Official Title of Study:

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

NCT Number: NCT03496168

Document Date (Date in which document was last revised): 27 October 2021

CLINICAL STUDY PROTOCOL

Protocol Number:	MYK-461-008
Protocol Title:	**AN OPEN-LABEL EXTENSION STUDY OF MAVACAMTEN (MYK-461) IN ADULTS WITH SYMPTOMATIC OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY PREVIOUSLY ENROLLED IN STUDY MYK-461-004 (PIONEER-HCM)**
Indication:	Hypertrophic Cardiomyopathy
Phase:	2
Investigational Medicinal Product:	Mavacamten (MYK-461)
Sponsor:	MyoKardia, Inc. 1000 Sierra Point Parkway Brisbane, CA 94005 USA
Key Sponsor Contacts:	[redacted] Medical Monitor [redacted] [redacted] Clinical Trial Lead [redacted]
Original Protocol Date	12 January 2018
Amendment 1	03 April 2018
Amendment 2	11 April 2019
Amendment 3	22 January 2021
Amendment 4	27 October 2021

Confidentiality Statement

PROTOCOL AMENDMENT
SUMMARY OF CHANGES TABLE

Protocol Amendment 4: 27 October 2021

Overall Rationale for the Amendment

The primary objectives of this amendment were to:

- Align the protocol language with updates to the Investigator's Brochure (IB) Ed 8.1
- Add an additional telehealth visit at Week 222

Changes are summarized in the table below.

Summary of Changes

Additional changes were made to add clarity, consistency in terminology, and accuracy throughout the document.

Summary of Change	Reason for Change	Section(s)
Home health assessments were removed and direct-to-participant delivery of mavacamten was retained	Home health assessments removed due to stabilization of COVID-19 pandemic	Global
[redacted] Medical Monitor [redacted]	Email address updated	Title Page
[redacted] **Clinical Trial Lead** [redacted]	[redacted] added as a Key Sponsor Contact	Title Page
Added telehealth assessment to Week 222	Administrative error - this was missed in protocol amendment 3	Synopsis, Table 3, Study Schema
Participants must use highly effective birth control from ~~43~~ months after last dose of investigational medicinal product	Align with IB Ed 8.1	Synopsis, Section 5.2., Section 8.2.2., Section 8.2.3.
The following abbreviations were deleted: ECHO = echocardiogram ID = identification MAD = multiple ascending dose SAD = single ascending dose	These abbreviations are not used in the body of protocol amendment 4	List of Abbreviations
Updated information on completed and ongoing studies with mavacamten and number of participants enrolled	Align with IB Ed 8.1	Section 1.2.

Summary of Change	Reason for Change	Section(s)
Updated text describing clinical benefits and known risks of mavacamten	Align with IB Ed 8.1	Section 1.3.
Updated Study Schema to include telehealth visit at Week 222 and Early Termination	To align with Table 3	Study Schema
Deleted IMP Compliance for Week 222	Week 222 is now a telehealth visit	Table 3
Updated text on symptomatic overdose	Align with IB Ed 8.1	Section 7.6.
Added term **dizziness** as a likely risk of mavacamten use	Align with IB Ed 8.1	Section 8.1.
Updated so participants will report pregnancies any time from first dose to **4**~~3~~ months after last dose of mavacamten	Align with IB Ed 8.1	Section 8.2.3.
Participants must abstain from blood or plasma donation for ~~3~~**4** months after the final study visit	Align with data on long terminal elimination half-life of mavacamten in IB Ed 8.1	Section 9.4.

PROTOCOL SYNOPSIS

Title	An Open-label Extension Study of Mavacamten (MYK-461) in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy Previously Enrolled in Study MYK-461-004 (PIONEER-HCM)
Study Number	MYK-461-008
Study Phase	2
Number of Centers	Up to 5 sites in the United States
Primary Objective	To assess the long-term safety and tolerability of mavacamten in individuals with symptomatic obstructive hypertrophic cardiomyopathy (oHCM)
Secondary Objectives	To assess in individuals with symptomatic oHCM the long-term effects of mavacamten on: • Left ventricular outflow tract (LVOT) obstruction • Functional capacity • oHCM symptoms
Pharmacokinetic Objective	To perform population pharmacokinetics (PK) analyses in individuals with symptomatic oHCM receiving mavacamten
Study Design	This is a Phase 2, open-label, multicenter study of adults with symptomatic oHCM who completed Study MYK-461-004 (PIONEER-HCM). Participants in this study will be screened to ensure they continue to meet eligibility criteria. Participants are allowed to stay on background therapy with either beta blockers or calcium channel blockers. Background cardiomyopathy therapy (eg, beta-blocker, verapamil, or diltiazem) may be adjusted or stopped after a participant has received 24 weeks of mavacamten treatment in this study as determined by the Investigator in conjunction with the MyoKardia Medical Monitor. Once enrolled into Study MYK-461-008, participants will undergo baseline assessments and receive mavacamten once daily (QD) for a duration of up to approximately 5 years or until mavacamten becomes commercially available (at the discretion of MyoKardia). Target dosing will be individualized for each participant based on his or her PK data obtained in the MYK-461-004 study. Specifically, the Target Dose for each participant will be individualized to obtain a steady-state trough plasma concentration of approximately 250 ng/mL to 500 ng/mL, based on PK modeling. The starting dose will be 5 mg for all participants. Participants will return at Week 4 (± 4 days) for a plasma PK sample to measure drug levels and to undergo echocardiography to determine LVOT gradient (at rest, after a Valsalva maneuver, and after exercise) and left ventricular ejection fraction (LVEF). Participants will return at Week 6 (± 7 days) for evaluation of Week 4 results and dose adjustment to Target Dose.

	Dose adjustment may also take place beyond Week 6 based on results of transthoracic echocardiogram (TTE), stress echocardiography and/or PK evaluation and based upon the opinion of the Investigator in conjunction with the MyoKardia Medical Monitor. A stress echocardiogram will be administered at Week 48 and Week 72 to evaluate the post-exercise LVOT gradient and to determine whether further dose adjustment may be needed. If the post-exercise LVOT gradient is measured ≥ 50 mmHg, further dose adjustment may be considered and discussed with the MyoKardia Medical Monitor. Dose adjustments beyond the Target Dose may only be exceeded for each given participant following discussion between the Investigator and the MyoKardia Medical Monitor. Lower doses are permissible. The dose will not be increased if one or more of the following criteria are met: • LVEF is < 55%, and/or • LVOT gradient is < 30 mmHg after exercise, and/or • Trough mavacamten plasma concentration is > 350 ng/mL, and/or • A dose increase is not warranted in the clinical judgment of the Investigator Dose Reduction Rule: The dose may be reduced or discontinued in the case of an exaggerated pharmacologic effect at any time during the study based on the clinical judgment of the Investigator. Participants who have had a dose adjustment (either in mavacamten or background cardiomyopathy therapy) should return to the clinic approximately 28 days later (± 7 days) for an unscheduled visit with resting TTE to confirm safety. Repeat of post-exercise echocardiographic assessment of LVOT gradient will be at the Investigator's discretion. Based on results and clinical symptoms at follow-up visits, subsequent dose adjustments will be discussed with the MyoKardia Medical Monitor. Temporary Discontinuation: If results as reported by the central laboratories from any visit show mavacamten plasma concentration is ≥ 1000 ng/mL, or LVEF < 50% (as read by site), or Fridericia-corrected QT interval (QTcF) meets the following criteria, the participant will be notified by the study site/Investigator for further instructions. • If QRS is narrow (< 120 milliseconds), then temporary discontinuation criteria are the smaller of: 15% increase from baseline QTcF OR QTcF ≥ 520 milliseconds • If QRS is wide (≥ 120 milliseconds), then temporary discontinuation criteria are the smaller of: a 15% increase from baseline QTcF OR QTcF ≥ 550 milliseconds If the participant is taking 5, 10, or 15 mg, study drug will be temporarily discontinued and he or she will return for an unscheduled visit (with electrocardiogram [ECG] and TTE assessments) 2 to 4 weeks later. If LVEF ≥ 55% (as read by site) and QTcF < 500 milliseconds at the unscheduled visit, then the study drug will be restarted at a lower dose as shown below (previous dose → restart dose):

	• 5 mg → resume 5 mg • 10 mg → 5 mg • 15 mg → 10 mg Participants on 5 mg who have been temporarily discontinued on treatment based on clinical evaluation can be considered for dose reintroduction at 5 mg following agreement between the Investigator and the MyoKardia Medical Monitor. If LVEF, plasma drug concentration, and/or QTcF persist out of range at the follow-up visit, then the participant will be discontinued from the study. Participants who prematurely discontinue from the PIONEER-OLE study may be considered for rescreening for participation. After Week 6, additional study visits will occur at Week 8 (± 7 days), Week 12 (± 7 days), and every 12 weeks (± 7 days) thereafter. Participants also will be contacted by phone in between clinic visits, at Week 18 and every 12 weeks thereafter. An end of study (EOS) visit will occur 8 weeks (± 7 days) after the last administration of study drug. Visits (including the Screening visit which serves as the baseline) will entail recording vital signs, targeted physical examination, ECGs, safety laboratory tests, N-terminal pro B-type natriuretic peptide (NT-proBNP), adverse events (AEs), New York Heart Association (NYHA) functional class, Kansas City Cardiomyopathy Questionnaire (KCCQ) score, and concomitant medications. Predose blood samples for assessment of drug concentration will be obtained at the time points indicated in the Schedule of Assessments. A standard TTE (including but not limited to assessment of LVOT gradient at rest and after Valsalva) will be performed at baseline and at the time points indicated in the Schedule of Assessments. In addition, a stress echocardiogram (with assessment of LVOT gradient post-exercise) will also be performed at baseline and at the time points indicated in the Schedule of Assessments. For females of childbearing potential, pregnancy testing will be performed in clinic or at home every 4 weeks. Participants will be followed through completion of EOS procedures. All AEs, including serious adverse events (SAEs), will be collected from the time of informed consent through the duration of the study, up to and including the Week 260/EOS visit. If there is a significant clinical abnormality or clinically significant laboratory abnormality in need of monitoring, the participant will be followed until resolution of the abnormality or until it is considered stable in the opinion of the Investigator. **End of Study (Week 260)** Participants who prematurely discontinue the study will attend an early termination visit and return to the study site 8 weeks later for an EOS visit. Participants who complete 252 weeks of mavacamten treatment and do not rollover onto commercially available mavacamten will attend an end of treatment visit and return to the study site 8 weeks later for an EOS visit.

	Participants who rollover onto commercially available mavacamten at any time will be contacted 8 weeks later by telephone or other technology for an EOS follow-up to assess AEs, concomitant medications, and pregnancy. **Telehealth Assessments** Telehealth assessments (conducted via telephone or other technology based on standard at institution) will be conducted at Weeks 18, 30, 42, 54, 66, 78, 90, 102, 114, 126, 138, 150, 162, 174, 186, 198, 210, 222, 234, and 246 to assess AEs, concomitant medications, and pregnancy.
Number of Participants	Up to 20 individuals with symptomatic oHCM will be enrolled.
Study Treatment	Participants will receive mavacamten immediate-release capsules 5, 10, or 15 mg administered QD. The starting dose will be 5 mg for all participants. Each participant has had a Target Dose determined based on his or her PK data from Study MYK-461-004. These doses may only be exceeded for each given participant following discussion between the Investigator and the MyoKardia Medical Monitor. Lower doses are permissible. The Investigator, in conjunction with the Medical Monitor, may also elect to dose reduce a participant after they are on a stable dose of 10 mg or 15 mg treatment for 24 weeks or longer. Participants that have been dose reduced will undergo a follow-up visit 4 to 8 weeks (± 7 days) later (to mirror Week 8 assessments, including a TTE assessment). Based on results and clinical symptoms at follow-up visits, subsequent dose decisions will be discussed with the MyoKardia Medical Monitor. This cycle of potential dose reduction and follow-up can be repeated more than once (after at least 24 weeks on a stable dose of 10 mg or 15 mg treatment) and will need to be discussed with the MyoKardia Medical Monitor each time before it is carried out.
Study Duration	The study duration is 264 weeks (up to 4 weeks Screening, 252 weeks treatment [5 years], and 8 weeks posttreatment follow-up) unless the development of mavacamten is stopped or until mavacamten becomes commercially available (at the discretion of MyoKardia). If mavacamten clinical development is discontinued, this study will be terminated. The EOS is defined as the date of the last observation of the last participant.
Inclusion Criteria	Each participant must meet the following criteria to be included in this study: 1. Has completed Study MYK-461-004. Prior participation in a non-interventional observational study is allowed. 2. Able to understand and comply with the study procedures, understand the risks involved in the study, and provide written informed consent according to federal, local, and institutional guidelines before the first study-specific procedure 3. Body weight > 45 kg at Screening 4. Has safety laboratory parameters (chemistry and hematology) within normal limits (according to the central laboratory reference range) at Screening; however, a participant with safety

	laboratory parameters outside normal limits may be included if he or she meets all of the following criteria: • The safety laboratory parameter outside normal limits is considered by the Investigator to be clinically unimportant • If there is an alanine aminotransferase or aspartate aminotransferase result, the value must be < 3 × the upper limit of the laboratory reference range • The body size–adjusted estimated glomerular filtration rate is ≥ 30 mL/min/1.73 m^2 5. Female participants must not be pregnant or lactating and, if sexually active, must use one of the following highly effective birth control methods from the Screening visit through 4 months after the last dose of investigational medicinal product. • combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation or progestogen-only hormonal contraception associated with inhibition of ovulation by oral, implantable, or injectable route of administration • intrauterine device • intrauterine hormone-releasing system • bilateral tubal occlusion • Female participant is surgically sterile for 6 months or postmenopausal for 1 year. Permanent sterilization includes hysterectomy, bilateral oophorectomy, bilateral salpingectomy, and/or documented bilateral tubal occlusion at least 6 months prior to Screening. Females are considered postmenopausal if they have had amenorrhea for at least 1 year or more following cessation of all exogenous hormonal treatments and follicle-stimulating hormone levels are in the postmenopausal range. Male partners must also use a contraceptive (eg, barrier, condom, or vasectomy)
Exclusion Criteria	A participant who meets any of the following exclusion criteria may not participate in this study: 1. Has QTcF > 500 milliseconds or any other ECG abnormality considered by the Investigator to pose a risk to participant safety (eg, second-degree atrioventricular block type II) 2. Since enrollment into Study MYK-461-004, has developed obstructive coronary artery disease (> 70% stenosis in one or more arteries) or known moderate or severe aortic valve stenosis 3. Since enrollment into Study MYK-461-004, has developed any acute or serious comorbid condition (eg, major infection or hematologic, renal, metabolic, gastrointestinal, or endocrine dysfunction) that, in the opinion of the Investigator or Medical Monitor, would pose a risk to participant safety or interfere with the study evaluation, procedures, or completion

	4. Has a positive serologic test at Screening for infection with human immunodeficiency virus, hepatitis C virus, or hepatitis B virus 5. Since enrollment into Study MYK-461-004, has developed clinically significant malignant disease 6. Is taking prohibited concomitant medications; background therapy on beta blockers or calcium channel blockers is allowed as long as the participant has been on a stable dose for at least 14 days prior to Screening 7. Has evidence of current abuse of drugs or alcohol or a history of abuse that, in the Investigator's opinion, would cause the participant to be noncompliant or would otherwise increase the risk to the participant 8. Is unable to comply with the study requirements, including the number of required visits to the clinical site.
Endpoints	**Safety** • Frequency and severity of treatment-emergent AEs and SAEs • Frequency of cardiovascular (CV) death • Frequency of sudden death • Frequency of CV hospitalization • Frequency of heart failure due to systolic dysfunction defined as a symptomatic LVEF < 50% • Frequency of myocardial infarction • Frequency of ventricular arrhythmias (ventricular tachycardia, ventricular fibrillation, ventricular flutter, torsade de pointe) • Frequency of syncope • Frequency of seizures • Frequency of stroke • Frequency of LVEF < 50% as measured by echocardiography • QT and QTcF intervals over time **Efficacy and pharmacodynamics** • Post-exercise, post-Valsalva, and resting LVOT gradient over time • NYHA functional class over time • KCCQ scores over time • NT-proBNP over time • Frequency of septal reduction therapy **Pharmacokinetics** • Mavacamten plasma concentration over time • Population PK

Sample Size and Statistical Considerations	No statistical hypothesis testing will be performed. Data will be summarized in tabular format, and concentration response plots may be constructed for selected variables. The sparse PK data will be combined with that of other studies to construct a population PK model across all studies.
In the context of COVID-19 or other pandemics, natural disasters, or major disruptions, provisions may be made to accommodate participants who are unable to attend onsite study visits for scheduled assessments and dispensation of mavacamten. Guidance on participant management in these situations is outlined in Appendix 4.	

