Cover Page for Study Protocol

Sponsor Name: MyoKardia, Inc.
NCT Number: NCT03442764
Sponsor Trial ID: MYK-461-006 (MAVERICK-HCM)
Study Title: A Randomized, Double-blind, Placebo-controlled, Concentration-guided, Exploratory Study of Mavacamten (MYK-461) in Patients with Symptomatic Non-Obstructive Hypertrophic Cardiomyopathy (nHCM) and Preserved Left Ventricular Ejection Fraction
Document Description: Study Protocol (Amendment 1.0)
Document Date: 04 April 2018

CLINICAL STUDY PROTOCOL

Protocol Number:	MYK-461-006 (MAVERICK-HCM)
Protocol Title:	A Randomized, Double-blind, Placebo-controlled, Concentration-guided, Exploratory Study of Mavacamten (MYK-461) in Patients with Symptomatic Non-obstructive Hypertrophic Cardiomyopathy (nHCM) and Preserved Left Ventricular Ejection Fraction
Indication:	Hypertrophic Cardiomyopathy
Phase:	2
Investigational Medicinal Product:	Mavacamten (MYK-461)
Sponsor:	MyoKardia, Inc. [redacted]
Key Sponsor Contacts:	Amy Sehnert, MD Medical Monitor [redacted]
Original Protocol Date:	04 December 2017
Amendment 1 Date:	04 April 2018

PROTOCOL AMENDMENT
SUMMARY OF CHANGES TABLE

Protocol Amendment 1: 04 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

[redacted]

Section(s)	Summary of Change	Reason(s) for Change
Title page	• Changed the title of clinical operations contact to "Associate Director" • Replaced the name and contact information [redacted]	• [redacted] • [redacted]
Entire document	• Moved Figure 1 Study Schema and Table 1 Schedule of Study Procedures immediately following Synopsis • Deleted Section 5.5 Withdrawal of Participants and replaced with Section 10 Treatment Discontinuation and Withdrawal From Study [redacted] • Reorganized and updated Section 11 (formerly Section 10) Evaluation, Recording, and Reporting of Adverse Events [redacted]	[redacted]

Section(s)	Summary of Change	Reason(s) for Change
Synopsis; Table 1 (including footnotes); Section 4; Section 9.1; Section 12.2.2	• [redacted] • Removed CCS chest pain grading scale assessment	• [redacted]
Synopsis (Inclusion Criteria); Section 5.2	• Deleted "initial diagnosis or" from inclusion criterion 4 • Added "and distinctly measurable from the LVOT gradient" to inclusion criterion 8	[redacted]
Synopsis (Exclusion Criteria); Section 5.3	• Added exclusion criteria regarding phenocopy diseases (exclusion criterion 4) and atrial fibrillation (exclusion criteria 8 and 9) • Deleted former exclusion criterion 7 • Changed several exclusion criteria (exclusion criteria 10, 13, 14, 23)	[redacted]
Synopsis (Safety Endpoints); Section 12.2.1	• Added "Safety" to Synopsis row name and Section 12.2.1 heading • Added "AESIs" to list of safety endpoints	[redacted]
Synopsis (Sample Size and Statistical Considerations); Section 12.1	Changed "95% confidence intervals" to "effect size estimates"	[redacted]
Figure 1 Study Schema	Removed stress echo at Week 16	[redacted]
Table 1 Schedule of Study Procedures; Section 9.2.1	[redacted]	[redacted]
Table 1 Schedule of Study Procedures	Added row for TSH	[redacted]
Table 1 Schedule of Study Procedures	Added IMP administered at site at Week 16	[redacted]

Section(s)	Summary of Change	Reason(s) for Change
Table 1 Schedule of Study Procedures	Changed footnotes e, h, o, q, r, s	[redacted]
Section 1.2; Section 1.3	Updated text	[redacted]
Section 2.1	• [redacted]	• [redacted]
Section 2.2	Updated dosing scheme	[redacted]
Section 4	[redacted]	[redacted]
Section 4.2	Changed “will be” to “is”	[redacted]
Sections 7.4.1, 7.4.2, 7.4.3, 7.6, 14.2.2	Replaced “mavacamten” with “study drug” in headings and text, as applicable	[redacted]
Section 7.5	Revised language and inserted Subsection 7.5.1	[redacted]
Section 7.6 (including Section 7.6.1)	Updated overdose text	[redacted]
Section 7.7.3; Appendix 2	[redacted]	[redacted]
Section 9.2.2.1	[redacted]	[redacted]
Section 9.2.3	Changed “Plasma” to “Serum”	[redacted]
Section 9.3.3	• Deleted triplicate 12-lead ECG • Reworded so that ECG is conducted predose on Day 1	[redacted]
Section 9.3.4	Updated language	[redacted]

Section(s)	Summary of Change	Reason(s) for Change
Section 9.3.5	Updated language	[redacted]
Section 12.3.6.2	[redacted]	[redacted]
Section 14.1.2	Added ECG machines and PRO devices to list of study supplies	[redacted]
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.)	[redacted]

Abbreviations: AESI, adverse event of special interest; AMA, American Medical Association; CCS, Canadian Cardiovascular Society; ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; IDMC, Independent Data Monitoring Committee; IMP, investigational medicinal product; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro b-type natriuretic peptide; PRO, patient-reported outcomes; TSH, thyroid-stimulating hormone.

