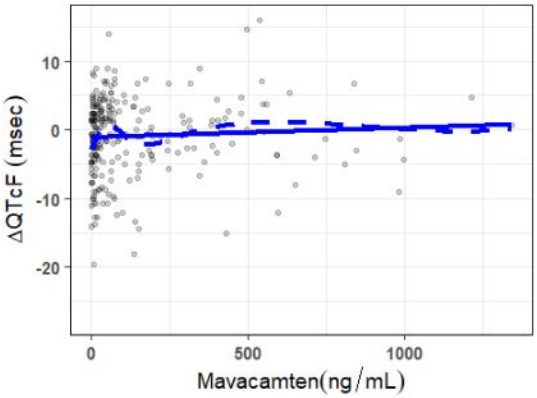


Figure 9: Assessment of linearity of concentration-QTc relationship (study 002)



4.5.2 QTc – Patients

The primary analysis in the patient population was conducted based on studies 005 and 006. All subjects with baseline and at a least one post-baseline ECG with time-matched PK were included. Studies 004, 007, and 008 were excluded from the primary analysis because these studies did not include a placebo control. In addition, studies 007 and 008 were extension studies with overlapping population and prior treatment from other trials.

The key assumptions for linear mixed effect modeling were evaluated in exploratory analysis.

Figure 2 shows the time course of ΔΔHR in the two studies and did not suggested a significant heart rate effect in the study populations. Figure 10 shows the time course of mavacamten concentration and ΔΔQTcF and does not appears to suggest a delay between trough concentration and QTc changes during the course of treatment when drug exposure steadily increase and remain relatively stable. Figure 13 shows the relationship between drug concentration and ΔQTcF in studies 004, 005, and 006. The figure supports the use of a linear model and a common slope in studies 005 and 006. The relationship between mavacamten concentration and ΔQTc in study 004 appears similar to those in studies 005 and 006, showing a trend for lower ΔQTcF with increasing concentration in a wider exposure range.

Figure 10: Time course of mavacamten concentration and ΔΔQTc.

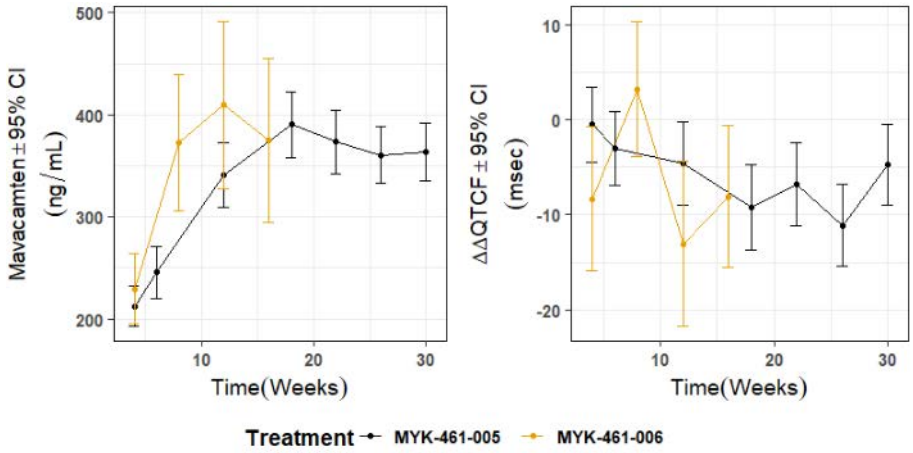
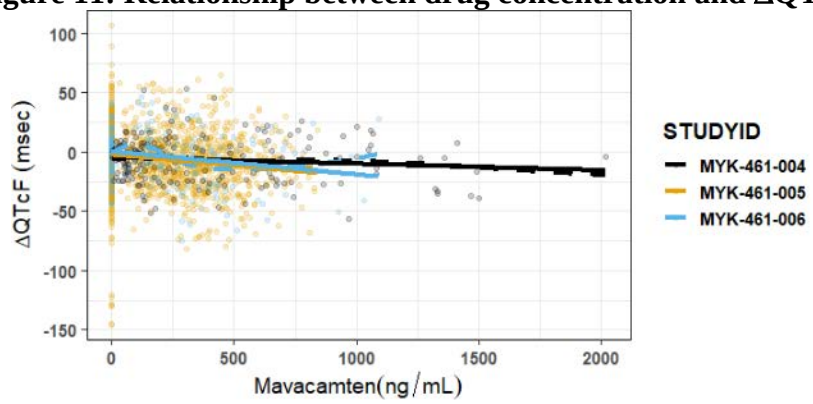


Figure 11: Relationship between drug concentration and ΔQTcF.