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LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta–human chorionic gonadotropin
BP	blood pressure
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CRF	case report form
CV	cardiovascular
CYP	cytochrome
DILI	drug-induced liver injury
EC	ethics committee; refers to an IRB or IEC or equivalent
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
EOT	end of treatment
ET	early termination
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HCM	hypertrophic cardiomyopathy
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system

IXRS	interactive response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
LV	left ventricular
LVEF	left ventricular ejection fraction
LVOT	left ventricular outflow tract
MedDRA	Medical Dictionary for Regulatory Activities
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
oHCM	obstructive hypertrophic cardiomyopathy
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PT	preferred term
PTAE	Pretreatment adverse event
QD	once daily
QoL	quality of life
QTc	corrected QT interval
QTcF	Fridericia-corrected QT interval
SAE	serious adverse event
SD	standard deviation
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TTE	transthoracic echocardiography, transthoracic echocardiogram
ULN	upper limit of normal
US	United States
UV	unscheduled visit
Wk	week

1. INTRODUCTION

1.1. Background

Hypertrophic cardiomyopathy (HCM), an autosomal dominant genetic disease, is defined clinically as unexplained left ventricular (LV) hypertrophy in the absence of known causes such as pressure overload, systemic diseases, or infiltrative processes (Gersh et al, 2011). The phenotypic hallmark of HCM is myocardial hypercontractility accompanied by reduced LV compliance, reflected clinically as reduced ventricular chamber size, often supranormal ejection fraction, and diastolic dysfunction. Mutations in cardiac myosin and other sarcomere proteins in participants with HCM appear to increase net power generation by the sarcomere (Chuan et al, 2012; Sommese et al, 2013; Sung et al, 2012), consistent with the generally hypercontractile state and impaired compliance of the myocardium observed clinically in participants with HCM.

Mavacamten is a novel small molecule allosteric modulator of striated muscle myosin that selectively targets cardiac myosin and reversibly inhibits its binding to actin. Mavacamten' s profile of myosin modulation is predicted to reduce dynamic left ventricular outflow tract (LVOT) obstruction in participants with obstructive HCM (oHCM) by reducing systolic hypercontractility and dynamic obstruction in the near term and reducing ventricular hypertrophy with chronic treatment. MyoKardia is developing mavacamten for the treatment of adults with symptomatic oHCM to relieve obstruction, improve symptoms, and increase exercise capacity.

In nonclinical studies, mavacamten was specific for striated muscle myosin and selective for the cardiac isoform (see the mavacamten Investigator's Brochure [IB]). Its targeted mechanism of action and high degree of specificity were reflected in its pharmacology in vitro and in vivo, as well as in the toxicology and safety pharmacology. In a feline model of HCM with LVOT obstruction, treatment with mavacamten reduced contractility and relieved obstruction in an exposure-dependent manner (Stern et al, 2016). The totality of the pharmacodynamic (PD) and tolerability data observed to date can be interpreted as direct or indirect consequences of reduced cardiac contractility.

Please refer to the mavacamten IB for more detailed information on mavacamten.

1.2. Clinical Studies

As of 30 October 2020, 15 clinical studies to investigate the safety and tolerability, efficacy, and pharmacokinetic (PK) profile of mavacamten have been completed. A total of 635 participants with HCM, healthy participants, or participants with hepatic impairment were enrolled across the completed studies, 464 of whom were exposed to at least 1 dose of mavacamten. Additionally, 294 participants have been enrolled across 3 ongoing studies of mavacamten. The results of the completed studies, as well as a description of the design and participants of the ongoing studies, are described in the IB.

1.3. Known and Potential Benefits and Risks

In nonclinical studies, safety testing in other mammalian species has demonstrated that dose-limiting toxicity is related to exaggerated pharmacologic effect and not to off-target adverse effects. Experiments with isolated adult rat ventricular myocytes in vitro and with anesthetized

rats in vivo have established that the pharmacological effects of mavacamten may be counteracted by positive inotropes (isoproterenol, dobutamine, or levosimendan).

Of the 18 clinical studies of mavacamten to date, clinical study reports are available for 15 studies. Overall, mavacamten appears well-tolerated with little evidence for off-target toxicity. In participants with oHCM, the clinical benefits of mavacamten treatment in the extension study (MAVA-LTE), which relies exclusively on clinical measures of cardiac function (including site-read echocardiographic measures) and participants' symptoms to guide dose titration, are consistent with the EXPLORER-HCM parent study, in which dose optimization was guided in part by plasma drug concentrations, specifically:

- reduced LVOT gradients
- improved New York Heart Association (NYHA) class
- improved diastolic function
- decreased left atrial volume index
- reduced wall stress (as measured by N-terminal pro B-type natriuretic peptide [NT-proBNP])

The known risks of mavacamten use from available nonclinical and/or clinical data to date include dizziness and cardiac failure due to systolic dysfunction (symptomatic left ventricular ejection fraction [LVEF] < 50%). Systolic heart failure is due to mavacamten's exaggerated on-target effect of reduction in cardiac contractility (ie, reduced LVEF). Potential risks of mavacamten use include embryofetal toxicity (observed in animal studies only), heart failure due to interaction with cytochrome (CYP) 2C19 and potent 3A4 inhibitors, and arrhythmia due to QT prolongation (observed in animal species and healthy volunteers).

2. RATIONALE FOR THE STUDY AND FOR DOSE AND DOSING SCHEDULE

2.1. Rationale for the Study

This study is an open-label extension of Study MYK-461-004 (PIONEER-HCM) to assess long-term safety, tolerability, and efficacy of mavacamten in participants with oHCM who had previously participated in the PIONEER-HCM study.

MyoKardia has designed the current study to generate long-term data in participants with symptomatic oHCM, using an approach that conforms to established ethical standards of safe human experimentation and the requirements of Good Clinical Practice (GCP).

2.2. Rationale for Dose and Dosing Schedule

Given that the mavacamten PK parameters of each PIONEER-HCM participant are known based on mavacamten plasma concentration measurements taken during that study, an individualized mavacamten dose was computed for each participant (Table 1) to target a mavacamten plasma concentration of 250 to 500 ng/mL. These plasma concentration levels have generally been associated with a marked reduction in LVOT gradient, and they have been well-tolerated without

excessive reductions in LVEF. To maximize safety, the starting dose will be 5 mg for all participants. If applicable, a dose increase to the Target Dose will occur at Week 6 based on Week 4 determinations of LVOT gradient, LVEF, and mavacamten plasma concentration (see Section 4).

Table 1 Individualized Target Doses

Participant Identification in Study MYK-461-004	Target Dose (mg)
[redacted]	10
	10
	5
	5
	10
	15
	5
	5
	10
	10
	10
	5
	5
	10
	15
	10
	15
	10
	10
	10

For eligible participants, a dose increase beyond the Target Dose at a later time point beyond Week 6 may also be possible; the Investigator first should discuss this with and get approval from the MyoKardia Medical Monitor (see Section 4).

At Week 48 and Week 72, a stress echocardiogram will be performed. If the post-exercise LVOT gradient is ≥ 50 mmHg, further dose adjustment may be considered and discussed with the MyoKardia Medical Monitor. If dose adjustment occurs at Week 24 or beyond, a follow-up visit should be scheduled 4 weeks later (± 7 days) to include a transthoracic echocardiography (TTE) assessment.

Dose adjustment may also take place beyond Week 6 based on results of TTE, stress echocardiography and/or PK evaluation, and based upon the opinion of the Investigator in conjunction with the MyoKardia Medical Monitor.

The Investigator, in conjunction with the Medical Monitor, may also elect to dose reduce a participant after they are on a stable dose of 10 or 15 mg mavacamten for 24 weeks or longer. Participants that have been dose reduced will undergo a follow-up visit 4 to 8 weeks (± 7 days) later (to mirror Week 8 assessments, including a TTE assessment). Based on results and clinical symptoms at follow-up visits, subsequent dose decisions will be discussed with the MyoKardia Medical Monitor. This cycle of potential dose reduction and follow-up can be repeated more than once (after at least 24 weeks on a stable dose of 10 or 15 mg treatment) and will need to be discussed with the MyoKardia Medical Monitor each time before it is carried out.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of this study is:

- To assess the long-term safety and tolerability of mavacamten in individuals with symptomatic oHCM

3.2. Secondary Objectives

The secondary objectives of this study are to assess in individuals with symptomatic oHCM the long-term effect of mavacamten on:

- LVOT obstruction
- Functional capacity
- oHCM symptoms

3.3. Pharmacokinetic Objective

The PK objective of this study is:

- To perform population PK analyses in individuals with symptomatic oHCM receiving mavacamten

4. OVERALL STUDY DESIGN AND PLAN

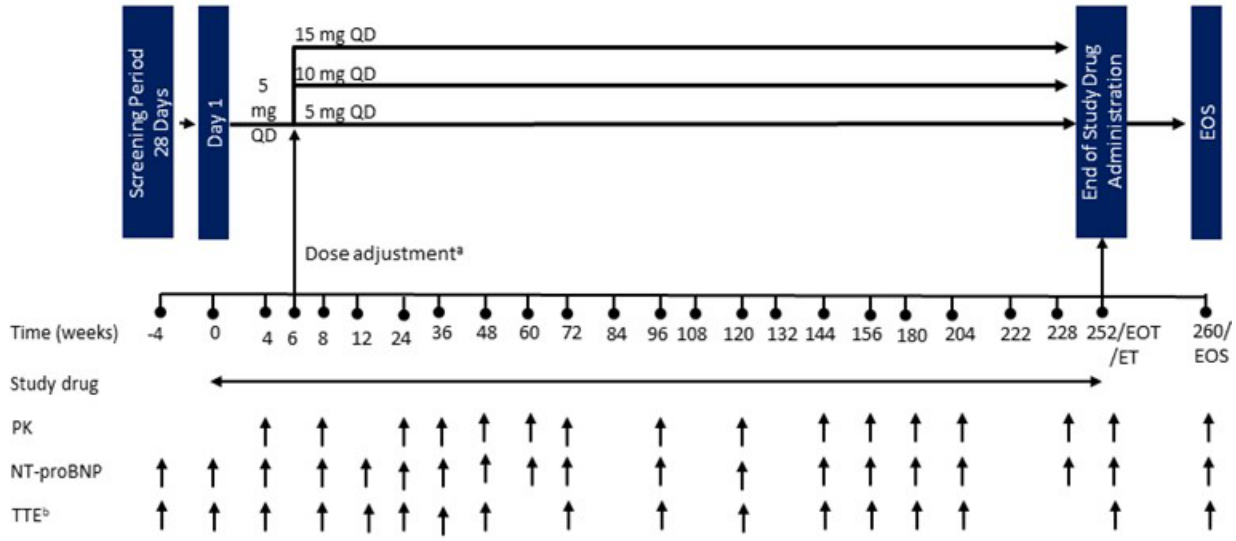
This is a Phase 2, open-label extension, multicenter study of individuals with symptomatic oHCM who completed Study MYK-461-004 (PIONEER-HCM).

Participants in this study will be screened to ensure they continue to meet eligibility criteria. Participants are allowed to stay on background therapy with either beta blockers or calcium channel blockers provided they have been on a stable dose for at least 14 days prior to Screening. Once enrolled into Study MYK-461-008, participants will undergo baseline assessments and

receive mavacamten QD for a duration of up to approximately 5 years (Figure 1) or until mavacamten becomes commercially available (at the discretion of MyoKardia).

The starting dose will be 5 mg. Participants will return at Week 4 for a plasma PK sample to measure drug levels and for an echocardiogram to determine LVOT gradient at rest and after exercise as well as to measure LVEF. If mavacamten clinical development is discontinued, this study will be terminated. The end of study (EOS) is defined as the date of the last observation of the last participant.

Figure 1 Study Schema



Abbreviations: EOS, end of study; ET, early termination; EOT, end of treatment; NT-proBNP, N-terminal pro B-type natriuretic peptide; PK, pharmacokinetic blood sample taken; QD, once daily; TTE, transthoracic echocardiogram.
Note: Dose reduction rule applies throughout.
Note: For all females of childbearing potential, a pregnancy test will be taken every 4 weeks at home when no clinic visit is scheduled.

[a] Dose adjustment to individual targeted dose: dose calculated to achieve mavacamten plasma concentration of 250-500 ng/mL in each participant. Dose adjustment may also take place beyond Week 6 based on results of TTE/stress echocardiogram and PK evaluation and based upon the opinion of the Investigator in conjunction with the MyoKardia Medical Monitor. Dose adjustments beyond the previous Target Dose may only be exceeded for each given participant following discussion between the Investigator and the MyoKardia Medical Monitor. Lower doses are permissible.

[b] Includes a stress TTE at Screening (Baseline), Weeks 4, 48, 72, 156, 204, 252/EOT, and 260/EOS. These are in addition to resting and post-Valsalva TTEs at all visits indicated with a vertical arrow.

Dose adjustment may occur at Week 6 based on Week 4 assessments. Target dosing will be individualized for each participant based on his or her PK data obtained in the MYK-461-004 study (Table 1). Specifically, the Target Dose for each participant is the dose associated with a steady-state trough plasma concentration of approximately 250 ng/mL to 500 ng/mL, and the Target Dose for a given participant may not exceed the dose (unless previously discussed between the Investigator and the MyoKardia Medical Monitor) as detailed in Table 1, although

lower doses are permissible. Participants will return at Week 6 for the results and dose adjustment. Note that at Week 4, the LVOT gradient will be measured at rest with Valsalva maneuver and post-exercise. If the LVOT gradient post-exercise is < 30 mmHg, then the dose will not be increased at Week 6.

The dose may be increased at Week 6 to the Target Dose provided in Table 1 unless one or more of the following criteria are met at Week 4:

- LVEF is < 55%, and/or
- LVOT gradient is < 30 mmHg after exercise, and/or
- Trough mavacamten plasma concentration is > 350 ng/mL, and/or
- A dose increase is not warranted in the clinical judgment of the Investigator

Note: if a participant is eligible for a dose increase at Week 6 but the dose is not increased due to Investigator judgment, a dose increase to the participant's Target Dose at a later time point beyond Week 6 may be possible; the Investigator should first discuss this with and get approval from the MyoKardia Medical Monitor.

For eligible participants, a dose increase beyond the Target Dose at a later time point beyond Week 6 may also be possible; the Investigator first should discuss this with and get approval from the MyoKardia Medical Monitor.

If one or more of the above 4 criteria are present, no dose increase will occur. Also, a dose decrease or discontinuation may be instituted at Week 6 or at any other visit according to the dose reduction rule described below.

Participants who have had a dose adjustment (either in mavacamten or background cardiomyopathy therapy) should return to the clinic approximately 28 days later (± 7 days) for an unscheduled visit with resting TTE to confirm safety. Repeat of post-exercise echocardiographic assessment of LVOT gradient will be at the Investigator's discretion. Based on results and clinical symptoms at follow-up visits, subsequent dose adjustments will be discussed with the MyoKardia Medical Monitor.

Dose Reduction Rule: The dose may be reduced or discontinued in the case of an exaggerated pharmacologic effect at any time during the study based on the clinical judgment of the Investigator.

If results as reported by the central laboratories from any visit show mavacamten plasma concentration is ≥ 1000 ng/mL, or LVEF < 50% (as read by site), or Fridericia-corrected QT interval (QTcF) meets the following criteria, the participant will be notified by the study site/Investigator with further instructions:

- If QRS is narrow (< 120 milliseconds), then temporary discontinuation criteria are the smaller of: 15% increase from baseline QTcF OR QTcF ≥ 520 milliseconds
- If QRS is wide (≥ 120 milliseconds), then temporary discontinuation criteria are the smaller of: a 15% increase from baseline QTcF OR QTcF ≥ 550 milliseconds

Dosing with study drug will be immediately stopped and the following procedures implemented:

- If the participant is taking 5, 10, or 15 mg, study drug will be temporarily discontinued and he or she will return for an unscheduled visit (with electrocardiogram [ECG] and TTE assessments) 2 to 4 weeks later
- If LVEF ≥ 55% (as read by site) and QTcF < 500 milliseconds at the unscheduled visit, then the study drug will be restarted at a lower dose, as shown below (previous dose → restart dose):
  - 5 mg → resume 5 mg
  - 10 mg → 5 mg
  - 15 mg → 10 mg

Participants on 5 mg who have been temporarily discontinued on treatment based on clinical evaluation can be considered for dose reintroduction at 5 mg following agreement between the Investigator and the MyoKardia Medical Monitor.

If LVEF (as read by site), plasma drug concentration, and/or QTcF persist out of range at the follow-up visit, then the participant will be discontinued from the study.

The Investigator, in conjunction with the Medical Monitor, may also elect to dose reduce a participant after they are on a stable dose of 10 or 15 mg mavacamten for 24 weeks or longer. Participants that have been dose reduced will undergo a follow-up visit 4 to 8 weeks (± 7 days) later (to mirror Week 8 assessments, including a TTE assessment). Based on results and clinical symptoms at follow-up visits, subsequent dose decisions will be discussed with the MyoKardia Medical Monitor. This cycle of potential dose reduction and follow-up can be repeated more than once (after at least 24 weeks on a stable dose of 10 or 15 mg treatment) and will need to be discussed with the MyoKardia Medical Monitor each time before it is carried out.

After Week 6, additional clinic visits will occur at Week 8 (± 7 days), Week 12 (± 7 days), and every 12 weeks (± 7 days) thereafter. Between clinic visits, participants will also be contacted by phone at Week 18 and every 12 weeks thereafter. An EOS visit will occur 8 weeks (± 7 days) after the last administration of study drug. Visits will entail recording vital signs, targeted physical examination, ECG, safety laboratory tests, NT-proBNP, adverse events (AEs), NYHA functional class, Kansas City Cardiomyopathy Questionnaire (KCCQ) score, and concomitant medications, as detailed in Table 2 and Table 3. Predose blood samples for assessment of drug concentrations will be performed at the visits indicated in Table 2 and Table 3. Resting and post-Valsalva TTEs and stress TTEs to determine post-exercise LVOT gradient will be performed at baseline and post-baseline, as indicated in Table 2 and Table 3. For females of childbearing potential, pregnancy testing will be performed in the clinic or at home every 4 weeks.