PROTOCOL SYNOPSIS

Title	A Randomized, Double-blind, Placebo-controlled, Concentration-guided, Exploratory Study of Mavacamten (MYK-461) in Patients with Symptomatic Non-obstructive Hypertrophic Cardiomyopathy (nHCM) and Preserved Left Ventricular Ejection Fraction
Study Number	MYK-461-006 (MAVERICK-HCM)
Study Phase	2
Number of Centers	Approximately 35 sites in the United States
Objective	• To evaluate the safety and tolerability of a 16-week course of mavacamten in individuals with symptomatic nHCM
[redacted]	• [redacted]
[redacted]	• [redacted]
Study Design	This is a multicenter, exploratory, randomized, double-blind study of the administration of mavacamten in 60 participants with symptomatic nHCM randomized to receive a 16-week course of mavacamten doses titrated to achieve 1 of 2 target drug concentrations (Group 1: ~200 ng/mL; Group 2: ~500 ng/mL) or placebo once daily (QD). Dose adjustments will be based on PK parameters. Assessments include safety, [redacted]

Number of Participants	Approximately 60, with approximately 20 participants in each of the 3 treatment groups
Study Treatment	Participants will be randomized via an interactive response system to 3 groups in a 1:1:1 ratio: 2 active treatment groups and 1 matching placebo. Participants in the 2 active treatment groups start at a dose of 5 mg QD and will undergo dose adjustment at Week 6 based on plasma concentration of mavacamten in samples taken at the Week 4 visit. Participants in the placebo group will undergo the same assessments in order to preserve the blind. Target trough concentration is approximately 200 ng/mL for active treatment (Group 1) and approximately 500 ng/mL for active treatment (Group 2). Dosing will continue to Week 16. During the study, participants who are treated for their hypertrophic cardiomyopathy (HCM) condition (eg, beta blocker or calcium channel blocker) should receive a stable dose of such treatment for at least 2 weeks prior to Screening, and every effort should be made to keep such treatment unchanged (ie, at the same dose) throughout the entire study duration until the final end of study visit at Week 24. Doses of mavacamten used in this study will be 2.5, 5, 10, and 15 mg. Randomization will be stratified according to current treatment with beta blocker (yes or no) and type of exercise testing (treadmill or bicycle). Study drug will be administered as 1 capsule QD by mouth.
Study Duration	The study duration for any individual participant will be 28 weeks (± 7 days); this includes a 4-week screening period, a 16-week treatment period, and an 8-week post-treatment follow-up period.
Inclusion Criteria	Each participant must meet the following criteria to be included in this study: 1. Able to understand and comply with the study procedures, including CPET, 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 2. Is at least 18 years old at Screening 3. Body weight is greater than 45 kg at Screening 4. Diagnosed with nHCM (hypertrophied and non-dilated left ventricle in absence of systemic or other known cause) consistent with current American College of Cardiology Foundation/American Heart Association and European Society of Cardiology guidelines, ie, the participant must meet at least 1 of the 2 following criteria at the time of Screening: • Left ventricular (LV) wall thickness ≥ 15 mm, or • LV wall thickness ≥ 13 mm with a positive family history of HCM 5. Has documented left ventricular ejection fraction ≥ 55% at the Screening visit as determined by the echocardiography central laboratory 6. Has adequate acoustic windows to enable accurate transthoracic