Linear mixed effect model was applied to data from studies 005 and 006. The results do not suggest a positive exposure-response relationship in the two studies (Figure 12). The predictions are shown in Table 8.

Figure 12: Goodness-of-fit plot for QTc

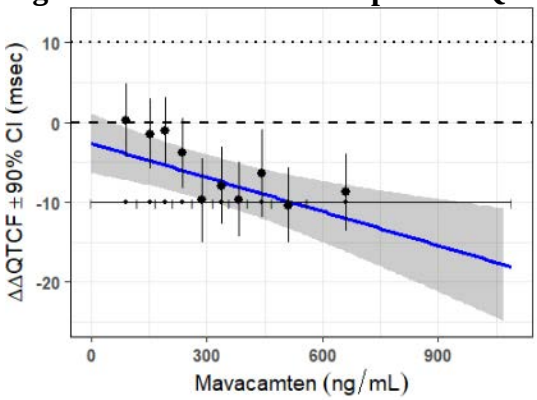


Table 8: Predictions from concentration-QTc model

Study ID	Mavacamten (ng/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
MYK-461-005	407.5	-8.4	(-11.4 to -5.4)
MYK-461-006	392.1	-8.2	(-11.2 to -5.2)
Sponsor's reported $C_{max,ss}$ (study 005)	452.0	-9.0	(-12.2 to -5.9)

4.5.3 Assay sensitivity

Not applicable.

5 APPENDIX I: REVIEW OF SUPPORTING NONCLINICAL DATA

Mavacamten (MYK-461) is a cardiac myosin inhibitor indicated for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in adults to improve exercise capacity, symptoms, (b) (4) The ΔQTcF vs concentration model revealed a positive slope for healthy volunteers and negative slope for oHCM and nHCM population. The nonclinical cardiovascular safety pharmacology data were evaluated to compare with clinical results, and multi-cardiac ion channel pharmacology were reviewed to understand the mechanistic basis of clinical ECG changes.

5.1 In vivo cardiovascular safety pharmacology evaluation

5.1.1 Sponsor's submission

Effects of mavacamten on cardiovascular safety and ECG parameters were evaluated in two *in vivo* studies in dogs (NC-15-0007 and NC-20-0060).

In the GLP study NC-15-0007, a total of 16 male Beagle dogs (4/group), previously implanted with telemetry devices, were administered 0 (0.5% methylcellulose in distilled water), 1, 3, or 10 mg/kg MYK-461, via oral gavage, in a single-dose experimental design. Blood samples were obtained for toxicokinetic analysis from all animals at 24 hours, 8, 15, 22 and 29 days after initial dose administration. At 10 mg/kg, mavacamten caused significant QTc prolongations at day 1 from 1 to 7 hours after dosing, and day 8. QTc were increased by 11-27 ms on day 1 from 1-7 hours, and by 18-30 ms on day 8. In addition, a single oral dose of 3 or 10 mg/kg produced a higher incidence of ventricular escape beat in 2 dogs up to Week 3. The mean Cmax at 10 mg/kg dose was 729 ng/mL.

Study NC-20-0060 (GLP compliant) evaluated the chronic in vivo effects of mavacamten on ECG parameters. A total of 4 male Beagle dogs received both a placebo (on Day 1) and mavacamten (on Days 2 to 15) via a dosing regimen designed to achieve sustained supra-therapeutic exposures over a 14-day period (1.5 mg/kg twice daily on Day 1, 0.3 mg/kg/day on Days 2 to 15 PO). QTcF prolongations reached 19 ± 2 msec at the end of the study (Day 15) and was due (primarily) to lengthening of the JTp (19 ± 4 ms on D15). Negligible changes were observed in the terminal portion of repolarization (Tpe: 3 ± 2 ms on D15). The mean Cmax of mavacamten were 415 ± 48 ng/mL on Day 8 and 426 ± 54 ng/mL on Day 15.