Participants will be followed through completion of EOS procedures. All AEs, including SAEs, will be collected from the time of informed consent through the duration of the study, up to and including the EOS visit. If there is a significant clinical abnormality or clinically significant laboratory abnormality in need of monitoring, the participant will be followed until resolution of the abnormality or until it is considered stable in the opinion of the Investigator.

In the context of COVID-19 or other pandemics, natural disasters, or major disruptions, provisions may be made to accommodate participants who are unable to attend onsite study visits

for scheduled assessments and dispensation of mavacamten. Guidance on participant management in these situations is outlined in Appendix 4.

4.1. Study Duration

The expected study duration is approximately 264 weeks: up to 4 weeks for Screening, a 252-week (5-year) treatment period, and an 8-week posttreatment follow-up period, or until mavacamten becomes commercially available. If mavacamten clinical development is discontinued, this study will be terminated. The EOS is defined as the date of the last observation of the last participant.

Table 2 Schedule of Assessments – Screening Through Year 2

	Year 1												Year 2								
Assessment[a]	**Screening Days -28 to -1**	**Day 1**	**Wk 4**	**Wk 6**	**Wk 8**	**Wk 12**	**Wk 18**	**Wk 24**	**Wk 30**	**Wk 36**	**Wk 42**	**Wk 48**	**Wk 54**	**Wk 60**	**Wk 66**	**Wk 72**	**Wk 78**	**Wk 84**	**Wk 90**	**Wk 96**	**Wk 102**
Telehealth Visit[b]							X		X		X		X		X		X		X		X
Informed consent	X																				
Medical history[c]	X																				
Vital signs[d]	X	X	X	X	X	X		X		X		X		X		X		X		X	
AEs/SAE[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[f]	X	X	X		X	X		X		X		X		X		X		X		X	
ECG[g]	X	X	X		X	X		X		X		X		X		X		X		X	
Resting TTE[h]	X		X		X	X		X		X		X				X				X	
Stress TTE[h]	X		X									X				X					
Mavacamten 5 mg daily		←	———	→																	
Dosing		←	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	→
Dose adjustment up to target[i]				←	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	→
IMP compliance check[j]			X	X	X	X		X		X		X		X		X		X		X	
Hepatitis panel and HIV test	X																				
PK sample[k]			X		X			X		X		X		X		X				X	
Chemistry	X		X			X				X				X		X				X	
Hematology	X		X		`	X				X				X		X				X	
NT-proBNP[l]	X	X	X		X	X		X		X		X		X		X				X	
FSH[m]	X																				
Pregnancy test (β-hCG)[n]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NYHA class, KCCQ	X	X	X		X			X				X				X				X	

Abbreviations: β-hCG, beta–human chorionic gonadotropin; AE, adverse event; BP, blood pressure; ECG, electrocardiogram; eCRF, electronic case report form; FSH, follicle-stimulating hormone; HCM, hypertrophic cardiomyopathy; HIV, human immunodeficiency virus; IMP, investigational medical product; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; PK, pharmacokinetic(s); SAE, serious adverse event; TTE, transthoracic echocardiography; Wk, week.
Note: The Week 4 visit has a visit window of ± 4 days; all remaining visits have a window of ± 7 days.

Table 2 Schedule of Assessments – Screening Through Year 2 (Continued)

[a] At the Investigator's discretion, unscheduled visits may be conducted at the investigational site for the assessment of AEs, physical examinations, vital signs, laboratory tests, drug dispensing, ECGs, and/or TTEs (see Table 3). Unscheduled safety assessments will be conducted for participants who temporarily discontinue study drug prior to resuming dosing, as outlined in Appendix 4. Study drug will be dispensed at the unscheduled visit; however, participants will not resume dosing until notified by the study site. All information collected from unscheduled visits will be recorded on the eCRF and included in the clinical database.

[b] Assessments as part of telehealth visits are to be conducted via telephone or other technology based on standard at institution.

[c] A complete medical history will be recorded at the Screening visit, which will include evaluation (past or present) of the following: general, head and neck, eyes, ears, nose, throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, gynecological/urogenital, musculoskeletal/extremities, skin, neurological/psychiatric, endocrine/metabolic, hematologic/lymphatic, allergies/drug sensitivities, past surgeries, substance abuse, or any other diseases or disorders as well as participation in clinical studies (study medication and/or device or other therapy). Specific history related to a participant's HCM diagnosis will also be collected.

[d] Vital signs will be taken in the sitting position prior to dosing and will include heart rate and BP after resting for at least 5 minutes. BP should be taken via an automated recorder. Respiratory rate will be obtained at Screening after resting for at least 5 minutes. Temperature will be obtained at Day 1.

[e] Any changes in baseline conditions that occur after the informed consent form is signed, but prior to the first dose of IMP, are recorded on the medical history eCRF, unless the change is related to a study procedure, in which case it is considered an AE. All changes that occur after administration of the first dose of IMP and meet the definition of an AE are recorded as AEs.

[f] At Screening, a complete physical examination will be conducted, including a neurological examination (gross motor and deep tendon reflexes), height and weight, and assessment of the following: general appearance, skin, head and neck, mouth, lymph nodes, thyroid, abdomen, musculoskeletal, cardiovascular, neurological, and respiratory systems. At all other onsite visits, an abbreviated cardiopulmonary physical examination will be conducted, with other systems assessed as directed by interval history; weight will also be recorded at all physical examinations.

[g] A 12-lead ECG will be performed after 10 minutes of rest. On Day 1, ECG will be performed predose.

[h] Instantaneous peak LVOT gradient (baseline) and provoked peak LVOT gradient (Valsalva maneuver) will be assessed. Ejection fraction (2-dimensional), left ventricular fractional shortening, global longitudinal strain by speckle tracking, and velocity timing interval will be analyzed. Resting TTE should be performed prior to stress echocardiography. All stress echocardiograms should include a 4-hour fast prior to exercise. If the post-exercise LVOT gradient is measured ≥ 50 mmHg, further dose adjustment may be considered and discussed with the MyoKardia Medical Monitor. If dose adjustment occurs at Week 24 or beyond, a follow-up visit (to mirror Week 8 assessments) should be scheduled 4 weeks later (± 7 days) to include a TTE assessment. All stress echocardiography visits will be conducted in the clinic.

[i] Dose adjustment is optional. Dose adjustments beyond the Target Dose may only be exceeded for each given participant following discussion between the Investigator and the MyoKardia Medical Monitor. Lower doses are permissible.

[j] Compliance with study drug will be monitored by capsule count at each clinic visit.

[k] A blood sample will be collected prior to dosing for assessment of trough study drug plasma concentrations. On days of visits, participants should not take their daily dose prior to visit. Study drug will be administered on site to facilitate collection of this sample.

[l] The blood draw for NT-proBNP will occur prior to stress echocardiography.

[m] FSH testing at Screening for postmenopausal females to confirm postmenopausal status.

[n] Pregnancy test (serum or urine) for females of childbearing potential, based on standard at institution. A urine pregnancy test is performed at home every 4 weeks when no clinic visit is scheduled.

Table 3 Schedule of Assessments – Year 3 Through End of Study

	Year 3									Year 4						Year 5							
Assessment	**Wk 108[a]**	**Wk 114**	**Wk 120[a]**	**Wk 126**	**Wk 132[a]**	**Wk 138**	**Wk 144[a]**	**Wk 150**	**Wk 156[a]**	**Wk 162**	**Wk 174**	**Wk 180[a]**	**Wk 186**	**Wk 198**	**Wk 204[a]**	**Wk 210**	**Wk 222**	**Wk 228**	**Wk 234**	**Wk 246**	**Wk 252 EOT/ ET[a,b]**	**Wk 260/ EOS[a,c]**	**UV[d]**
Telehealth Visit[e]		X		X		X		X		X	X		X	X		X	X		X	X			
Vital signs[f]	X		X		X		X		X			X			X			X			X	X	X
AEs/SAEs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[h]	X		X		X		X		X			X			X			X			X	X	X
ECG[i]	X		X		X		X		X			X			X			X			X	X	X
Resting TTE[j]			X				X		X			X			X			X			X	X	X
Stress TTE[j]									X						X						X	X	
Dosing	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→		
Dose adjustment up to target[k]	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→		
IMP compliance check[l]	X		X		X		X		X			X			X			X			X	X	X
PK sample[m]			X				X		X			X			X			X			X	X	X
Chemistry			X				X		X			X			X			X			X	X	X
Hematology			X				X		X			X			X			X			X	X	X
NT-proBNP[n]			X				X		X			X			X			X			X	X	X
Pregnancy test (β-hCG)[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NYHA class, KCCQ			X				X		X			X			X			X			X	X	

Abbreviations: β-hCG, beta–human chorionic gonadotropin; AE, adverse event; BP, blood pressure; ECG, electrocardiogram; eCRF, electronic case report form; EOS, end of study; EOT, end of treatment; ET, early termination; IMP, investigational medical product; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; PK, pharmacokinetic; SAE, serious adverse event; TTE, transthoracic echocardiography; UV, unscheduled visit; Wk, week.

Note: The Week 4 visit has a visit window of ± 4 days; all remaining visits from Week 6 to Week 260/EOS have visit windows of ± 7 days.

[a] Stress TTE assessment must be performed at site.

[b] Participants who prematurely discontinue the study will attend an ET visit and return to the study site 8 weeks later for an EOS visit.

Table 3 Schedule of Assessments – Year 3 Through End of Study (Continued)

[c] Participants who complete 252 weeks of mavacamten treatment and do not rollover onto commercially available mavacamten will attend an EOT visit and return to the study site 8 weeks later for an EOS visit. Participants who rollover onto commercially available mavacamten at any time will be contacted 8 weeks later by telephone or other technology for an EOS follow-up to assess AEs, concomitant medications, and pregnancy.

[d] At the Investigator's discretion, unscheduled visits may be conducted at the investigational site for the assessment of AEs, physical examinations, vital signs, laboratory tests, drug dispensing, ECGs, and/or TTEs. Unscheduled safety assessments will be conducted for participants who temporarily discontinue study drug prior to resuming dosing, as outlined in Appendix 4. Study drug will be dispensed at the unscheduled visit; however, participants will not resume dosing until notified by the study site. All information collected from unscheduled visits will be recorded on the eCRF and included in the clinical database.

[e] Assessments as part of telehealth visits are to be conducted via telephone or other technology based on standard at institution.

[f] Vital signs will be taken in the sitting position prior to dosing and will include heart rate and BP after resting for at least 5 minutes. BP should be taken via an automated recorder. Respiratory rate will be obtained at the Week 260/EOS visit after resting for at least 5 minutes. Temperature will be obtained at the Week 260/EOS visit.

[g] Any changes in baseline conditions that occur after the informed consent form is signed, but prior to the first dose of study medication, are recorded on the medical history eCRF, unless the change is related to a study procedure, in which case it is considered an AE. All changes that occur after administration of the first dose of study medication and meet the definition of an AE are recorded as AEs.

[h] At the visits indicated, an abbreviated cardiopulmonary physical examination will be conducted, with other systems assessed as directed by interval history; weight will also be recorded at all physical examinations.

[i] A 12-lead ECG will be performed after 10 minutes of rest.

[j] Instantaneous peak LVOT gradient (baseline) and provoked peak LVOT gradient (Valsalva maneuver) will be assessed. Ejection fraction (2-dimensional), left ventricular fractional shortening, global longitudinal strain by speckle tracking, and velocity timing interval will be analyzed. Resting TTE should be performed prior to stress echocardiography. All stress echocardiograms should include a 4-hour fast prior to exercise. If the post-exercise LVOT gradient is measured ≥ 50 mmHg, further dose adjustment may be considered and discussed with the MyoKardia Medical Monitor. If dose adjustment occurs after Week 24, a follow-up visit (to mirror Week 8 (Table 2) assessments) should be scheduled 4 weeks later (± 7 days) to include a TTE assessment. All stress echocardiography visits will be conducted in the clinic.

[k] Dose adjustment is optional. Dose adjustments beyond the Target Dose may only be exceeded for each given participant following discussion between the Investigator and the MyoKardia Medical Monitor. Lower doses are permissible.

[l] Compliance with study drug will be monitored by capsule count at each clinic visit.

[m] A blood sample will be collected prior to dosing for assessment of trough study drug plasma concentrations. Study drug should be administered on site to facilitate collection of this sample.

[n] The blood draw for NT-proBNP will occur prior to stress echocardiography.

[o] Pregnancy test (serum or urine) for females of childbearing potential, based on standard at institution. A urine pregnancy test is performed at home every 4 weeks when no clinic visit is scheduled.

5. SELECTION AND WITHDRAWAL OF STUDY POPULATION

5.1. General Study Population and Clinical Sites

Up to approximately 20 participants with symptomatic oHCM are expected to enroll in this study at up to 5 clinical sites in the United States (US).

5.2. Inclusion Criteria

Each participant must meet the following criteria to be enrolled in this study.

1. Has completed Study MYK-461-004. Prior participation in a non-interventional observational study is allowed
2. Able to understand and comply with the study procedures, understand the risks involved with participating in the study, and provide written informed consent according to federal, local, and institutional guidelines before the first study-specific procedure
3. Body weight > 45 kg at Screening
4. Has safety laboratory parameters (chemistry and hematology) within normal limits (according to the central laboratory reference range) at Screening; however, a participant with safety laboratory parameters outside normal limits may be included if he or she meets all of the following criteria:
    - The safety laboratory parameter outside normal limits is considered by the Investigator to be clinically unimportant
    - If there is an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) result, the value must be < 3 × the upper limit of the laboratory reference range
    - The body size–adjusted estimated glomerular filtration rate is ≥ 30 mL/min/1.73 m^2
5. Female participants must not be pregnant or lactating and, if sexually active, must use one of the following highly effective birth control methods from the Screening visit through 4 months after the last dose of investigational medicinal product (IMP).
    - combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation or progestogen-only hormonal contraception associated with inhibition of ovulation by oral, implantable, or injectable route of administration
    - intrauterine device (IUD)
    - intrauterine hormone-releasing system (IUS)
    - bilateral tubal occlusion
    - Female participant is surgically sterile for 6 months or postmenopausal for 1 year. Permanent sterilization includes hysterectomy, bilateral oophorectomy, bilateral salpingectomy, and/or documented bilateral tubal occlusion at least 6 months prior to Screening. Females are considered postmenopausal if they have had amenorrhea for at least 1 year or more following cessation of all exogenous hormonal treatments and follicle-stimulating hormone (FSH) levels are in the postmenopausal range.

Male partners must also use a contraceptive (eg, barrier, condom, or vasectomy).

5.3. Exclusion Criteria

A participant who meets any of the following criteria will be excluded from the study.

1. Has QTcF > 500 milliseconds or any other ECG abnormality considered by the Investigator to pose a risk to participant safety (eg, second-degree atrioventricular block type II)
2. Since enrollment into Study MYK-461-004, has developed obstructive coronary artery disease (> 70% stenosis in one or more arteries) or known moderate or severe aortic valve stenosis
3. Since enrollment into Study MYK-461-004, has developed any acute or serious comorbid condition (eg, major infection or hematologic, renal, metabolic, gastrointestinal, or endocrine dysfunction) that, in the opinion of the Investigator or Medical Monitor, would pose a risk to participant safety or interfere with the study evaluation, procedures, or completion
4. Has a positive serologic test at Screening for infection with human immunodeficiency virus, hepatitis C virus, or hepatitis B virus
5. Since enrollment into Study MYK-461-004 has developed clinically significant malignant disease
6. Is taking prohibited concomitant medications (see Section 7.7.3); background therapy on beta blockers or calcium channel blockers is allowed as long as the participant has been on a stable dose for at least 14 days prior to Screening
7. Has evidence of current abuse of drugs or alcohol or a history of abuse that, in the Investigator's opinion, would cause the participant to be noncompliant or would otherwise increase the risk to the participant
8. Is unable to comply with the study requirements, including the number of required visits to the clinical site

5.4. Screening and Enrollment

Eligible individuals who completed Study MYK-461-004 may be enrolled. An informed consent form (ICF) must be signed and dated by the participant before any study-specific tests or procedures may be performed.

If possible, each participant should keep his or her unique identification number that was assigned upon entry into Study MYK-461-004. Numbers do not include identifiable information. The identification number will be used to identify the participant throughout the study and should appear on all study-related documentation. Rescreening may be allowed at the discretion of the Investigator and the MyoKardia Medical Monitor.

5.5. Withdrawal of Participants

5.5.1. Withdrawal from the Study

The degree to which a study participant withdraws can vary. However, every effort should be made to collect important safety data if feasible and the study participant agrees. Study participants can:

- Withdraw from treatment (permanent treatment discontinuation) and agree to participate in the early termination (ET) and EOS visits
- Withdraw from treatment (permanent treatment discontinuation) and agree to participate in the ET visit
- Withdraw from treatment (permanent treatment discontinuation) and all follow-up

Participants may withdraw from the study before study completion if they decide to do so, at any time, for any reason. Withdrawal of consent for treatment (permanent treatment discontinuation) should be distinguished from withdrawal of consent for ongoing study participation with scheduled visits and from withdrawal of consent for non-participant contact follow-up (eg, medical records check).

If possible, and prior to the withdrawal of consent for ongoing study participation, the participants will be assessed using the procedures normally planned for the ET visit.

Participants who withdraw from the study should be explicitly asked about the reason and the contribution of any possible AE(s) that led to their decision, and all AE information elicited should be documented. The participant may withdraw consent verbally or in writing. If the consent is withdrawn verbally, the site should document it appropriately. Preferably, the participant should withdraw consent in writing and, if the participant or the participant's representative refuses or is physically unavailable, the site should document and sign the reason for the participant's failure to withdraw consent in writing.