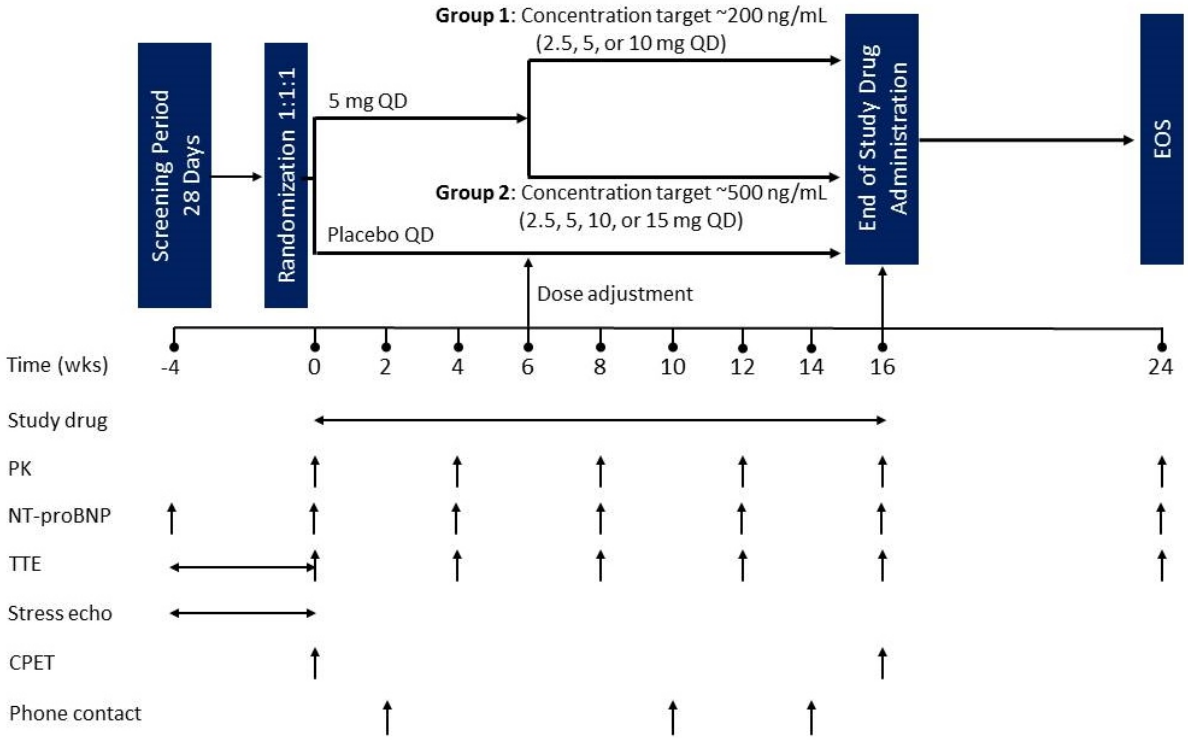
	echocardiograms 7. Left ventricular outflow tract (LVOT) peak gradient at rest AND during Valsalva AND post-exercise < 30 mmHg as determined by the echocardiography central laboratory 8. If intracavitary gradient is present and distinctly measurable from the LVOT gradient, then maximal intracavitary gradient at rest AND during Valsalva AND post-exercise < 30 mmHg as determined by the echocardiography central laboratory 9. Has New York Heart Association (NYHA) Class II or III symptoms at Screening 10. Has an elevated NT-proBNP at rest (> 300 pg/mL) at Screening 11. Has safety laboratory parameters (chemistry, hematology, coagulation, and urinalysis) 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 12. Female participants must not be pregnant or lactating and, if sexually active, must be using one of the following acceptable birth control methods from the Screening visit through 3 months after the last dose of study drug. Hormonal contraceptives are not considered highly effective contraception for this study because mavacamten could reduce the effectiveness of hormonal contraceptives. • Double-barrier method (eg, male using a condom and female using a diaphragm or cervical cap) • Barrier plus nonhormonal contraception (eg, male using a condom and female using a nonhormonal intrauterine device or nonhormonal intrauterine system) • Female is surgically sterile for 6 months or postmenopausal for 2 years. 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 2 years or more following cessation of all exogenous hormonal treatments and follicle-stimulating hormone levels are in the postmenopausal range 13. Male participants with sexual partners must agree to use condoms for the duration of the study and for 3 months after the last dose of study medication in order to prevent passing mavacamten to the partner in the ejaculate