5.1.2 Reviewer's assessment

The results of in vivo studies are summarized in the following table:

Table 9. Summary of mavacamten on QTc changes in dog studies

	NC-15-0007	NC-20-0060
GLP	Yes	Yes
Species	Beagle Dogs (4 animals in 4 groups)	Beagle Dogs (4 animals)
Dose	0, 1, 3 and 10 mg/kg, single PO	1.5 mg/kg bid on day one; 0.3 mg/kg days 2 to 15, PO
Cmax	729 ng/mL (10 mg/kg)	415 ng/mL on Day 8; 426 ng/mL on Day 15
QTc	10 mg/kg group: Prolonged by 11-27 ms 1-7 hours after dosing; Prolonged 18-30 ms on day 8.	Prolonged by 19 ms on Day 15; JTp prolonged by 19 ms on Day 15; no effect on TPe interval.
Positive control	No	No

Cmax in human: 439 ng/mL on day 28, 12.5 mg qd.

In summary, the cardiovascular safety pharmacology in dogs showed that oral administration of mavacamten caused QTc prolongations. Mavacamten prolonged J-Tpeak interval and didn't affect the Tp-e interval in dogs. No positive controls were used in both in vivo studies.

5.2 Multi-cardiac ion channel assessment

The sponsor evaluated effects of mavacamten (MYK-461) and its major metabolite MYK-1078 on hERG current Cav1.2 and Nav1.5 (peak and late) currents in recombinant cell lines or in human myocytes using manual or automated whole cell patch clamp methods. In addition, hERG trafficking inhibition was also assessed by monitoring surface expression of the wild-type (WT) hERG channel.

5.2.1 Sponsor's submission

5.2.1.1 hERG assay

There are two manual hERG studies (NC-14-0061 , NC-20-0061) and three automated hERG studies (NC-19-0034 , NC-19-0035, and NC-20-0039). The manual hERG studies were conducted at 33–35°C or 37°C; the automated hERG studies were conducted at room temperature.

The hERG study (NC-20-0061) assessed the effects of mavacamten and MYK-1078 on IKr in human myocytes using manual patch clamp method. The experiments were performed at 37°C using a voltage protocol that is different from the recommended hERG current protocol by the FDA (link). Mavacamten and MYK-1078 inhibited the IKr current by 5.5% and 34.1%, respectively, at the concentration of 3 µM.

The GLP hERG study report (NC-14-0061) describes the potential effects of mavacamten on the hERG current in HEK293 cells. The hERG current was assessed at a temperature of 33-35 °C, using a voltage that is similar to the recommended hERG current protocol by the FDA (link). Each recording ended with a final application of a supramaximal concentration of the reference substance (E-4031, 500 nM) to assess the contribution of endogenous currents. The positive control (60 nM terfenadine) inhibited hERG potassium current by 80 ± 2.8% (Mean ± SD, n=2). Samples of the test article formulations (nominal concentrations at 10 and 60 µM) collected from the outflow of the perfusion apparatus were analyzed for concentration verification. These results were within ± 5.0% of nominal, thereby meeting the acceptance criteria. Mavacamten inhibited hERG currents by 5 % at 10 µM and 9.6 % at 60 µM. The IC50 of mavacamten on hERG was expected to be greater than 60 µM.

The sponsor assessed the effects of mavacamten (NC-19-0034) and metabolite MYK-1078 (NC-19-0035) on hERG currents in HEK cells using an automated patch clamp system (Qpatch). The hERG current was assessed at room temperature, using a step-step voltage protocol (from a holding potential of -80 mV to +40 mV for 2 s, followed by a 2 s repolarizing pulse to -40 mV) that is different from the recommended hERG current protocol by the FDA (link). The positive control cisapride (50 nM) inhibited the hERG current by 65.7%. No drug concentration was verified in this study. Mavacamten (30 µM) and MYK-1078 (30 µM) inhibited the hERG currents by 7.8% and 4%, respectively.