All study withdrawals should be recorded by the Investigator in the appropriate electronic case report form (eCRF) and in the participant's medical records when considered as confirmed. The date of the withdrawal and the reason should be documented.

For participants who do not withdraw consent for ongoing study participation but fail to return to the site, the Investigator should make every effort to contact the participant (eg, contacting participant's family or private physician, reviewing available registries or health care databases) and to determine the participant's health status, particularly vital status. Attempts to contact such participants must be documented in the participant's records (eg, number of attempts and dates of attempted telephone contact and receipt for sending a registered letter).

Participants who have withdrawn from the study cannot be treated further in the study. Their study identification numbers must not be reused.

Treatment Discontinuation

The Investigator should discontinue a participant's study treatment permanently for any of the following reasons:

- Pregnancy

- Heart failure related to systolic dysfunction
- Study termination
- Study site termination by MyoKardia (eg, in the case of major, noncorrectable protocol deviations)
- Undergoing septal reduction therapy
- Participant withdrawal from treatment or withdrawal from study

Study treatment will be discontinued in the case of exaggerated pharmacologic effect (systolic dysfunction), higher than expected plasma concentration, or excessive QT prolongation (see Section 7.5).

In addition, study treatment may be temporarily discontinued in the case of an AE or SAE at the Investigator's discretion if there is a safety concern.

In all cases, the reason(s) for permanent treatment discontinuation or study withdrawal will be recorded in the source document and on the appropriate eCRF.

5.5.2. Handling of Participants After Permanent Treatment Discontinuation

After permanent discontinuation of treatment, participants will be followed according to the study procedures as specified in this protocol through the scheduled date of study completion, or through the recovery or stabilization of any AE to be followed as specified in this protocol, whichever comes last.

After permanent discontinuation of treatment, the participants will be assessed using the procedures planned for the ET and EOS visits.

6. RANDOMIZATION AND BLINDING PROCEDURES

6.1. Randomization

Participants will not be randomized to treatment in this study.

6.2. Study Blinding

Treatment will not be blinded in this study.

7. STUDY TREATMENT

All participants will receive mavacamten in an open-label manner.

7.1. Formulation, Packaging, and Labeling of Study Drug

Mavacamten presentation is size 2, blue opaque capsules printed with a yellow band on the body and black band on the cap. Each capsule contains white to off-white powder. The active capsules are supplied in 3 strengths: 5, 10, and 15 mg.

Mavacamten capsules have been manufactured according to current Good Manufacturing Practice (cGMP) regulations. They will be supplied in high-density polyethylene bottles with induction seals and child-resistant caps at 30 count per bottle. All study drug will be labeled according to applicable local regulatory guidelines.

Mavacamten capsules must be stored at 2°C to 25°C (36°F to 77°F) in the packaging supplied by MyoKardia. Study medication at the investigational site will be stored in a secure area with access limited to authorized study personnel.

7.2. Administration and Schedule of Study Drug

Study drug will be supplied to participants in 30-count high-density polyethylene bottles that are appropriately labeled. The participants will be instructed to store their supply of study drug capsules and bottles in a cool, dry place.

Participants will take study drug as directed by the Investigator. Participants should be instructed to take the study drug at approximately the same time every day (± 8 hours). Study drug should be taken with approximately 8 ounces of water. If the dosing window is missed, the participant should not take study drug that day. Participants should never take 2 doses of study drug within an 8-hour period. At Week 4, dosing should occur in the clinic after a blood draw for a plasma PK sample.

7.3. Treatment Compliance

Compliance with study drug will be monitored by capsule count at each clinic visit (Table 2 and Table 3).

7.4. Hepatotoxicity Stopping and Rechallenge Rules

Participants with abnormal hepatic laboratory values (eg, alkaline phosphatase [ALP], AST, ALT, total bilirubin [TBL], or international normalized ratio) or signs/symptoms of hepatitis may meet the criteria for withholding study medication or other protocol-required therapies. Withholding is either permanent or conditional depending on the clinical circumstances discussed below (as specified in the US Food and Drug Administration Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, 2009).

7.4.1. Criteria for Permanent Withholding of Mavacamten Due to Potential Hepatotoxicity

Mavacamten should be discontinued permanently and the participant should be followed according to the recommendations in Appendix 3 for possible drug-induced liver injury (DILI) if all the criteria below are met:

- TBL > 2 × upper limit of normal (ULN) or international normalized ratio > 1.5
- AND increased AST or ALT if the baseline value was < ULN and AST or ALT elevation is > 3 × ULN
- AND no other cause for the combination of laboratory abnormalities is immediately apparent. Important potential causes for abnormal AST/ALT or TBL values include, but are not limited to, the following:

- Obstructive gall bladder or bile duct disease
- Viral or alcoholic hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, varicella)
- Hypoxic or ischemic hepatopathy or congestive hepatopathy in association with significant right-sided heart failure
- Concomitant administration of other hepatotoxins, including drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir, irinotecan) or herbal or dietary supplements
- Heritable disorders causing impaired glucuronidation (eg, Gilbert syndrome); α-1 antitrypsin deficiency
- Autoimmune hepatitis
- Nonalcoholic steatohepatitis or other fatty liver disease

If an alternative cause for hepatotoxicity is identified or less stringent conditions developed than what is noted above, the Investigator will determine whether study drug and other protocol-required therapies should be permanently or temporarily discontinued based on participant population and/or severity of the hepatotoxicity or event, as deemed appropriate for the safety of the participant.

7.4.2. Criteria for Conditional Withholding of Mavacamten Due to Potential Hepatotoxicity

For participants who do not meet the criteria for permanent withholding of study medication outlined above, mavacamten should be withheld if ANY of the following criteria are met, and the participant should be evaluated for DILI:

- Elevation of either AST or ALT, regardless of baseline AST or ALT value, if:
  - > 8 × ULN at any time
  - > 5 × ULN and < 8 × ULN for ≥ 2 weeks
  - >5 × ULN and < 8 × ULN and unable to adhere to enhanced monitoring schedule
- OR: clinical signs or symptoms that are, in the opinion of the Investigator, consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice, rash, or eosinophilia > 5%). If such signs or symptoms are coupled with ALT or AST elevations > 3 × ULN, study medication should be withheld
- OR: TBL > 3 × ULN at any time
- OR: ALP > 8 × ULN at any time

Mavacamten should be withheld pending an investigation into alternative causes of DILI. If study medication is withheld, the participant should be followed according to recommendations in Appendix 3 for possible DILI. Rechallenge may be considered if an alternative cause, such as acute hepatitis B infection, is discovered and the laboratory abnormalities resolve to normal or baseline (Section 7.4.3).

7.4.3. Criteria for Rechallenge of Mavacamten After Potential Hepatotoxicity

The decision to rechallenge the participant should be discussed and unanimously agreed upon by the Investigator and Sponsor.

If signs or symptoms recur with rechallenge, then mavacamten will be permanently discontinued. Participants who clearly meet the criteria for permanent discontinuation (as described in Section 7.4.1) should never be rechallenged.

7.5. Guidelines for the Management of Exaggerated Pharmacologic Effect (Systolic Dysfunction), Excessive QT Prolongation, or Higher Than Expected Plasma Concentration

If results, as reported by the central laboratories from any visit, show mavacamten plasma concentration is ≥ 1000 ng/mL, or LVEF < 50% (as read by site), or QTcF meets the following criteria, the participant will be notified by the study site/Investigator for further instructions.

- If QRS is narrow (< 120 milliseconds), then temporary discontinuation criteria are the smaller of: 15% increase from baseline QTcF OR QTcF ≥ 520 milliseconds.
- If QRS is wide (≥ 120 milliseconds), then temporary discontinuation criteria are the smaller of: a 15% increase from baseline QTcF OR QTcF ≥ 550 milliseconds.

It will be communicated to the Investigator and Sponsor that a stopping criterion has been met and the procedures outlined in Section 4 will be implemented. If a participant discontinues study drug permanently, the participant will be encouraged to undergo ET and EOS assessments.

Any participant who experiences heart failure related to systolic dysfunction will be managed as per site-specific standard of care.

7.6. Overdose

An overdose is defined as taking more capsules of study drug than directed. An overdose may be suspected by the Investigator or spontaneously reported by the participant. An overdose may be symptomatic or asymptomatic. Reporting and follow-up of overdose are described below in Section 7.6.1.

In the event of symptomatic overdose or in the presence of significant symptoms and/or clinical compromise, including depressed cardiac contractility or asystole, the Investigator should contact the MyoKardia Medical Monitor, and no further study drug should be administered until further notice.

The participant should be closely monitored clinically for AEs/SAEs, with supportive measures undertaken as clinically indicated. There is no specific antidote for mavacamten. In acute overdose or toxic ingestion, gastrointestinal decontamination should be considered. If necessary, corrective measures, as described in the 2013 ACCF/AHA Guideline for the Management of Heart Failure (Yancy et al, 2013) and in the 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (Ponikowski et al, 2016) should be implemented. Based on its almost exclusive hepatic metabolism through the CYP 2C19 and CYP 3A4 enzymes, avoidance of inhibitors of these enzymes (eg, omeprazole) is important and administration of inducers of CYP 2C19 and CYP 3A4 may be helpful. The efficacy of other

measures of elimination has not been established. Reintroduction of study drug must be approved by the MyoKardia Medical Monitor.

7.6.1. Reporting and Follow-up of Overdose

If a participant should experience an overdose, the Investigator will report the overdose within 24 hours, even if there are no signs or symptoms associated with the overdose in the participant. Follow-up on the participant's condition will be conducted.

7.7. Prior and Concomitant Treatment

7.7.1. Prior Therapy

At the time of signing the ICF, participants will be asked about their medication history over the previous 30 days, including prescription and nonprescription medications, herbal medications, vitamins, and minerals.

If participants have not taken any prohibited medications in the past 14 days they may proceed to Screening. Participants taking prohibited medications must discontinue treatment for 14 days before proceeding to the Screening assessments.

7.7.2. Concomitant Therapy

Document all concomitant therapies on the appropriate eCRF, whether prescription or over-the-counter, vitamin and/or mineral supplements, herbs, and medications taken for an event or procedure (eg, biopsy). Include start/stop dates, route, and indication.

Background therapy with either beta blockers or calcium channel blockers is permitted if the dose has been stable for 4 weeks at the time of enrollment.

Background cardiomyopathy therapy (eg, beta-blocker, verapamil, or diltiazem) may be adjusted or stopped after a participant has received 24 weeks of mavacamten treatment in this study as determined by the Investigator in conjunction with the MyoKardia Medical Monitor.

The occurrence of concomitant diagnostic/surgical/therapeutic procedures and available details will also be documented on the appropriate eCRF.

7.7.3. Prohibited Therapy

Prior or concomitant treatment with cardiotoxic agents such as doxorubicin or similar is prohibited, as is prior or concomitant treatment with antiarrhythmic drugs with negative inotropic activity (eg, flecainide or propafenone).

The use of disopyramide or ranolazine is prohibited from 14 days before Screening to EOS.

Additional prohibited medications are listed in Appendix 2.

8. RISKS AND PRECAUTIONS

8.1. General

Based on nonclinical data and the available clinical data, the most likely risks are those associated with higher exposures potentially resulting in dizziness or an excessive decrease in LVEF. This could result in the development or worsening of signs or symptoms of systolic heart failure or reduced cardiac output.

Safety testing in other mammalian species has demonstrated that dose-limiting toxicity is related to exaggerated pharmacologic effect and not to off-target adverse effects. For overdose, see Section 7.6.

8.2. Pregnancy

8.2.1. Avoidance of Pregnancy

Females of childbearing potential must use appropriate methods of birth control as listed in Section 8.2.2. Females of nonchildbearing potential are defined as females who are permanently (surgically) sterilized or are postmenopausal. Permanent sterilization includes hysterectomy, bilateral oophorectomy, and bilateral tubal occlusion or ligation at least 6 months prior. Females are considered postmenopausal if they have had amenorrhea for at least 1 year or more following cessation of all exogenous hormonal treatments and follicle-stimulating hormone levels are in the postmenopausal range.

8.2.2. Acceptable Forms of Contraception

Highly effective methods of birth control are defined as those that result in a low failure rate (< 1% per year) when used consistently and correctly. From the time of Screening through 4 months after the last dose of study drug, female participants should practice true abstinence or use effective means of contraception as follows:

- combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation or progestogen-only hormonal contraception associated with inhibition of ovulation by oral, implantable, or injectable route of administration
- IUD
- hormone-releasing IUS
- bilateral tubal occlusion
- Female participant is surgically sterile for 6 months or postmenopausal for 1 year. Permanent sterilization includes hysterectomy, bilateral oophorectomy, bilateral salpingectomy, and/or documented bilateral tubal occlusion at least 6 months prior to Screening. Females are considered postmenopausal if they have had amenorrhea for at least 1 year or more following cessation of all exogenous hormonal treatments and FSH levels are in the postmenopausal range.

Male partners must also use a contraceptive (eg, barrier, condom, or vasectomy).

8.2.3. Reporting and Follow-up of Pregnancies

All pregnancies in female participants and female partners of male participants receiving at least 1 dose of study drug will be reported if they occur anytime from first dose to 4 months after the last dose of study drug. The Investigator is responsible for informing MyoKardia within 24 hours of knowledge of the pregnancy, even if no AE has occurred, per the reporting guidelines in Section 10.1.4 . The participant will be asked to provide information on the outcome of the pregnancy through 6 months after birth or details of premature termination. Spontaneous miscarriage and congenital abnormalities will be reported as SAEs.

9. STUDY ASSESSMENTS AND PROCEDURES

The Investigator is responsible for ensuring that all staff involved in the study are familiar and comply with the content of this section.

The following describes the study procedures to be performed during the study. Additional details are provided in Table 2. When several assessments are to be conducted at the same time point, the preferred order of assessments is ECG, vital signs, PK, and then TTE. The order of assessments may vary slightly at specific time points (eg, 1-hour postdose) to facilitate the most contemporaneous performance of the required assessments. Unscheduled or additional safety assessments may be performed if necessary in the opinion of the Investigator.

For assessments that require the participants to be in a semi-recumbent or supine position, assessments should be conducted with participants in the same position at all time points.

9.1. Efficacy and Pharmacodynamic Assessments

9.1.1. Echocardiography

Details are provided in the Study Reference Manual. Echocardiography should be performed prior to dosing. Echocardiograms will be site-read and not blinded to the Investigator or the site. All echocardiography data will be sent to the interactive response system (IXRS) for LVEF stopping criterion (LVEF < 50% by local site-read). Echocardiograms will also be sent to a central imaging laboratory for possible future assessment. If necessary, contrast may be administered to ensure that high quality echocardiogram images are obtained.

9.1.1.1. Resting Transthoracic Echocardiography

Resting TTE will be assessed throughout the study, as indicated in Table 2 and Table 3. Instantaneous peak LVOT gradient at rest and provoked peak LVOT gradient (Valsalva maneuver) will be assessed. LVEF and other parameters will be obtained (see Study Reference Manual).

Resting TTE should be performed prior to stress echocardiography.

9.1.1.2. Stress Echocardiography

Participants will undergo a standard symptom-limited exercise test (stress echocardiography), after a 4-hour fast, at the visits indicated in Table 2 and Table 3. The instantaneous peak LVOT gradient will be assessed immediately post-exercise by TTE. Any concomitant medication or

standard therapies for the treatment of HCM should be taken, as prescribed, on the day of the exercise test.

9.1.2. New York Heart Association Functional Class

The NYHA Functional Classification of heart failure assigns participants to 1 of 4 categories based on the participant's symptoms (Table 4). Heart failure classification will be assessed at every clinical site study visit indicated in Table 2.

Table 4 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's Classes of Heart Failure, 2015.

9.1.3. Kansas City Cardiomyopathy Questionnaire

The KCCQ is a self-administered 23-item questionnaire that quantifies physical limitation, symptoms, quality of life (QoL), social interference, and self-efficacy (Green et al, 2000). The total symptom score is derived from the symptom frequency and symptom burden scores. The clinical summary score is derived from the physical limitation and total symptom scores. The overall summary score is derived from the physical limitation, symptom, QoL, and social interference domains. Scores range from 0 to 100, with higher scores reflecting better health status. The KCCQ will be administered to participants as indicated in Table 2.

9.2. Pharmacokinetic Assessments

9.2.1. Pharmacokinetic Assessments

Blood samples will be collected for mavacamten plasma concentration assessments throughout the treatment period as indicated in Table 2. At all time points, a blood draw for drug concentration must be obtained prior to dosing.

9.2.2. NT-proBNP

Blood samples will be collected for NT-proBNP concentrations throughout the study, as indicated in Table 2 and Table 3. Unscheduled or additional blood samples may be collected if appropriate in the opinion of the Investigator and/or Sponsor. At all visits in which a stress echocardiography is performed, the blood draw for NT-proBNP will occur prior to stress echocardiography.

9.3. Safety Assessments

Safety will be assessed throughout the study. Safety assessments include medical history, physical examinations, ECGs, vital signs, observed and participant-reported AEs, and safety laboratory results. Any abnormal findings judged by the Investigator to be clinically important will be recorded as an AE.

9.3.1. Medical History

A complete medical history will be recorded at the Screening visit, which will include evaluation (past or present) of the following: general, head and neck, eyes, ears, nose, throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, gynecological/urogenital, musculoskeletal/extremities, skin, neurological/psychiatric, endocrine/metabolic, hematologic/lymphatic, allergies/drug sensitivities, past surgeries, substance abuse, or any other diseases or disorders as well as participation in clinical studies (study medication and/or device or other therapy). Specific history related to a participant's HCM diagnosis will also be collected.

9.3.2. Physical Examination

At the Screening visit, a complete physical examination will be conducted including a neurological examination (gross motor and deep tendon reflexes), height and weight, and assessment of the following: general appearance, skin, head and neck, mouth, lymph nodes, thyroid, abdomen, musculoskeletal, cardiovascular, neurological, and respiratory systems. At all other visits, an abbreviated cardiopulmonary physical examination will be conducted, with other systems assessed as directed by interval history; weight will also be recorded.

Height (cm) and body weight (kg) will be measured at Screening, and body mass index (kg/m^2) will be calculated. Participants will be required to remove their shoes and wear clothing as specified by the clinical site. Weight will also be collected at all subsequent onsite visits.

9.3.3. 12-lead ECG

Twelve-lead ECG evaluations will be performed after 10 minutes of rest throughout the study, as indicated in Table 2 and Table 3. All ECG data will be sent to a central cardiac laboratory.

On Day 1, ECG will be performed predose. At all other visits, ECGs may be obtained at any time.

The Investigator will judge the overall interpretation as normal or abnormal with clinical significance. The Investigator will review the ECG and correlate abnormal findings with any other clinical findings, participant's medical history, and laboratory data to determine the clinical importance of the finding.

The Investigator may add extra 12-lead ECG safety assessments if there are any abnormal findings or if the Investigator considers it is required for any other safety reason. These assessments should be recorded as an unscheduled assessment.

9.3.4. Vital Signs

Vital signs are to be assessed throughout the study as indicated in Table 2, including temperature, heart rate (HR), respiratory rate, and blood pressure (BP) after resting for at least

5 minutes. Vital signs will be obtained with the participant in the same position; BP will be taken via an automated recorder.

Vital signs will be taken prior to dosing. Refer to the Study Reference Manual for additional details.

9.3.5. Other Safety Assessments

Refer to Section 10 for information on AE assessment and Section 7.7.2 for concomitant therapy assessments.

Safety laboratory results will be assessed in an ongoing manner. A central safety laboratory will be used. Laboratory parameters are provided in Appendix 1.

9.4. Participant Restrictions During this Study

The following restrictions apply for the specified times during the study period. If a participant does not comply with these restrictions or tests positive in any laboratory tests (eg, pregnancy), he or she may be excluded or withdrawn from the study.

- Starting at Screening, participants will be required to abstain from blood or plasma donation until 4 months after the final study visit
- Starting on Day 1 until the final follow-up visit, participants will be asked to abstain from grapefruit or grapefruit juice, Seville oranges, and quinine (eg, tonic water)
- Contraception requirements are discussed in Section 8.2

9.5. Study Procedures by Visit

Study procedures are presented by visit in Table 2 and Table 3. Every effort should be made to avoid protocol deviations.

At the Investigator's discretion, unscheduled visits may be conducted for the assessment of AEs, physical examinations, vital signs, laboratory tests, drug dispensing, ECGs, and/or TTEs. All information collected from unscheduled visits will be recorded on the eCRF and included in the clinical database.

9.6. Visit Scheduling

All visits should occur within the visit window (± 4 days for Week 4; ± 7 days for all remaining visits from Week 6 to Week 260/EOS). If an evaluation is missed, reschedule and perform it as close as possible to the original date.

10. EVALUATION, RECORDING, AND REPORTING OF ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND ADVERSE EVENTS OF SPECIAL INTEREST

Safety assessments will consist of monitoring and recording of AEs, including SAEs and adverse events of special interest (AESIs), performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Hospitalization or procedural intervention for endpoint events (myectomy, septal ablation) will not be captured as SAEs, but will be recorded on specialized eCRFs.

10.1. Definitions of Pretreatment Adverse Events, Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

10.1.1. Pretreatment Adverse Events

A pretreatment adverse event (PTAE) is an AE that occurs in a participant who has signed informed consent to participate in a study but has not received any study drug. A PTAE may result from a protocol-mandated procedure (eg, phlebotomy, invasive procedure, such as biopsy) but does not necessarily have to have a causal relationship with study participation.

10.1.2. Adverse Events

- According to the International Council for Harmonisation (ICH) guideline for GCP, an AE is defined as any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product; it does not necessarily have to have a causal relationship with this treatment.
- An AE can therefore be any unfavorable and unintended sign (eg, tachycardia, enlarged liver, clinically important or abnormal laboratory finding), symptom (eg, nausea, chest pain), or evidence of disease activity temporally associated with the use of a study medication, whether or not related to the study medication.
- Each AE should be recorded as a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should not be recorded as additional AEs. If a diagnosis is unknown, signs or symptoms should be recorded appropriately as a PTAE or AE.
- Any new disease or exacerbation of an existing disease (eg, a worsening in the character, frequency, or severity of a known condition) is an AE except as described below:
  - Preexisting medical conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should not be recorded as PTAEs or AEs. However, if the participant experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTAE (worsening or complication occurs before the first dose of study drug) or an AE (worsening or complication occurs after the first dose of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, “worsening of ….”).
- Recurrence of an intermittent medical condition (eg, headache) not present prior to the first dose of study drug
- Any deterioration in a laboratory value or other clinical test (eg, ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug

The following additional points should be considered for PTAEs and AEs:

- Preplanned medical or surgeries or procedures
  - Preplanned surgeries or procedures that were scheduled prior to signing of informed consent are not considered PTAEs or AEs. However, if a planned procedure is performed early (eg, as an emergency) due to worsening of a preexisting condition, the worsening of the condition should be captured appropriately as a PTAE or AE.
- Hospitalization for elective surgeries or procedures
  - Elective procedures performed for which there is no change in the participant's medical condition should not be recorded as PTAEs or AEs.
  - A hospitalization that was planned prior to the study or was scheduled during the study when the elective surgery or procedure became necessary because of the expected normal progression of the disease should not be recorded as PTAEs and AEs.
- Insufficient clinical response (lack of efficacy)
  - Insufficient clinical response, lack of efficacy, or pharmacologic action should not be recorded as an AE. The Investigator must make the distinction between exacerbation of preexisting medical condition and lack of therapeutic efficacy.
- Overdose
  - Cases of overdose with any medication without manifested side effects are not considered PTAEs or AEs.

The following should not be recorded as PTAEs or AEs:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the disease/disorder being studied, unless judged by the Investigator to be more severe than expected for the participant's condition
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of a preexisting disease or condition present or detected at the start of the study that do not worsen

10.1.3. Serious Adverse Event

An SAE is defined as any untoward medical occurrence at any dose that:

- Results in death
- Is immediately life-threatening (places the participant at immediate risk of death from the event as it occurred)

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital abnormality or birth defect
- Is an important medical event that may not result in death, be life-threatening, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it may require medical or surgical intervention to prevent any of the outcomes listed above

PTAEs that fulfill any of the criteria above are also to be considered SAEs and should be reported and followed up in the same manner.

- The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (eg, rated as mild, moderate, or severe); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).
- An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.
- Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.
- SAEs are required to be reported by the Investigator to the Sponsor within 24 hours after learning of the event.

10.1.4. Adverse Events of Special Interest

Symptomatic overdose, outcomes of a pregnancy, and LVEF ≤ 30% are considered AESIs.

AESIs are required to be reported by the Investigator to the Sponsor within 24 hours, irrespective of regulatory seriousness criteria.

10.2. Collection and Reporting of Adverse Events

10.2.1. Pretreatment Adverse Events and Adverse Events Collection Periods

Collection of PTAEs will commence from the time the participant signs the informed consent to participate in the study and continue until the participant receives the first dose of study drug. For participants who discontinue prior to study drug administration, PTAEs are collected until the participant discontinues study participation.

Collection of treatment-emergent adverse events (TEAEs) (as defined in Section 10.1.2) will commence at the time the participant receives the first dose of study drug. Routine collection of TEAEs will continue until the end of the study. Assessments of the relationship of AEs to study drug will be captured for TEAEs and not PTAEs.

10.2.2. Pretreatment Adverse Events and Adverse Events Reporting Periods

At each study visit, the Investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Participants may report AEs occurring at any other time during the study.

All participants experiencing PTAEs or TEAEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to screening levels or until there is a satisfactory explanation for the changes observed. All PTAEs and TEAEs will be documented in the PTAE/AE page of the eCRF, whether or not the Investigator concluded that the event was related to the study drug. The information to be documented for each event is described in the following sections.

10.2.2.1. Event description

When collecting PTAEs and TEAEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms (eg, anemia, not low hemoglobin). However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Death is an outcome and not the name of the event. In this situation, the event that led to the death is the name of the event.

10.2.2.2. Start Date/Time and Stop Date/Time

The date (and time during the period of residency) that the PTAE or TEAE started and the date (and time during the period of residency) that the event ended will be recorded. For events that continue for long periods of time, recording the end date as the day the event stabilized will be acceptable.

10.2.2.3. Relationship to Study Drug (Suspected Adverse Reactions)

The Investigator will assess causality by answering either "related" or "not related" to the question "Is there a reasonable possibility that the event may have been caused by the IMP/study medication?"

The following factors can be used in consideration of causality assessment:

- Dechallenge: Did the event abate after study medication was reduced or interrupted?
- Rechallenge: Did the event reappear after study medication was reintroduced?
- Temporal relationship and time to onset plausibility
- Confounding risk factors
- Amount and duration of study drug exposure
- Concomitant medications

10.2.2.4. Severity/Intensity

The intensity or severity of the PTAE or TEAE will be recorded using the following guidance:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)
- Life-threatening (urgent intervention indicated)
- Fatal (event led to death)

10.2.2.5. Seriousness

A PTAE or TEAE that meets any of the criteria for an SAE outlined in Section 10.1.3 will be recorded as an SAE, along with the criteria that were met.

It is important to distinguish between seriousness (PTAE or AE compared with SAE) and severity/intensity (mild, moderate, severe, life-threatening, or fatal) of AEs as outlined in Section 10.2.2.4.

10.2.2.6. Outcome

The outcome of a PTAE or TEAE will be recorded according to the options provided on the eCRF.

10.2.3. Reporting of Serious Adverse Events

All SAEs occurring during the treatment-emergent period (defined as the period from the first dose of study drug to the last dose of study drug + 56 days), regardless of causality, will be reported by the Investigator or designee to MyoKardia/designee within 24 hours of knowledge of the event or sequelae. Deaths and SAEs occurring after the treatment-emergent period and considered related to study drug or study procedure must also be reported. SAE reporting instructions are provided in the Study Reference Manual.

Medical records may be requested to support documentation of an SAE. The Investigator is responsible for summarizing the pertinent aspects of the event (including discharge summaries, diagnostic procedures, laboratory data, interventions) and updating the SAE eCRF with this information.

MyoKardia retains the right to request additional information for any participant with any ongoing AEs/SAEs at the end of the study, if judged necessary.

Spontaneously reported SAEs after completion of the study should be promptly reported by the Investigator to the Sponsor.

Prompt notification by the Investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities for the safety of participants and the safety of a study intervention under clinical investigation are met.

10.2.4. Follow-Up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and AESIs, will be followed until

resolution, stabilization, the event is otherwise explained, or the participant is considered lost to follow-up at the end of the study.

10.3. Suspected Unexpected Serious Adverse Event Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that qualify for mandatory expedited reporting to regulatory authorities where the SAE is suspected to be caused by the study treatment and is considered unexpected (ie, not defined as expected in the current IB, clinical protocol, or approved labeling for marketed products). In this case, MyoKardia or its designee will report the SUSAR to the relevant regulatory authority(ies). A report describing the SUSAR will be sent to all Investigators. Each Investigator must then notify his/her ethics committee (EC) of the SUSAR, as required by local regulatory authorities and in accordance with their EC policy.

11. STATISTICAL METHODS

11.1. Determination of Sample Size

No statistical hypothesis testing will be performed in this long-term extension study. Up to 20 individuals with symptomatic oHCM who completed Study MYK-461-004 will be enrolled.

11.2. Study Endpoints

11.2.1. Safety Endpoints

- Frequency and severity of treatment-emergent AEs and SAEs
- Frequency of cardiovascular (CV) death
- Frequency of sudden death
- Frequency of CV hospitalization
- Frequency of heart failure due to systolic dysfunction, defined as a symptomatic LVEF < 50%
- Frequency of myocardial infarction
- Frequency of ventricular arrhythmias (ventricular tachycardia, ventricular fibrillation, ventricular flutter, torsade de pointe)
- Frequency of syncope
- Frequency of seizures
- Frequency of stroke
- Frequency of LVEF < 50% as measured by echocardiography
- QT and QTcF intervals over time

11.2.2. Efficacy and Pharmacodynamic Endpoints

- Post-exercise, post-Valsalva, and resting LVOT gradient over time
- NYHA functional class over time
- KCCQ scores over time
- NT-proBNP over time
- Frequency of septal reduction therapy

11.2.3. Pharmacokinetic Endpoints

- Mavacamten plasma concentration over time
- Population PK

11.3. Statistical Analysis

The analyses presented here represent an outline of the intended methodology.

11.3.1. Analysis Populations

Three analysis populations are defined in this study:

- Safety Analysis Population: all participants who receive at least 1 dose of study drug
- PK Analysis Population: all participants who receive at least 1 dose of study drug and have at least 1 evaluable mavacamten plasma drug concentration
- PK/PD Analysis Population: all participants who receive at least 1 dose of study drug, have at least 1 evaluable mavacamten plasma drug concentration, and have post-baseline PD data; at least one 1 post-baseline PD data point must coincide temporally with an evaluable mavacamten plasma drug concentration

11.3.2. General Considerations

Data will be summarized in tabular format and concentration response plots may be constructed for selected variables. The sparse PK data will be combined with that of other studies to construct a population PK model across all studies.

Descriptive summary statistics for continuous variables will include the number of participants, mean, standard deviation (SD) or standard error, median, minimum, and maximum. Nominal categorical variables will be summarized using counts and percentages. Ordinal variables may be tabulated but no formal statistical test will be conducted.

11.3.3. Participant Disposition

The number and percentage of participants who complete and discontinue, as well as reasons for early discontinuation, will be presented.

11.3.4. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively.

11.3.5. Extent of Study Treatment Exposure and Compliance

The extent of study treatment exposure and compliance will be assessed and summarized by actual treatment received within the safety population.

The duration of study drug exposure is defined as last dose date – first dose date + 1 day, regardless of intermittent discontinuations.

A given administration will be considered noncompliant if the participant did not take the planned dose of treatment as required by the protocol. No imputation will be performed for participants with missing or incomplete data.

Treatment compliance will be summarized descriptively (number [n], mean, SD, median, minimum, and maximum). Participants with compliance < 80% will be fully described and summarized. In addition, number and percentage of participants with at least 1 dosing administration will be given.

11.3.6. Efficacy and Pharmacodynamic Analyses

All efficacy and PD analyses will be performed on the safety population.

11.3.7. Pharmacokinetic Analyses

Plasma concentrations of mavacamten will be determined and summarized using descriptive statistics. In addition, a PK analysis, as well as PK/PD analysis, will be performed using nonlinear mixed effect modeling. Both analyses will be reported in separate reports. Data from previously conducted studies might be added for model development for PK and PK/PD.

11.3.8. Safety Analyses

All safety analyses will be performed on the Safety Analysis Population using the following common rules:

- The baseline value is defined generally as the last available value before the first administration of study drug
- For quantitative safety parameters based on central laboratory measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group; said changes may be presented in shift tables or scattergrams
- The analysis of the safety variables will be descriptive, and no hypothesis testing is planned

The safety analysis will focus on the treatment-emergent period, which is defined as the time from the first administration of study drug to the last administration of study drug + 56 days.

11.3.8.1. Adverse Events

AEs will be mapped to system organ classes (SOCs) and preferred terms (PTs) using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be monitored during the study and the data analyzed with respect to overall incidence as well as severity and potential relationship of AEs to study medication. AEs with onset during the treatment-emergent period or with an onset

before the first dose of study medication that increases in severity or becomes serious during the treatment-emergent period, will be considered treatment-emergent.

Adverse event incidence tables will present the number (n) and percentage (%) of participants experiencing at least 1 TEAE by SOC and PT. Multiple occurrences of the same event in the same participant will be counted only once in the tables. The denominator for computation of percentages is the safety population within each treatment group.

AE incidence tables will be provided by treatment group for all types of TEAEs: all TEAEs, all treatment-emergent SAEs, and all TEAEs leading to permanent treatment discontinuation.

Potential Drug-induced Liver Injury

The incidence of liver-related AEs will be summarized by treatment group. The selection of PTs will be based on standardized MedDRA query hepatic disorder.

Deaths

- Deaths will be summarized and listed.

Pregnancy

- Participants who became pregnant during the study will be listed.

Overdose

- Onstudy overdoses will be listed.

11.3.8.2. 12-Lead Electrocardiogram

Twelve-lead ECGs will be obtained in the resting supine position. The RR, PR, QRS, and QT intervals will be measured and read by a central laboratory. Heart rate will be calculated as 60/(RR × 1000) (with RR expressed in milliseconds) and rounded to the nearest integer.

Correction for Heart Rate

Corrected QT interval (QTc) will be calculated using the manually over-read QT values. Each individual ECG QT value will be corrected for HR. The measured QT data will be corrected for HR using QTcF, as per the following formulae/method (with QT, RR, and QTc expressed in milliseconds):

Fridericia's Correction:

$$QTcF = \frac{QT}{(RR/1000)^{(1/3)}}$$

ECG Numeric Variables

HR, PR, QRS, and QTcF will be summarized using descriptive statistics. The change from baseline of these ECG parameters at each time point will be listed for each participant. For each time point of measurement, the changes from baseline will be summarized using descriptive statistics.