The IC50s of mavacamten and MYK-1078 against hERG are provided below:

Table 10: Effects of Mavacamten and MYK-1078 on hERG Current

Study	Manual or automated	concentration verification	mavacamten IC_{50} (µM)	MYK-1078 IC_{50} (µM)
NC-14-0061	Manual	Yes	>60	N/A
NC-20-0061	Manual	No	>3	>3
NC-19-0034	Automated	No	>10	N/A
NC-19-0035	Automated	No	>30	>30
NC-19-0039	Automated	No	>30	>30

5.2.1.2 The hERG trafficking inhibition assay

In the hERG trafficking inhibition assay (NC-19-0040), the sponsor assessed the effects of mavacamten and MYK-1078 on surface expression of the hERG channel. Average surface expression in the presence of each test article concentration was normalized to the average for vehicle control. Both mavacamten and MYK-1078 were tested at concentrations of 0.1, 0.3, 1, 3, 10 and 30 µM, respectively. None of the test articles included in this study resulted in a significant decrease in hERG-WT surface expression at any concentration tested. The positive control geldanamycin (1 µM) produced the expected result with greater than a 30% decrease in hERG surface expression.

5.2.1.3 Cav1.2 assay

There is a manual patch clamp study (NC-20-0061) and two automated patch clamp studies (NC-19-0034, NC-19-0035) for assessment of mavacamten and MYK-1078 on Cav1.2 current. Manual patch clamp study was conducted at 37°C and automated patch clamp studies were conducted at room temperature, using a protocol with a depolarizing step to 0 mV (150 msec) from a holding potential of -40 mV, repeated at 5 s intervals. Positive controls (verapamil in study NC-20-0061 and nifedipine in study NC-19-0034 and NC-19-0035) inhibited the Cav1.2 by 55% (0.5 µM verapamil) or 92.6 (1 µM nifedipine). Drug concentrations were not verified in Cav1.2 studies.

Table 11. Effects of mavacamten and MYK-1078 on Cav1.2 current

Study	Manual or automated	Concentration verification	mavacamten IC_{50} (µM)	MYK-1078 IC_{50} (µM)
NC-20-0061	Manual	No	>30	> 30
NC-19-0034	Automated	No	>10	N/A
NC-19-0035	Automated	No	>30	>30

5.2.1.4 Peak Nav1.5 assays

The automated patch clamp studies (NC-19-0034 and NC-19-0035) assessed the effects of mavacamten and MYK-1078 on peak Nav1.5 current. Peak Nav1.5 current was assessed at room temperature, using a voltage protocol consisting of a hyperpolarizing step from -80 mV to +20 mV (300 msec), at 10 s interval. Positive control lidocaine at 2 mM inhibited the Nav1.5 current by 69.8%. Drug concentrations were not verified in the assay. Mavacamten and MYK-1078 inhibited the Nav1.5 currents by 3.6% and 2.7%, at 30 µM, respectively.

Table 12. Effects of mavacamten and MYK-1078 on peak Nav1.5 current

Study	Manual or automated	Concentration verification	mavacamten IC_{50} (µM)	MYK-1078 IC_{50} (µM)
NC-19-0034	Automated	No	>10	N/A
NC-19-0035	Automated	No	>30	>30

5.2.1.5 Late Nav1.5 assays

The manual patch clamp study(NC-20-0061) assessed effects of the mavacamten and MYK-1078 on late Nav1.5 current in CHO cells and in native myocytes. The late Nav1.5 was recorded at 37°C and in the presence of 50 µM veratridine, using a voltage protocol consisting of a pre-pulse from -80 mV to -15 mV (50 msec), followed by a depolarizing step to 40 mV (200 msec). The voltage waveform was repeated every 10 seconds. Late Nav1.5 was measured at the end of the -15 mV pulse. Positive control ranolazine at 7µM inhibited the late sodium current by 62.1%. Drug concentrations were not verified in the assay.

Table 13. Effects of mavacamten and MYK-1078 on late Nav1.5 currents

Study	Manual or automated	Concentration verification	Acute or chronic	mavacamten IC_{50} (µM)	MYK-1078 IC_{50} (µM)
NC-20-0061	Manual (cell line)	No	Acute	> 30 (40.4%)	10.9
NC-20-0061	Manual (myocyte)	No	chronic	30.4	9.4

5.2.2 Reviewer's assessment and data reanalysis

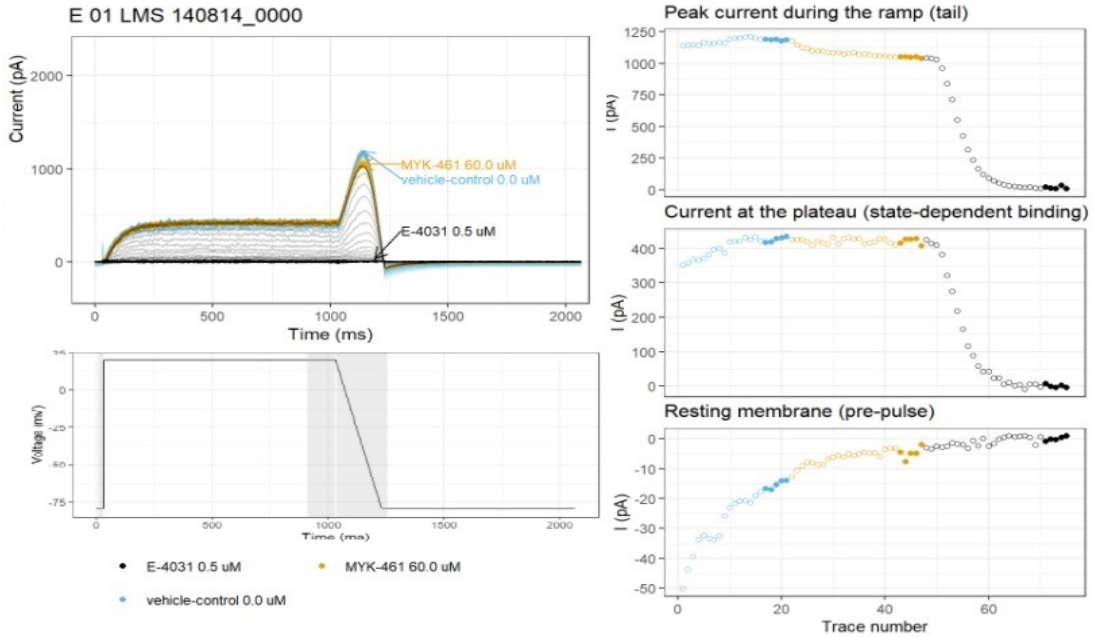
Original electrophysiology records for one hERG assay (study NC-14-0061) were provided by the sponsor. An IRT reviewer reanalyzed these records to assess data quality and verify study report conclusions. For data quality assessment, holding current from all traces were examined to verify stability, and time course plots were constructed to verify that current amplitude in control solution were stable prior to drug application, and that drug effects reached steady state. In addition, reviewers also provided assessment on other ion studies based on sponsor's reports.

5.2.2.1 hERG assay

The voltage protocols used and stimulation frequencies are quite similar to that recommended by the FDA (link), and the reviewer does not anticipate protocol differences to impact hERG current pharmacology.

Representative analysis from one cell of hERG study (E 01 LMS 140814_0000) is shown in **Figure 13**. The top left panel shows all recorded traces from this cell; the bottom left panel, voltage waveform used to evoke hERG current (shaded gray region highlights where peak hERG tail current was measured). Traces recorded in control solution are shown in blue, following 60 µM mavacamten application in orange; and following application of E-4031, a selective hERG blocker, in black. Time course plots (peak ramp current, step current and resting membrane current) of hERG current are shown on the right panel.

Figure 13: Representative hERG assay from cell E 01 LMS 140814_0000



HERG current amplitudes from the last 5 traces acquired in control (blue solid circles) and in drug solutions were then averaged to calculate % inhibition by that concentration. E-4031 subtraction was performed to eliminate those non-hERG currents. Results of mavacamten and positive control on hERG current are summarized in **Table 14**.

Table 14. Effects of mavacamten on hERG current

Test article	N	Mean (%)	SD (%)	SEM(%)
Vehicle Control	3	6.0	4.8	2.8
mavacamten 10 µM	4	9.7	2.0	1.0
mavacamten 60 µM	4	12.3	2.2	1.1
Terfenadine 60 nM	2	77.5	4.2	3.0

While there are numerical differences in the results from FDA's independent analysis compared to the sponsor's, these do not change overall interpretation and conclusions. That is, FDA's independent analysis of the submitted electrophysiology data shows that maralixibat acutely inhibited hERG current by 9.7% and 12.3% at 10 µM and 60 µM, respectively. Thus, IC50 is far greater than 60 µM and cannot be determined from this study.