Categorical Analysis

The incidence count and percentage of participants with any postdose QTcF values of > 450 milliseconds, > 480 milliseconds, and > 500 milliseconds will be tabulated for all participants. Participants with QTc values > 500 milliseconds will be listed with corresponding baseline values, ΔQTcF, and baseline and treatment HR. The incidence count and percentage of participants with ΔQTcF increase from baseline of > 30 milliseconds and > 60 milliseconds will be tabulated.

Morphology Findings

New ECG morphologies for each participant not present on any ECG at baseline for that participant will be summarized for all observation time points combined.

The number and percentage of participants having T-wave morphology changes and/or the occurrence of abnormal U-waves that represent the appearance or worsening of the morphological abnormality from baseline will be reported.

Concentration-QTc Analyses

A concentration-QTc regression analysis, based on data collected from the ECG recordings after drug administration and concentration values for each participant at each matching time point, will be performed. The concentration-ECG relationship will be first evaluated by some descriptive plots to investigate any potential delayed or sustained effects and explore the shape of the relationship. Then, linear or nonlinear models will be implemented to estimate the slope and 95% confidence intervals of the relationship. Predictions at selected concentration values will be computed within the model.

11.3.8.3. Laboratory Data

The summary statistics (including number, mean, median, SD, minimum, and maximum) of all laboratory variables (laboratory values and changes from baseline) may be calculated for each visit (baseline and post-baseline time points) and presented by treatment group.

Listings of participants with laboratory values that are out of the reference range will be produced. Shift tables reflecting changes from baseline may be presented in lieu of descriptive statistics of changes from baseline.

Potential Drug-induced Liver Injury

The liver function tests, namely ALT, AST, ALP, and TBL, are used to assess possible drug-induced liver toxicity.

A graph of distribution of peak values of ALT versus peak values of TBL will be presented. Note that the ALT and TBL values are presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 × ULN for ALT and a horizontal line corresponding to 2 × ULN for TBL.

The normalization (to ≤ 1 × ULN or return to baseline if baseline > ULN) of elevated liver function tests will be summarized by categories of elevation (3 × ULN, 5 × ULN, 10 × ULN, 20 × ULN for ALT and AST, 1.5 × ULN for ALP, and 1.5 × ULN and 2 × ULN for TBL), with the following categories of normalization: never normalized or normalized after permanent

discontinuation of study drug. Note that a participant will be counted only under the maximum elevation category (1-3 × ULN, 3-5 × ULN, 5-10 × ULN, 10-20 × ULN, > 20 × ULN).

11.3.8.4. Vital Signs Data

The summary statistics (including number, mean, median, SD, minimum, and maximum) of all vital signs' variables (values and changes from baseline) may be calculated for each visit (baseline and post-baseline time points) and presented by treatment group.

Shift tables reflecting changes from baseline may be presented in lieu of descriptive statistics of changes from baseline.

11.3.8.5. Other Safety Analyses

Abnormal physical examination results will be listed. Concomitant medications will be summarized.

11.3.9. Interim Analyses

Interim analyses may be conducted. No multiplicity adjustment will be done for these interim analyses.

11.3.10. Exploratory Analyses

Exploratory analyses may be performed.

12. STUDY COMPLIANCE AND ETHICAL CONSIDERATIONS

12.1. Compliance Statement

This study will be conducted in accordance with the ICH GCP guidelines; US Title 21 Code of Federal Regulations (CFR) Parts 11, 50, 54, 56, and 312; European Union GCP; cGMP; the principles enunciated in the Declaration of Helsinki; and all human clinical research regulations in the countries where the study is to be conducted.

12.2. Informed Consent

The ICFs used for the study must comply with the Declaration of Helsinki, US 21 CFR Part 50, ICH GCP guidelines, and any other local regulations. The Investigator, or a person delegated by the Investigator, must explain the medical aspects of the study including the nature of the study and the treatment, orally and in writing, in such a manner that the potential participant is aware of potential benefits and risks. Potential participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Participants, or a legal guardian if the participant is unable to, must give informed consent in writing.

Prior to participation in any study-related procedures, participants must sign and date an EC-approved written ICF in a language the participant can understand. The informed consent process must be conducted, documented in the source document (including the date), and the form must be signed before the participant undergoes any study-specific procedures.

The language in the written information about the study should be as nontechnical as practical and should be understandable to the potential participant. Before informed consent is obtained, the Investigator should provide the potential participant ample time and opportunity to inquire about the study and to decide whether or not to participate.

All questions about the study should be answered to the satisfaction of the participant. The written ICF should be signed and personally dated by the participant and by the person who conducts the informed consent discussion. All participants will receive a copy of his/her signed and dated ICF.

12.3. Ethics Committee

The term EC used in this document refers to an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) or equivalent. The EC must review and, if appropriate, approve the following documents, as applicable:

- Study protocol and amendment(s)
- Written ICF(s) and consent form updates
- Participant recruitment procedures/documents (eg, advertisements)
- Written information to be provided to participants
- IB and available safety information (Note: ECs do not approve IBs but are responsible for acknowledging receipt)
- Information about payments and compensation available to participants

The EC approval must be in writing, clearly identifying the study (by protocol date and/or version), the documents reviewed, including informed consent, and date of the review. The Investigator has the responsibility to provide MyoKardia with the written EC approval prior to initiating any study-related procedures.

The Investigator also has the responsibility to inform the EC of the following, according to the EC's policy:

- All SUSARs (as described in Section 10.3)
- Any new information that may affect adversely the safety of the participants or the conduct of the trial
- Protocol deviations
- A synopsis of the study report upon study completion

Documentation of subsequent reviews of the study must also be forwarded to MyoKardia.

13. ADMINISTRATIVE PROCEDURES

13.1. Sponsor's Responsibilities

MyoKardia reserves the right to terminate the study at any time. MyoKardia and the Investigators will assure that adequate consideration is given to the protection of the participants'

interests. MyoKardia retains the right to terminate the study and remove all study materials from a clinical site at any time. Specific circumstances that may precipitate such termination are:

- Request by Health Authority to terminate the study
- Unsatisfactory participant enrollment with regard to quality or quantity
- Significant or numerous deviations from study protocol requirements, such as failures to perform required evaluations on participants, maintain adequate study records or inaccurate, incomplete, or late data recording on a recurrent basis
- The incident or severity of AEs in this or other studies indicating potential health hazard caused by the study treatment

13.1.1. Participant Confidentiality

The processing of personal data in pursuit of this study will be limited to those data that are reasonably necessary to investigate the utility of the study medications used in this study. These data will be processed with adequate precautions to ensure confidentiality according to applicable laws.

MyoKardia ensures that the personal data are:

- Collected for a specified and legitimate purpose
- Processed fairly and lawfully
- Accurate and up to date

Explicit consent for the processing of personal data will be obtained prospectively from the participating participant.

MyoKardia, whose responsibilities require access to personal data, agrees to keep the identity of participants confidential. This confidentiality will be maintained throughout the complete data processing.

Participants will be entitled to request confirmation of the existence of personal data held by MyoKardia and will have the right to rectify erroneous or inaccurate data up until database lock.

13.1.2. Study Supplies

MyoKardia will supply or ensure the coordination of sufficient quantities of the following materials to each clinical site:

- Mavacamten active capsules in 3 strengths (5, 10, and 15 mg) in 30-count bottles
- Supplies for laboratory assessments
- Study Reference Manual
- Pharmacy Manual
- IXRS Manual
- IB

13.1.3. Investigator Training

All clinical sites will have a center-specific study initiation meeting to ensure the center staff understands the protocol, study requirements and procedures, and data capture processes. This training will take place before the first participant is enrolled. Each clinical site will be provided with information regarding GCP and regulations specific to the conduct of the clinical studies. Each clinical site will be responsible for ensuring that new team members are adequately trained, and the training is documented.

13.1.4. Ongoing Communication of Safety Information During the Study

MyoKardia will provide the Investigator(s) with documentation of SAEs from this study and other studies that are related to mavacamten study medication and are unexpected (refer to Section 10.3), as appropriate. The Investigator(s) must forward this documentation to the EC as described in Section 10.3.

MyoKardia will also notify the Investigator(s) about any other significant safety findings that could alter the safety profile of the IMP from what is described in the protocol and significantly affect the safety of participants, affect the conduct of the study, or alter the EC's opinion about the continuation of the study.

13.1.5. Study Monitoring

MyoKardia will monitor this clinical study through remote data checks and monitoring visits to check the adequacy of clinical site staff and facilities, and to ensure adherence to the protocol, study procedures, and applicable regulations. The clinical site monitor will also assess proper eCRF completion and source document retention. The Investigator(s) and clinical site staff are expected to provide adequate space for monitoring visits and to allocate sufficient time to permit adequate review of the study's progress. The Investigator(s) will permit study-related monitoring, audits, EC review, and regulatory inspection(s), providing direct access to source data/documents and study-related facilities (eg, pharmacy, diagnostic laboratories).

13.1.6. Study Auditing and Inspecting

MyoKardia may audit the study conduct, compliance with the protocol, and accuracy of the data in 1 or more clinical sites.

The Investigator(s)/institution(s) will permit study-related monitoring, audits, and inspections by MyoKardia, EC, government regulatory authority(ies), and MyoKardia's quality assurance personnel or its designees by providing direct access to source data/documents after appropriate notification from MyoKardia.

13.2. Investigator's Responsibilities

13.2.1. Screening Log

The Investigator must keep a record that lists all participants who signed an informed consent and the reason for noninclusion if the potential participant does not ultimately enroll and receive IMP.

13.2.2. Mavacamten Accountability

The Investigator must ensure that the study drug at the investigational site is kept secured and accounted for with access limited to only those individuals authorized by the Investigator. The Investigator, his/her designee, or pharmacist must also maintain adequate records of distribution, dispensing, and destruction of all study drug at the end of the study. The study drug records must be readily available for inspection by the site monitor and/or auditor. Only those sites with institutional, local, state, or federal restrictions in the destruction of material will be allowed to return study drug to the depot. No study drug can be destroyed or returned to depot until the clinical site monitor has verified the accuracy of the study drug records at the clinical site.

13.2.3. Reporting and Recording of Study Data

Data will be captured and compiled using procedures developed by MyoKardia or designee. Electronic data capture (EDC) technology will be used for this study. Clearly record all requested study data on the eCRF and other forms as required. Whenever possible, record the reason for missing data in the source document. Only individuals who are identified on the study personnel responsibility/signature log and who have received appropriate training on the EDC system may enter or correct data in the eCRF. Incomplete or inconsistent data on the eCRF will result in data queries that require resolution by the Investigator or designee. Corrections to the eCRF, including the reason for the change, will be automatically documented through the EDC system's audit trail.

Participant source data must be maintained as original records or a certified copy (ie, copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original). The Investigator and affiliated institution should take measures to prevent the accidental or premature destruction of documents. Data collected on the eCRF must match the source documents.

An eCRF must be completed for each participant who signs an ICF. All entries into the eCRF are ultimately the responsibility of the Investigator before approving them via an electronic signature. The Investigator is responsible for ensuring accurate, authentic, and complete records for each participant.

An electronic copy of the eCRF casebooks will be sent to the clinical site for retention with other study documents after full completion of the study.

13.2.4. Source Data and Source Documents

The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the company and clinical site staff. The source documents are to be accessible for verification by the clinical site monitor.

Source documents should at minimum include the following information for each participant:

- Participant identification and contact information (name, date of birth, sex, address, phone)
- Documentation verifying participant eligibility (ie, medical history, physical examination)
- Informed consent process documentation and ICF

- Record of all visits and other contacts
- Record of all AEs and other safety parameters and all event attributes
- Record of all concomitant therapy (including start/stop dates, indication for use, dose)
- Date of study completion and reason for early discontinuation, if applicable

The author of an entry in the source documents should be identifiable as well as the date of the entry. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. The Investigator will provide certified copies of the participant's medical records in the event that the clinical site's policy does not permit direct access to the electronic medical records.

13.2.5. Participant Identification Information

To permit easy identification of the individual participant during and after the study, the Investigator is responsible for keeping an updated log that contains the participant identification information. This document will be reviewed by the clinical site monitor for completeness. However, to ensure the participant's confidentiality, the document will be maintained at the clinical site and no copy will be made.

13.2.6. Records Retention

MyoKardia will inform the Investigator in writing when it is acceptable to dispose of any study records. To enable evaluation and/or audits from regulatory authorities or MyoKardia, the Investigator agrees to keep records, including the identity of all participants (eg, participant identification code list and all source documents), all original signed ICFs, copies of all eCRFs, original laboratory reports, detailed records of study medication disposition, and all essential documents for the conduct of a clinical study. To comply with international regulations, the records should be retained by the Investigator for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. However, the Investigator may need to retain these documents for a longer period if required by the local regulatory requirements or by an agreement with MyoKardia.

13.2.7. Protocol Deviations

Unless there is a safety concern, there should be no deviations from the study protocol. In the event of a safety concern, the Investigator or designee must document and explain the reason for any deviation from the approved protocol. The Investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to participants without prior EC approval. Immediately after the implemented deviation or change, the Investigator must submit a report explaining the reasons for the protocol deviation to the EC and MyoKardia, if required. The Medical Monitor will notify the study monitor of the decision.

13.2.8. Blood Sample Collection/Storage

Blood samples that are collected as part of routine medical care or as part of protocol procedures may be stored and analyzed for PK or PD analyses.

After the study, samples may be used for additional investigation to help identify factors that may influence response to therapy. Such samples will be used in compliance with guidelines defined by US Food and Drug administration Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens That Are Not Individually Identifiable (issued 25Apr2006) and European Medicines Agency's Reflection Paper on Pharmacogenomic Samples, Testing and Data Handling.

13.3. Clinical Trial Insurance

Clinical trial insurance has been undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating clinical sites upon request.

13.4. Protocol Amendments and Study Administrative Letters

Study procedures will not be changed without the mutual agreement of the Investigator and MyoKardia.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and, where required, in a new version of the study protocol.

The amendment should be approved by the EC and the appropriate regulatory authority(ies) before implementation, as appropriate. Local requirements should be followed for revised protocols.

If a protocol amendment requires a change to the ICF, the EC will need to approve the revised ICF before the revised form is used.

If there are nonsubstantial changes, such as clarification of statement or corrections to obvious errors/typos/inconsistencies in the protocol, or changes to logistical or administrative aspects, then MyoKardia may issue an Administrative Letter. If local regulations require any administrative change, it will be communicated to or approved by the EC.

14. DATA QUALITY ASSURANCE

Quality assurance and quality control systems will be implemented and maintained per Standard Operating Procedures by MyoKardia, as appropriate, to ensure that this clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, ICH E6 GCP: consolidated guidance and the applicable regulatory requirements.

15. ADMINISTRATIVE CONSIDERATIONS

15.1. Use of Computerized Systems

This study will require the use of the following electronic data collection methods:

- EDC system to capture protocol-required participant data: clinical sites will enter data from source documents onto eCRFs for each study visit using a web-based interface.

Study monitors and data management personnel will use this system to review data and generate queries and reports as needed

- Cardiac clinical data management systems will be used to analyze ECG and echocardiographic data from digital equipment used by clinical site personnel to collect participant data
- IXRS to facilitate drug distribution

In addition, other central data management systems/databases and software may be used to collect and analyze study data:

- Laboratory Information Systems or proprietary systems will be used by laboratories for storing and/or analyzing bioanalytical laboratory data collected throughout the study
- Statistical software will be used for the statistical analysis of the study data

Information on the above systems will be provided to the Investigator, clinical site personnel, and other personnel as appropriate. Measures will be taken to ensure data security and accuracy, including but not limited to user training, granting of user accounts and privileges to trained and authorized personnel in a role-based manner, username/password/electronic signature requirements enforcement, programmed and manual edit checks as outlined in data validation specifications, computer generated audit trails, centralized data management, and routine study monitoring. The systems used will be compliant with US 21 CFR Part 11 and Annex 11 to the Rule Governing Medicinal Products in the European Union and the data collected will be archived (at minimum) for the period specified by applicable regulatory requirements.

15.2. Study Records

The Investigator and affiliated institution shall maintain the study documents and records as specified in "Essential Documents for the Conduct of a Clinical Trial" (ICH E6 Section 8), and as required by the applicable regulatory requirement(s). This includes, but is not limited to, the protocol, eCRFs, AE reports, participant source data (original records or certified copies), correspondence with health authorities and EC, consent forms, Investigator's curriculum vitae, monitor visit logs, laboratory reference ranges and laboratory certification or quality control procedures, and laboratory director curriculum vitae.

The eCRF must be completed at the time of, or shortly after the participant's visit or upon receipt of test results. Information will be provided to clinical site staff on the proper way to complete the eCRF.

A copy of each participant's eCRF will be maintained by the Investigator.

16. PUBLICATION

The data and results of the study will be owned solely by MyoKardia and shall be confidential information of MyoKardia, participant to the Investigator's publication rights, all as outlined in the agreement between the Investigator/institution and MyoKardia regarding the conduct of the clinical study (the "Clinical Study Agreement"). It is understood by the Investigator that

MyoKardia may use the information developed in this study in connection with the development of MyoKardia's proprietary IMP and, therefore, may disclose such information as necessary or useful to other clinical Investigators or regulatory agencies. To allow for the use of the information derived from the study, the Investigator understands that he/she has an obligation to provide and disclose all study results and all data developed during this study to MyoKardia.