Those hERG assays (NC-20-0061, NC-19-0034, NC-19-0035, and NC-19-0039) didn't meet the best practice according to the draft S7B Q&As (e.g., no drug concentration verification or performed at room temperature). The safety margins of mavacamten and its metabolite against hERG currents are provided in the following table:

Table 15: **Safety margins of mavacamten on hERG current**

	Cmax (ng/mL)	Protein Binding	Free Cmax (ng/mL)	hERG IC50 (µM)	Mol Weight (g/mol)	Safety Margin (Ratio)
Mavacamten	439	93.1%	30.2	>60	273.3	> 542x
MYK-1078	<22	N/A (0%)	<22	>30	292.1	>398x

Cmax was 439 ng/mL with 12.5 mg QD, at Day 28. MYK-1078 <5% parent exposure.

5.2.2.2 Cav1.2 assay

The manual patch clamp study (NC-20-0061) and two automated patch clamp studies (NC-19-0034 , NC-19-0035) didn't verify drug concentrations, and two automated patch clamp studies were performed at room temperature. The safety margins of mavacamten and its metabolite against Cav1.2 currents are provided in the following table:

Table 16: **Safety margin of mavacamten on Cav1.2 current**

	Cmax (ng/mL)	Protein Binding	Free Cmax (ng/mL)	hERG IC50 (µM)	Mol Weight (g/mol)	Safety Margin (Ratio)
Mavacamten	439	93.1%	30.2	>30	273.3	> 271x
MYK-1078	<22	N/A (0%)	<22	>30	292.1	>398x

Cmax was 439 ng/mL with 12.5 mg QD, at Day 28. MYK-1078 <5% parent exposure.

5.2.2.3 Nav1.5 peak current

Two automated patch clamp studies ((NC-19-0034 , NC-19-0035) were performed at room temperature and drug concentrations were not verified. The safety margins of mavacamten and its metabolite against Nav1.5 currents are provided in **Table 17**:

Table 17: **Safety margin of mavacamten on Nav1.5 current**

	Cmax (ng/mL)	Protein Binding	Free Cmax (ng/mL)	hERG IC50 (µM)	Mol Weight (g/mol)	Safety Margin (Ratio)
Mavacamten	439	93.1%	30.2	>30	273.3	> 271x
MYK-1078	<22	N/A (0%)	<22	>30	292.1	>398x

Cmax was 439 ng/mL with 12.5 mg QD, at Day 28. MYK-1078 <5% parent exposure.

5.2.2.4 Nav1.5 late current

The manual patch clamp study (NC-20-0061) assessed effects of the mavacamten and MYK-1078 on late Nav1.5 current in CHO cells and in native myocytes. The late Nav1.5 was recorded at 37oC and in the presence of 50 µM veratridine. However, data have shown that veratridine may damage the channel pore and change the channel gating. FDA has recommended voltage protocol and current enhancer (ATX-II) for late Nav1.5 assay. In addition, the drug concentrations were not verified in the study. The safety margins of mavacamten and its metabolite against Nav1.5 currents are provided in the following table:

Table 18: **Safety margin of mavacamten on late Nav1.5 current**

	Cmax (ng/mL)	Protein Binding	Free Cmax (ng/mL)	hERG IC50 (µM)	Mol Weight (g/mol)	Safety Margin (Ratio)
Mavacamten	439	93.1%	30.2	30.4	273.3	275x
MYK-1078	<22	N/A (0%)	<22	9.4	292.1	>125x

Cmax was 439 ng/mL with 12.5 mg QD, at Day 28. MYK-1078 <5% parent exposure.

5.3 Summary

The in vitro hERG assay NC-14-0061 met the best practice considerations for an in vitro assay according to the new ICH S7B Q&A 2.1 (link). The hERG safety margin of mavacamten and MYK-1078 is provided in **Table 19**:

Table 19: Safety margins of mavacamten and MYK-1078 on hERG channel

	Cmax (ng/mL)	Protein Binding	Free Cmax (ng/mL)	hERG IC50 (µM)	Mol Weight (g/mol)	Safety Margin (Ratio)
Mavacamten	439	93.1%	30.2	>60	273.3	> 542x

MYK-1078	<22	N/A (0%)	<22	>30	292.1	>398x

Cmax was 439 ng/mL with 12.5 mg QD, at Day 28. MYK-1078 <5% parent exposure.

The assay results showed mavacamten and MYK-1078 had safety margins > 542x (12.3.6% at 60 µM) and > 398x (4% at 30 µM), respectively, indicating that mavacamten and MYK-1078 don't acutely interact with hERG current. Both mavacamten and MYK-1078 didn't affect the hERG-WT surface expression at any concentration up to 30 µM, indicating mavacamten and MYK-1078 don't chronically interact with hERG current.

The mechanisms of mavacamten-induced QT prolongations in dogs remain unknown.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	June 22, 2021
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214998
Product Name, Dosage Form, and Strength:	Camzyos (mavacamten) Capsules, 2.5 mg, 5 mg, 10 mg, and 15 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	MyoKardia, Inc.
FDA Received Date:	January 28, 2021 and May 13, 2021
OSE RCM #:	2021-190
DMEPA Safety Evaluator:	Mariette Aidoo, PharmD, MPH
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

MyoKardia, Inc. (MyoKardia) submitted a 505(b)(1) for Camzyos (mavacamten) capsules under NDA 214998. Camzyos is being proposed for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in adults to improve functional capacity, (b) (4) and symptoms.

We evaluated the proposed Camzyos Prescribing Information (PI), Medication Guide, and container labels for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

MyoKardia submitted a 505(b)(1) New Drug Application for Camzyos (mavacamten), an allosteric, selective, and reversible inhibitor of cardiac myosin being proposed for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in adults to improve functional capacity, (b) (4) and symptoms.

We performed a risk assessment of the proposed container label, prescribing information (PI) and Medication Guide for Camzyos to identify deficiencies that may lead to medication errors and areas for improvement. We note the container labels have multiple pages which have to be peeled to read the subsequent information. As such, we sent an Information Request (IR) on May 6, 2021 to MyoKardia asking for an image depicting the bottle bearing the labels to show how the information will be presented. On May 14, 2021 MyoKardia responded by providing images depicting the extended content label (ECL), images depicting the bottle bearing the ECL showing how the information will be presented upon peeling the label back and a 3D rendering

of the ECL. They indicated that due to the small bottle size, an ECL was proposed to ensure compliance with the April 2013 FDA Draft Guidance for industry. Additionally, DMEPA sought guidance from the Division regarding the enlargement of the product container in order to ensure all relevant information could be placed on a single label so as to alleviate the need for a 3-ply label. However, the team concluded this was not a viable option as stability studies in the proposed bottle have been completed.

Our review of the proposed Camzyos PI, Medication Guide, and container labels identified areas of vulnerability that may lead to medication errors. For the Division, we recommend inclusion of the route of administration and clarity on the dosage amount required for incremental titration every 12 weeks based on echocardiograph assessment of the left ventricular ejection fraction (LVEF). For the Applicant we recommend revisions to the information presented on the principle display panel (PDP) (e.g. recommended dosage statement, prominence of established name, position of the net quantity statement and linear barcode as well as the name of the manufacturer).

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Camzyos Prescribing Information, Medication Guide, and container labels may be improved to promote the safe use of this product from a medication error perspective. We provide recommendations below in Section 4.1 for the Division and Section 4.2 for the Applicant.

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. We recommend replacing all instances of 'Tradename' with the conditionally acceptable proprietary name 'Camzyos'.

B. We recommend removing [redacted] (b) (4) and consider including the route of administration (i.e. orally) after the dose throughout the Highlights and Section 2 of the PI [redacted] (b) (4)

   1. For example, revise as follows: [redacted] (b) (4)

C. Highlights of Prescribing Information (HPI)

   1. Dosage and Administration Section

      a. [redacted] (b) (4)

b. (b) (4)

D. Full Prescribing Information (FPI)

1. Dosage and Administration Section

a. (b) (4)

b.

c.

d.

e. We note the inclusion of the statement in the Medication Guide that the capsules should be swallowed whole without breaking, opening, (b) (4), or chewing. However, this information is not present in Section 2. We recommend adding the statements "Swallow capsules whole. Do not break, open, or chew the capsules.".

f. We note the inclusion of the statement in the Medication Guide on what should be done if a dose is missed. However, this information is not present in Section 2. We recommend including "If a dose of Camzyos is not taken at the scheduled time wait and take the dose at the normal schedule the following day. Do not take extra doses of Camzyos to make up for the missed dose.".