Any publication or presentation of the results or data of this clinical study by the Investigator may only be made in strict compliance with the provision of the Clinical Study Agreement. The Investigator understands that it is not MyoKardia's intention to prevent publication of the data generated in the study; rather, MyoKardia reserves the right to control the form and timing of such publication for commercial reasons and desires to confirm the scientific accuracy of such information prior to such publication or presentation.

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APPENDIX 1. LABORATORY ASSESSMENTS

The following safety laboratory parameters will be measured by the central laboratory:

Hematology/Coagulation	Serum Chemistry
• CBC, including differential count	• Sodium
• Platelet count	• Potassium
• INR	• Chloride
• aPTT	• Bicarbonate
	• Calcium
	• Magnesium
	• BUN
	• Creatinine
	• ALP
	• ALT
	• AST
	• Total bilirubin
	• CPK[a]
	• Glucose
	• Protein
	• Albumin

Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood count; CPK, creatine phosphokinase; INR, international normalized ratio.
[a] If CPK is high, troponin I will be performed and reported.

At the Investigator's discretion, safety laboratory assessments may be repeated on Day 1 to confirm study eligibility before dosing of study medication.

The following non-safety laboratory parameters will be measured at Screening:

- Hepatitis panel (hepatitis B virus and hepatitis C virus)
- Human immunodeficiency virus test
- Follicle-stimulating hormone

APPENDIX 2. PROHIBITED MEDICATIONS

Cardiotoxic Agents

Prior or concomitant treatment with cardiotoxic agents, such as doxorubicin or similar, is prohibited. Prior or concomitant treatment with antiarrhythmic drugs with negative inotropic activity, such as flecainide or propafenone, is also prohibited.

Disopyramide and Ranolazine

Use of disopyramide or ranolazine is prohibited from 14 days before Screening to EOS.

Moderate and Potent CYP 2C19 Inhibitors and Potent CYP 3A4 Inhibitors

Potent and moderate CYP 2C19 inhibitors and potent CYP 3A4 inhibitors are prohibited from 14 days before Screening through the end of study. Examples are listed below.

- Efavirenz
- Etravirine
- Fluconazole
- Fluvoxamine
- Fluoxetine
- Moclobemide
- Omeprazole
- Ticlopidine
- Voriconazole

APPENDIX 3. POTENTIAL DRUG-INDUCED LIVER INJURY REPORTING AND ADDITIONAL ASSESSMENTS REPORTING

To facilitate appropriate monitoring for signals of drug-induced liver injury (DILI), cases of concurrent aspartate/alanine aminotransferase (AST/ALT) and total bilirubin (TBL) elevation according to the criteria specified in Section 7.4 (3 × upper limit of normal [ULN] for AST/ALT and 2 × ULN for TBL in participants with no underlying liver disease and eligibility criteria requiring normal liver function at baseline) require the following:

- The event is to be reported to MyoKardia as a serious adverse event (SAE) within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate case report form (CRF) (eg, Adverse Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities are to be completed and sent to MyoKardia

Other events of hepatotoxicity and potential DILI are to be reported as SAEs if they meet the criteria for an SAE defined in Section 10.1.3.

Additional Clinical Assessments and Observation

All participants for whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI or who experience AST/ALT elevations > 3 × ULN are to undergo a period of "close observation" until abnormalities return to normal or to the participant's baseline levels. Assessments that are to be performed during this period include the following:

- Repeat liver chemistries within 24-48 hours (ALT, AST, alkaline phosphatase [ALP], TBL); in cases of TBL > 2 × ULN or AST/ALT much greater than 3 × ULN, retesting is to be performed within 24 hours.
  - For participants that are far away from the trial site, it may be difficult for the participants to return to the trial site promptly. In this case, the participants should be retested locally, but normal laboratory ranges should be recorded, results should be made available to trial Investigators immediately, and the data should be included in the case reports.
  - Participants are to be monitored at least twice weekly; testing frequency may decrease to once per week or less if laboratory abnormalities stabilize or the investigational product(s) or protocol-required therapies have been discontinued AND the participant is asymptomatic.
- Obtain prothrombin time/international normalized ratio, fractionated bilirubin, and any other potentially relevant laboratory evaluations of liver function or disease
- Obtain complete blood count with differential to assess for eosinophilia
- Obtain appropriate blood sampling for pharmacokinetic analysis, if it has not already been collected
- Obtain a more detailed history of the following:

  - Prior and/or concurrent diseases or illness
  - Exposure to environmental and/or industrial chemical agents
  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting, and fever
  - Prior and/or concurrent use of alcohol, recreational drugs, and special diets
  - Concomitant medications (including nonprescription medicines and herbal and dietary supplements)
- Initiate full viral and autoimmune hepatitis evaluation (serologies for hepatitis A, B, C, D, E, Epstein-Barr virus, herpes simplex virus, etc); evaluate for other potential causes of DILI, including but not limited to nonalcoholic steatohepatitis, hypoxic/ischemic hepatopathy, and biliary tract disease
- Obtain gastroenterology or hepatology consult
- Perform appropriate liver imaging or biopsy if clinically indicated; strongly consider these tests in cases of concurrent transaminase and TBL elevation, as specified in Section 7.4
- Follow the participant until all laboratory abnormalities return to baseline or normal. The "close observation period" is to continue for a minimum of 4 weeks after investigational product(s) or protocol-required therapies discontinuation

The potential DILI event and additional information, such as medical history, concomitant medications, and laboratory results must be captured in corresponding CRFs.

APPENDIX 4. MANAGEMENT OF PARTICIPANTS WHO ARE UNABLE TO ATTEND ONSITE STUDY VISITS FOR PROTOCOL-SPECIFIED ASSESSMENTS AND MAVACAMTEN DOSE ADJUSTMENTS (EG, COVID-19 OR OTHER PANDEMICS, NATURAL DISASTERS, OR MAJOR DISRUPTIONS)

The following provisions may be made to accommodate participants who are unable to attend onsite study visits for scheduled assessments and dispensation of mavacamten:

- Participants who are unable to be seen at the clinic may be required to temporarily discontinue mavacamten.
- Participants may be tested for COVID-19 at the discretion of the Investigator and/or Sponsor.
- Mavacamten may be shipped directly from the study site to the participant, as necessary.

Temporary Discontinuation of Mavacamten

If the participant does not complete a visit within 4 weeks of the expected visit date, the participant will be contacted by the site at the end of the 4-week period and will be instructed to stop taking mavacamten.

Participants who temporarily discontinue from mavacamten should be contacted by the site every 2 weeks from the time of discontinuing mavacamten to assess for AEs and to document concomitant medications until the next study visit.

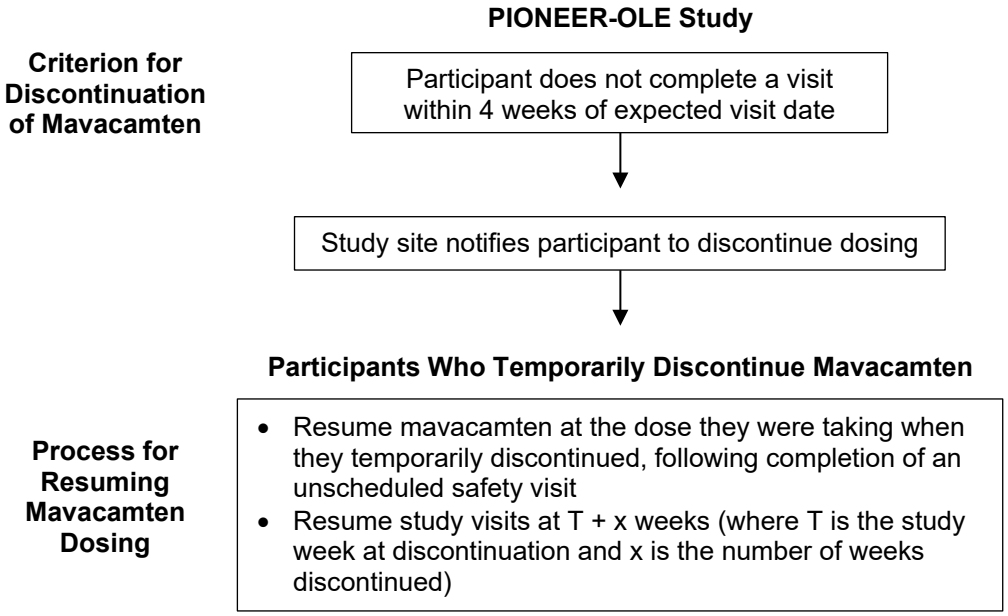
Resumption of Mavacamten Dosing

Participants who temporarily discontinue mavacamten may resume mavacamten dosing as follows:

- Resume mavacamten at the dose they were taking when they temporarily discontinued, following completion of an unscheduled safety visit
- Resume study visits at T + x weeks (where T is the study week at discontinuation and x is the number of weeks discontinued)

Participants who have discontinued and resumed treatment according to these guidelines may repeat the discontinuation/resumption cycle as often as necessary.

Schema for Dose Discontinuation and Resumption for Participants Who Are Unable to Attend Onsite Study Visits for Protocol-Specified Assessments and Mavacamten Dose Adjustments (eg, COVID-19 or Other Pandemics, Natural Disasters, or Major Disruptions)



Note: Unscheduled safety assessments will be conducted for participants who temporarily discontinue study drug prior to resuming dosing, as outlined in Table 2. Study drug will be dispensed at the unscheduled visit; however, participants will not resume dosing until notified by the study site.

APPENDIX 5. INVESTIGATOR'S SIGNATURE

I have read and understood the contents of the clinical protocol, MYK-461-008 Amendment 4, An Open-label Extension Study of Mavacamten (MYK-461) in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy Previously Enrolled in Study MYK-461-004 (PIONEER-HCM), and I agree to the following:

- To assume responsibility for the proper conduct of this clinical study at this clinical site and to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by MyoKardia/designee
- That I am aware of, and will comply with, the internationally recognized code of Good Clinical Practices (GCP) and all other applicable regulatory requirements to obtain written and dated approval for the Ethics Committee (EC; eg, Institutional or Central Review Board [IRB] or Independent Ethics Committee [IEC]) for the study protocol, written informed consents, consent form updates, study participant recruitment procedures, and any other written information to be provided to the study participants before initiating this clinical study
- Not to implement any changes to, or deviations from, the protocol without prior agreement from MyoKardia and review and documented approval from the EC, except to eliminate an immediate hazard to the study participants, or when change(s) involves only logistical or administrative aspects of the clinical study
- To permit direct monitoring and auditing by MyoKardia or MyoKardia's representatives and inspection by the appropriate regulatory authority(ies)
- That I am thoroughly familiar with the appropriate use of the Investigational Medicinal Product (IMP) and other study medication(s) (if applicable), as described in this protocol, and any other information provided by MyoKardia or designee, including, but not limited to the current Investigator's Brochure (IB) or equivalent document and marketed prescription information (if applicable)
- To provide sufficient time and adequate numbers of qualified staff and facilities for the foreseen duration of the clinical study to conduct the study properly, ethically, and safely
- To ensure that all persons assisting in this study are adequately informed about the protocol, IMP/study medication(s), and their clinical study-related duties and functions

Signed: _____ Date: _____
(sign name with credentials)

Printed Name: _____

PROTOCOL AMENDMENT
SUMMARY OF CHANGES TABLE

Protocol Amendment 3: 22 January 2021

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The primary objectives of this amendment are to:

- Extend the duration of the study to 5 years
- Add guidance for COVID-19 and other disruptions of clinical conduct
- Adjust echocardiogram core laboratory assessments to be site-read and not blinded to the Investigator or site in addition to sending to a central imaging laboratory for possible future assessment
- Update text regarding the evaluation, recording, and reporting of adverse events, serious adverse events, and adverse events of special interest to be consistent with global changes that have been made across the mavacamten program

Changes are summarized in the table below. Additional changes were made for clarity, consistency, and accuracy throughout the document.

Summary of Changes

Section(s)	Summary of Change	Reason(s) for Change
Title Page	MyoKardia, Inc. ~~333 Allerton Avenue~~ ~~South San Francisco, CA 94080~~ **1000 Sierra Point Parkway** **Brisbane, CA 94005**	MyoKardia address was updated.
Synopsis/ Section 7.7.2 Concomitant Therapy	**Background cardiomyopathy therapy (eg, beta-blocker, verapamil, or diltiazem) may be adjusted or stopped after a participant has received 24 weeks of mavacamten treatment in this study as determined by the Investigator in conjunction with the MyoKardia Medical Monitor.**	Investigator in conjunction with MyoKardia Medical Monitor may adjust background cardiomyopathy therapy. Clarification was provided regarding monitoring subjects following reduction of doses of mavacamten and background cardiomyopathy therapy.
Synopsis/ Section 4 Overall Study Design and Plan/ Section 4.1 Study Duration/ Figure 1 Study Schema	The study duration is ~~172~~**264** weeks (up to 4 weeks Screening, ~~156~~**252** weeks treatment **[5 years]**, and ~~12~~ **8** weeks posttreatment follow-up) unless the development of mavacamten is stopped~~The~~	Overall study duration was extended to be up to 260 weeks, with treatment duration extended to up to approximately 5 years. Circumstances for

Section(s)	Summary of Change	Reason(s) for Change
Table 2 Schedule of Assessments Table 3 Schedule of Assessments	~~protocol may be amended to allow an extension beyond 3 years should~~ **or until** mavacamten ~~remain in clinical development but not yet be available~~ **becomes commercially available (at the discretion of MyoKardia).**	participant/study termination were clarified. Treatment duration and study duration were updated throughout the document as appropriate and the schedule of assessments was updated and divided into 2 tables.
Synopsis/ Section 9.1.1 Echocardiography	**Echocardiograms will be site-read and not blinded to the Investigator or the site.** All echocardiography data will be sent to **the IXRS for LVEF stopping criterion (LVEF < 50% by local site read). Echocardiograms will also be sent to** a central imaging laboratory **for possible future assessment. If necessary, contrast may be administered to ensure that high quality ECHO images are obtained.**	Echocardiograms will be site-read and not blinded to the Investigator or the site and will be sent to the IXRS for LVEF stopping criterion. Echocardiograms will also be sent to a central imaging laboratory for possible future assessment.
Synopsis/ Figure 1 Study Schema/ Table 2 Schedule of Assessments/ Table 3 Schedule of Assessments	**Telehealth assessments (conducted via telephone or other technology based on standard at institution) will be conducted at Weeks 18, 30, 42, 54, 66, 78, 90, 102, 114, 126, 138, 150, 162, 174, 186, 198, 210, 234, and 246 to assess AEs, concomitant medications, and pregnancy.**	Telehealth visits added for assessment of AEs, concomitant medications, and pregnancy.
Table 2, Schedule of Assessments	[e] All changes that occur after the administration of the study medication **and meet the definition of an AE** are recorded as AEs.	Updated footnote to specify that the definition of AE has been met to be recorded as AE.
Table 2, Schedule of Assessments	[h] …**All stress echocardiography visits will be conducted in the clinic and not in the home health setting.**	Updated footnote to clarify that stress echocardiography visits need to occur in the clinic.
Table 3, Schedule of Assessments	[a] **Visit may be conducted by properly trained home health agency if appropriate delegation of authority is documented at study site; however, if scheduled, stress**	Clarified that with the exception of stress TTE assessments, other assessments scheduled to be conducted on-site may be conducted by properly trained home health agency if appropriate

Section(s)	Summary of Change	Reason(s) for Change
	TTE assessment must be performed at site.	delegation of authority is documented at study site.
Global	~~Women~~ **Females**	Changed "women" to "females" throughout protocol to be more consistent with regulatory practice.
Synopsis/ Section 5.2 Inclusion Criteria	1. Has completed Study MYK-461-004. **Prior participation in a non-interventional observational study is allowed.**	Text was added to clarify that participants who had previously participated in a non-interventional study were included.
Synopsis/ Section 11.2.1 Safety Endpoints	Frequency of heart failure ~~requiring the initiation of oral loop diuretics or the administration of intravenous loop diuretics~~ **due to systolic dysfunction, defined as a symptomatic LVEF <50%**	Previous heart failure endpoint replaced with heart failure due to systolic function
Section 1.2 Clinical Studies	Details provided in Section 1.2	Updated the status of the completed and ongoing studies in the mavacamten clinical program.
Section 7.2 Administration and Schedule of Study Drug	Participants should be instructed to take the study drug ~~under fasting conditions (≥ 8 hours)~~ at approximately the same time every day (±8 hours).	Requirement for mavacamten dosing under fasting conditions was removed in accordance with the results of a recent food effect study.
Section 7.7.2 Concomitant Therapy	**The occurrence of concomitant diagnostic/surgical/therapeutic procedures and available details will also be documented on the appropriate eCRF.**	Added language regarding the collection of data regarding concomitant diagnostic/surgical/therapeutic procedures.
Synopsis/ Section 4 Overall Study Design and Plan/ Appendix 4	**In the context of COVID-19 or other pandemics, natural disasters, or major disruptions, provisions may be made to accommodate participants who are unable to attend onsite study visits for scheduled assessments and dispensation of mavacamten. Guidance on participant management in these situations is outlined in Appendix 4.**	Text was added to introduce provisions in study conduct for participants who may be affected in the context of a pandemic (eg, COVID-19) or other pandemics, natural disasters, or major disruptions.

Abbreviations: AE, adverse event; COVID-19, corona virus disease; CYP, cytochrome P450; eCRF, electronic case report form; ECHO, echocardiogram; HCM, hypertrophic cardiomyopathy; IXRS, interactive response system; LVEF, left ventricular ejection fraction; TTE, transthoracic echocardiogram.