2. Dosage Forms and Strengths

(b) (4)

3. How Supplied/Storage and Handling Section

a. As currently presented, there is a hyphen (-) in between the temperature ranges. Revise the storage information to read:

    i. Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (between 59°F to 86°F). [See USP for controlled room temperature].

4. Medication Guide
    a. For improved clarity and readability, revise the bolded REMS statement to: "**Because of the serious risk of heart failure** (b) (4) **[TRADENAME] is only available through a restricted program called the [TRADENAME] Risk Evaluation and Mitigation Strategy (REMS) Program."**
    b. We note information describing the REMS Program is outlined in the Medication Guide. We defer for the team on the need to include this type of information in the Medication Guide.

4.2 RECOMMENDATIONS FOR MYOKARDIA, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels
    1. We recommend replacing all instances of the proprietary name placeholder [TRADENAME] with the conditionally acceptable proprietary name 'Camzyos'.
    2. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product's linear barcode to each individual bottle as required per 21CFR 201.25(c)(2). In addition, consider orienting the linear barcode to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to vial curvature.[a]
    3. Per 21 CFR 208.24(d) we recommend adding the following statement on the principal display panel "Dispense the enclosed Medication Guide to each patient" or similar statement.
    4. To ensure consistency with the terminology in the Prescribing Information, revise the recommended dosage statement from (b) (4) to the following: "Recommended Dosage: See Prescribing Information."
    5. The net quantity statement is in close proximity to the product strength. Relocate the net quantity statement away from the product strength, such as to the bottom left corner of the principle display panel. From post-marketing

[a] Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.

6. As currently presented the statement "Rx Only" appears in bold and more prominent than other important information on the container label. We recommend decreasing the font and debolding "Rx only" as currently presented it is competing in prominence with other information on the principal display panel.

7. As currently presented, there is a hyphen (-) in between the temperatures. Revise the storage information to read: Store at "20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (between 59°F to 86°F). [See USP for controlled room temperature.]" for consistency with the Prescribing Information.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Camzyos received on January 28, 2021 from MyoKardia, Inc., and the listed drug (LD).

Table 2. Relevant Product Information for Camzyos	
Initial Approval Date	N/A
Active Ingredient	(mavacamten)
Indication	Approved for the treatment symptomatic obstructive hypertrophic cardiomyopathy (oHCM) in adults to improve functional capacity, (b) (4) and symptoms.
Route of Administration	Oral
Dosage Form	capsules
Strength	2.5 mg, 5 mg, 10 mg, and 15 mg
Dose and Frequency	2.5 mg to 15 mg/day (One capsule daily) Recommended starting dose is 5 mg orally once daily. *Maximum dose: 15 mg once daily.
How Supplied	30-count bottle
Storage	Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C to 30°C (between 59°F to86°F) *[see USP Controlled Room Temperature]*.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 20, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, camzyos and mavacamten. Our search identified no previous reviews, and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX F. INFORMATION REQUEST

On May 6, 2021, we sent the following information request to the Applicant:

We refer to your NDA 214998 for Camzyos (mavacamten) capsules submitted January 28, 2021.

We note the container labels have multiple pages which have to be peeled to read the subsequent information. Please provide an image depicting the bottle bearing the labels to show how information will be presented when peeled back.

Please respond to this request by close of business May 14, 2021.

On May 13, 2021, the Applicant responded with images highlighting:

1. Extended content label (ECL) images depicting the bottle bearing the ECL showing how information will be presented when the label is peeled back

2. 3D rendering of the ECL

The applicant indicates that due to the bottle size, an ECL is proposed to ensure compliance with the April 2013 FDA Draft Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*. Of note, the final design of the ECL is not yet complete; the images provided are mockups to assist the Agency in visualizing the ECL, and the final ECL may differ from the provided images.

(b) (4)

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