PROTOCOL AMENDMENT
SUMMARY OF CHANGES TABLE

Protocol Amendment 2: 11 April 2019

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

This protocol amendment is being submitted in order to update text based on the Investigator's Brochure (IB) version 6, to change the Medical Monitor, to allow for increases in dose beyond Week 6, to allow for increments in dosing beyond the previous Maximum Target Dose, to provide updated language on overdose, to provide updated listing of contraception requirements, to include an additional stress echocardiogram at Week 72, and to extend the study duration from 2 to 3 years.

Section(s)	Summary of Change	Reason(s) for Change
Title page	Removed clinical operations contact Replaced the name and contact information for [redacted] with that of [redacted]	Clinical operations contact no longer accurate To change the Medical Monitor
Section 1.2	Revised to reflect updated Investigator's Brochure (IB) including additional studies, enrollment data, and clinical study report completion status	New IB version 6 was released
Synopsis, Figure 1, Table 2, Section 2.2, Section 4	Added stress echocardiography at Week 72	To further evaluate left ventricular outflow tract (LVOT) gradient and to subsequently be able to dose adjust the participants accordingly if required
Synopsis, Figure 1, Section 4	Added text to indicate that participants can be dose adjusted/uptitrated beyond Week 6	To allow Investigators the flexibility to dose adjust the participants based on the results of transthoracic echocardiography (TTE)/stress echocardiography beyond Week 6
Section 7.4.3	Removed reference to Independent Data Monitoring Committee	There is no Independent Data Monitoring Committee for this study

Section(s)	Summary of Change	Reason(s) for Change
Synopsis, Section 5.2	Inclusion Criteria #5 (contraception) updated	Updated listing of appropriate birth control methods for participants who are women of childbearing potential, in this case, a requirement for at least one "highly effective" form per the Clinical Trial Facilitation Group (CTFG) guidance on contraception in clinical trials. The previously described option of the use of the "double barrier" method with the male using a condom and female using a diaphragm or cervical cap has been removed as neither of these methods is considered "highly effective" by CTFG. In addition, with data from Study MYK-461-010 now available, the statement warning about mavacamten potentially reducing the effectiveness of hormonal contraceptives has been removed.
Section 8	Pregnancy and contraception guidance updated	To harmonize with updated eligibility criteria on highly effective contraception based on new available information from MyoKardia drug-drug interaction studies
Section 11.3.9	Allowed for the possibility of an interim analysis	To allow the flexibility for an interim analysis, if needed
Synopsis, Section 4	Added text to allow for dose increments above the previous Maximum Target Dose upon discussion between the Investigator and the MyoKardia Medical Monitor	To allow flexibility to the Investigator to be able to dose adjust a participant beyond the Target Dose for participants who were noted to have a subtherapeutic pharmacokinetic (PK) or pharmacodynamic (PD) response.

Section(s)	Summary of Change	Reason(s) for Change
Synopsis, Section 4	Participants on 5 mg who have met the stopping criteria will be temporarily discontinued on treatment. Based on clinical evaluation, these participants can be considered for dose reintroduction at 5 mg following discussion between the Investigator and the MyoKardia Medical Monitor.	To allow for careful clinical consideration of treatment discontinuation or study retention for a participant on 5 mg who meets the stopping criteria
Synopsis, Section 4	Updated language to Fridericia-corrected QT interval (QTcF) stopping criteria	Rules were changed from static single QTcF value to take into consideration QRS width and percent change in QTcF from baseline. These rules are more reflective of the expected variances in QT interval and conduction abnormalities prevalent in hypertrophic cardiomyopathy (HCM) patients.
Table 2	Respiratory rate should be recorded at Screening and end of study (EOS)	Clarification that respiratory rate in addition to other protocol stipulated vital signs will be taken at Screening and EOS
Table 2	Added language clarifying that vital signs are to be measured prior to dosing and respiratory rate should be obtained after at least 5 minutes of resting	To clarify instructions for when to obtain vital signs
Table 2	Added additional PK samples to be taken at Weeks 36 and 60	In view of optionality to dose titrate beyond Week 6, additional PK samples are required at these 2 time points.
Section 7.5	Instructions for managing a participant experiencing heart failure related to systolic dysfunction were updated to site-specific standard of care.	To accommodate potential variances in the way heart failure related to systolic dysfunction may be managed across sites, as well as changes that might take place in management guidelines
Section 7.6	New language on overdose	To clarify clinical threshold when participants are to be dose discontinued following a drug overdose

Section(s)	Summary of Change	Reason(s) for Change
Throughout document	Style changes	To make document more consistent with the American Medical Association (AMA) Manual of Style or with MyoKardia preference
Throughout document	The treatment period was extended by 52 weeks, from 104 weeks (2 years) to 156 weeks (3 years), with study duration extending from 120 weeks to 172 weeks. Study assessments were accordingly extended, with additional time points added throughout.	To allow more time to provide participants treatment access until MYK-461 receives marketing approval
Throughout document	Maximum Target Dose wording changed to Target Dose	To clarify that the Target Dose is a dose obtained from the parent MYK-461-004 study that is no longer a maximum dose as participants in the current study can be given a dose higher than the Target Dose
Section 5.5.1	"Participant withdrawal from treatment or withdrawal from study" was added as a reason the Investigator should discontinue a participant's study treatment permanently.	To allow for study treatment discontinuation with participant withdrawal from the study.
Synopsis, Table 2, Section 4, Section 9.1.4, Section 11.2.2	"Frequency of angina burden" and Canadian Cardiovascular Society chest pain grading scale were removed as endpoints and assessment.	The study did not require this assessment for evaluation of chest pain.
Synopsis, Section 2.2, Section 4	Allowance was added for participants on a stable dose of 10 or 15 mg (for 24 weeks or longer) to be dose reduced by the Investigator in conjunction with the Medical Monitor.	This addition is to allow participants on stable treatment who are deemed to have achieved clinical benefit in the opinion of the Investigator and Medical Monitor, based on clinical assessments demonstrating symptomatic and functional improvement, to be dose reduced to a dose considered appropriate by both the Investigator and Medical Monitor.

Section(s)	Summary of Change	Reason(s) for Change
Synopsis, Table 2, Section 9.2.1	All PK blood draws after Week 4 were specified to be predose draws.	Due to the option to be able to dose adjust the participant beyond Week 6, trough PK measures are required to be able to accurately conduct dose adjustments.
Section 11.3, Section 11.3.6, Section 11.3.10, Section 15.1	References to a statistical analysis plan (SAP) were removed.	For an open-label single arm extension study, analyses may be documented in an abbreviated document instead of a full SAP.

Abbreviations: CTFG, Clinical Trial Facilitation Group; EOS, end of study; IB, Investigator's Brochure; PK, pharmacokinetics; QTcF, Fridericia-corrected QT interval; SAP=statistical analysis plan.

PROTOCOL AMENDMENT
SUMMARY OF CHANGES TABLE

Protocol Amendment 1: 03 April 2018

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

This protocol amendment is being submitted in order to clarify items, ensure consistency, and change the medical monitor.

Section(s)	Summary of Change	Reason(s) for Change
Title page	• Changed the title of clinical operations contact to [redacted] • Replaced the name and contact information for [redacted] with that of [redacted]	• To update the title of the clinical operations contact • To change the medical monitor
Synopsis (Study Design); Section 7.7.2	Changed "and/or" to "or"; added "either" in conjunction with the "or"	To be consistent with the requirement that a participant cannot be on both beta blockers and calcium channel blockers simultaneously
Synopsis (Study Design)	Changed "individualized to *target* a steady-state trough plasma concentration" to "individualized to *obtain* a steady-state trough plasma concentration"	To eliminate repeating words
Synopsis (Study Design); Section 4	Inserted "PK" in "plasma sample"	To improve clarity and to be consistent throughout the protocol
Synopsis (Study Design)	Changed visit window at Week 6 to ± 7 days (from ± 4 days)	To be consistent with study visit windows in Table 1 Schedule of Study Procedures
Synopsis (Study Design); Section 4	Added and deleted text in dose reduction rule, including adding an electrocardiogram in addition to the echocardiogram (TTE) at the unscheduled visit and allowing the unscheduled visit to be within 2-4 weeks instead of within 2-3 weeks	To clarify the dose reduction rule

Section(s)	Summary of Change	Reason(s) for Change
Synopsis (Study Design); Figure 1 Study Schema, footnote b; Section 4	• Added Week 116 to any mention of EOS visit • Added ET to any mention of Week 104 visit	To improve clarity and consistency
Synopsis (Study Design)	• Replaced "standard echocardiogram" with "standard TTE" • Added standard TTE at Week 116/EOS	• To clarify that echocardiogram means TTE • To clarify that the TTE should be conducted at EOS, consistent with Section 4
Synopsis (Study Design); Figure 1 Study Schema; Table 1 Schedule of Study Procedures, footnote h (old); Section 4; Section 9.1.1.2	• Deleted language about the post-exercise stress TTE needing to be within 4 weeks prior to the last dose of study drug and replaced with "Week 104/ET" in Synopsis (Study Design), Section 4, and Section 9.1.1.2; also changed Figure 1 (including footnote b) so the TTE is at Week 104/ET; deleted Table 1, footnote h • Added post-exercise TTEs at Weeks 4 and 48 in Figure 1 and at Week 48 in Section 9.1.1.2	• Because there is no CPET in the study, there is no need to have the post-exercise TTE within 4 weeks prior to last dose of study drug at Week 104/ET; the post-exercise TTE should be conducted at the Week 104/ET visit • To be consistent with Table 1 and text in Synopsis (Study Design) and Section 4
Synopsis (Study Design); Figure 1 Study Schema; Table 1 Schedule of Study Procedures, table and footnote k; Section 4	• Changed "premenopausal women" to "women of childbearing potential" • Changed frequency of pregnancy tests from every 4-6 weeks (Figure 1) or 6 weeks (Synopsis [Study Design],Table 1 footnote k, and Section 4) to every 4 weeks; in Table 1 Schedule of Study Procedures, added a pregnancy test at Week 8 to ensure a pregnancy test is taken every 4 weeks • Added "urine" to Table 1, footnote k	• To be consistent with other mavacamten protocols • To be consistent regarding the frequency of at-home pregnancy tests for women of childbearing potential (every 4 weeks) • To clarify that it is a urine pregnancy test
Synopsis (Study Duration); Section 4.1	• In Synopsis (Study Duration): Changed the study duration from 116 weeks to 120 weeks in Synopsis (Study Duration) • In Section 4.1: Changed the study duration from 116 weeks to 120 weeks and posttreatment duration from 8 weeks to 12 weeks	• To correct an arithmetic error in the previous protocol's Synopsis (Study Duration) • To correct study duration and posttreatment duration in Section 4.1

Section(s)	Summary of Change	Reason(s) for Change
Synopsis (Inclusion Criteria); Section 5.2	Deleted urinalysis as a safety laboratory assessment in inclusion criterion 4	To be consistent with the fact that urinalysis is not being done (per Table 1 Schedule of Study Procedures)
Synopsis (Exclusion Criteria) item 5; Section 5.3 item 5	Deleted "a history of"	To eliminate extraneous words
Synopsis (Exclusion Criteria) item 6; Section 4; Section 5.3 item 6	Changed "for at least 4 weeks" to "for at least 14 days prior to Screening"	To clarify the criterion and to be consistent with other protocols
Table 1 Schedule of Study Procedures	Deleted rows for body height and body weight since they are already included in the physical examinations and described in footnote e	To simplify the table
Table 1 Schedule of Study Procedures (table and footnote h); Section 7.3	Added row in Table 1 for IMP compliance and a footnote (h) indicating that compliance will be checked by capsule count; added "clinic" to "at each visit" in Section 7.3	To clarify when compliance will be checked
Table 1 Schedule of Study Procedures	• In Table 1, changed "Plasma sample for drug level" to "PK sample" and added "PK" to the abbreviations • In footnote i, changed wording from "plasma sample" to "blood sample for PK"	To be consistent with other mavacamten protocols
Table 1 Schedule of Study Procedures	Eliminated NYHA functional class, KCCQ, and CCS assessments at Weeks 12, 36, 60, 84, and 96	To reduce the number of assessments
Table 1 Schedule of Study Procedures, note	Added a note that the visit window is ± 4 days at Week 4 and ± 7 days at all remaining visits from Week 6 to Week 116/EOS	To clarify the visit windows
Table 1 Schedule of Study Procedures, footnote b; Section 9.3.1	Added that a participant's HCM history will be collected	To record participants' HCM histories as part of their medical histories
Table 1 Schedule of Study Procedures, footnote c	Changed timing of body temperature assessment from every clinic visit to only Day 1 and Week 116/EOS visits	To reduce the number of body temperature assessments

Section(s)	Summary of Change	Reason(s) for Change
Table 1 Schedule of Study Procedures, footnote e	Added "at all physical examinations"	To clarify when weight will be collected
Table 1 Schedule of Study Procedures, footnote f; Section 9.3.3; Section 11.3.8.2	• Deleted triplicate 12-lead ECG language • Deleted "within 2 hours" (Table 1 and Section 9.3.3)	• To eliminate the need for triplicate 12-lead ECGs • To eliminate the 2-hour restriction
Table 1 Schedule of Study Procedures, footnote g	Added sentence "All post-exercise stress echocardiograms should include a 4-hour fast prior to exercise."	To clarify the procedure in the table and to be consistent with Section 9.1.1.2
Table 1 Schedule of Study Procedures, footnote i	Deleted "≤ 2 hours"	To eliminate the requirement that PK blood sample needs to be collected within 2 hours prior to dosing
Section 2.2; Section 4	Added that an eligible participant's dose may be increased to the maximum target dose after Week 6 if it is first discussed with and approved by the MyoKardia medical monitor	To allow the possibility of increasing the dose after Week 6 in this 2-year study in participants who were eligible for a dose increase at Week 6 but whose dose was not increased at that time due to investigator judgment
Section 4	Changed "Dose adjustment *will* occur at Week 6" to "Dose adjustment *may* occur at Week 6" and "The dose *will* be increased at Week 6" to "The dose *may* be increased at Week 6"	To clarify that a principal investigator does not need to increase the dose at Week 6 if he or she does not think a dose increase is justified in his or her clinical judgment
Section 4	Changed the final sentence in the third paragraph	To clarify the criterion for not increasing the dose
Section 4	• Changed visit windows at Week 8 and Week 12 from ± 4 days to ± 7 days • Inserted "functional" into "NYHA class" • Replaced "symptom assessments" with KCCQ score and CCS chest pain grading scale	• To correct an error in the text and to be consistent with the Synopsis • To be more precise and to be consistent with the Synopsis • To provide more detail and to be consistent with the Synopsis
Section 5.4	Added sentence "Rescreening may be allowed at the discretion of the investigator and the sponsor's medical monitor."	To clarify that rescreening is permitted

Section(s)	Summary of Change	Reason(s) for Change
Section 7.2	• Changed the drug administration window from ± 4 hours to ± 8 hours • Deleted "immediately" • Changed "drug blood level is obtained" to "a plasma PK sample"	• To be consistent with MYK-461-005 EXPLORER-HCM • To be consistent with Table 1, footnote i • To be consistent with other plasma PK sample language throughout the protocol
Section 7.5	Added "…and the procedures outlined in Section 4 will be implemented", deleted a sentence, and changed "After the participant" to "If a participant"	To clarify what procedures will happen and to be consistent with Section 4
Section 7.7.3; Appendix 2	Updated both sections, including adding ranolazine as a prohibited therapy in Appendix 2	To be internally consistent without being repetitive and to be consistent with prohibited therapy in MYK-461-005 EXPLORER-HCM
Section 8.2.4	Added text regarding reporting guidelines and extending reporting outcomes to 6 months after birth	To update language after pharmacovigilance review
Section 9.1.1.1	Deleted "or cardiopulmonary exercise testing (CPET)"	To be consistent with the fact that CPET is not being performed in this study
Section 9.1.1.2	Changed "baseline" to "Screening"	To be consistent with usage throughout the protocol
Section 9.2.2	• Deleted sentence that plasma concentrations of NT-proBNP will be evaluated in a blinded manner • Added Weeks 4, 48, 104, and 116 to NT-proBNP blood draw time points • Deleted sentence that on Day 1 and at Week 16, blood draws for NT-proBNP will be performed before and immediately after CPET	• To be consistent with the fact that NT-proBNP is not being evaluated in a blinded manner in this open-label study • To be consistent with sequence of NT-proBNP blood draw before stress echo • To be consistent with the fact that CPET is not being performed in this study (see item above)
Section 10	Reorganized and updated section	To follow recommendations made after pharmacovigilance team review
Appendix 1	Deleted thyroid-simulating hormone assessment	To eliminate this assessment since it is not being conducted in this study

Section(s)	Summary of Change	Reason(s) for Change
Throughout document	Replaced “β-blockers” with “beta blockers”	To be consistent with other recent MyoKardia protocols
Throughout document	Style changes (eg, spaces around mathematical operators) (Note: these are not shown in track changes since they do not affect clinical operations or patient safety)	To make document more consistent with the AMA Manual of Style or with client preference

Abbreviations: AMA, American Medical Association; CCS, Canadian Cardiovascular Society; CPET, cardiopulmonary exercise test; ECG, electrocardiogram; EOS, end of study; ET, early termination; HCM, hypertrophic cardiomyopathy; IMP, investigational medicinal product; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; NT-proBNP, N-terminal pro b-type natriuretic peptide; PK, pharmacokinetics; TTE, transthoracic echocardiogram.