Exclusion Criteria	A participant who meets any of the following exclusion criteria may not participate in this study: 1. Previously participated in a clinical study with mavacamten 2. Hypersensitivity to mavacamten or any of the components of the mavacamten formulation 3. Participated in a clinical trial where the participant received any investigational drug (or is currently using an investigational device) within 30 days prior to Screening or 5 times the respective elimination half-life (whichever is longer) 4. Has a known infiltrative or storage disorder causing cardiac hypertrophy that mimics nHCM, such as Fabry disease, amyloidosis, or Noonan syndrome with LV hypertrophy 5. Has any medical condition that precludes upright exercise stress testing 6. Has a history of syncope or a history of sustained ventricular tachyarrhythmia with exercise within the past 6 months 7. Has a history of resuscitated sudden cardiac arrest at any time or known appropriate implantable cardioverter defibrillator (ICD) discharge within 6 months prior to Screening 8. Has paroxysmal, intermittent atrial fibrillation with atrial fibrillation present per the investigator's evaluation of the participant's electrocardiogram (ECG) at the time of Screening 9. Has persistent or permanent atrial fibrillation not on anticoagulation for at least 4 weeks prior to Screening and/or is not adequately rate-controlled within 6 months prior to Screening (note: patients with persistent or permanent atrial fibrillation who are anticoagulated and adequately rate-controlled are allowed) 10. Is currently treated with disopyramide or ranolazine (within 14 days prior to Screening) or treatment with disopyramide or ranolazine is planned during the study 11. For participants on beta blocker, verapamil, or diltiazem, any dose adjustment < 14 days before Screening (see Section 7.7.2) 12. Currently treated or planned treatment during the study with a combination of beta blocker and verapamil or a combination of beta blocker and diltiazem 13. Has been treated with invasive septal reduction (surgical myectomy or percutaneous alcohol septal ablation) within 6 months prior to Screening (note: if a participant has had prior septal reduction therapy, the diagnostic wall thickness criteria and all other eligibility criteria must be met at time of Screening) 14. Documented history of resting or post-exercise LVOT or intracavity gradient > 30 mmHg unless subsequently treated by septal reduction therapy 15. Fridericia-corrected QT interval (QTcF) > 480 ms or any other ECG abnormality considered by the investigator to pose a risk to participant safety (eg, second-degree atrioventricular block type II)

	16. Has documented obstructive coronary artery disease (> 70% stenosis in one or more epicardial coronary arteries) or myocardial infarction within the past 6 months 17. Has known moderate or severe (as per the investigator's judgment) aortic valve stenosis at Screening 18. Has any acute or serious comorbid condition (eg, major infection or hematologic, renal, metabolic, gastrointestinal, or endocrine dysfunction) that, in the judgment of the investigator, could lead to premature termination of study participation or interfere with the measurement or interpretation of the efficacy and safety assessments in the study 19. Has pulmonary disease that limits exercise capacity or systemic arterial oxygen saturation 20. Positive serologic test at Screening for infection with human immunodeficiency virus, hepatitis C virus, or hepatitis B virus 21. History of clinically significant malignant disease within 10 years of Screening: • Participants who have been successfully treated for nonmetastatic cutaneous squamous cell or basal cell carcinoma or have been adequately treated for cervical carcinoma in situ can be included in the study • Participants with other malignancies who are cancer-free for more than 10 years before Screening can be included in the study 22. History or evidence of any other clinically significant disorder, condition, or disease (with the exception of those outlined above) that, in the opinion of the investigator or the medical monitor, would pose a risk to participant safety or interfere with the study evaluation, procedures, or completion 23. Currently taking, or has taken within 14 days prior to Screening, a prohibited medication such as a cytochrome P450 (CYP) 2C19 inhibitor (eg, omeprazole), a strong CYP 3A4 inhibitor, or St. John's Wort (see APPENDIX 2 for more details) 24. Prior treatment with cardiotoxic agents such as doxorubicin or similar (see APPENDIX 2) 25. Unable to comply with the study requirements, including the number of required visits to the clinical site 26. Employed by, or a relative of someone employed by MyoKardia, the investigator, or his/her staff or family
Safety Endpoints	• Frequency and severity of treatment-emergent adverse events, adverse events of special interest, and serious adverse events; laboratory abnormalities; vital signs; and cardiac rhythm abnormalities
[redacted]	[redacted]

[redacted]	[redacted]
Sample Size and Statistical Considerations	This study will include a total of approximately 60 participants, or approximately 20 participants per treatment group. Such a sample size will be sufficient to obtain sound variability estimates while yielding reasonable effect size estimates for future planning purposes.

Figure 1 Study Schema



Abbreviations: CPET, cardiopulmonary exercise testing; EOS, end of study; NT-proBNP, N-terminal pro b-type natriuretic peptide; PK, pharmacokinetic blood sample taken; QD, once daily; stress echo, stress echocardiography; TTE, transthoracic echocardiogram.

Table 1 Schedule of Study Procedures

Assessment[a]	Screening[b] Day -28 to Day -1	Day 1	Week 2 (telephone call)[c]	Week 4[c]	Week 6[c]	Week 8[c]	Week 10 (telephone call)[c]	Week 12[c]	Week 14 (telephone call)[c]	Week 16[c]/ET	Week 24[c]/EOS
General Procedures											
Informed consent	X										
Medical history[d]	X										
Vital signs[e]	X	X		X		X		X		X	X
AEs[d]	X	X	X	X	X	X	X	X	X	X	X
ICD information downloaded[f]	X									X	
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Physical examination including height and weight[g]	X	X		X		X		X		X	X
ECG[h]	X	X		X		X		X		X	X
Resting TTE[i]	X	X		X		X		X		X	X
Post-exercise stress echocardiography[j]	X										
CPET[k]		X								X	
Accelerometer attached[l]	X							X			
Apply cardiac monitoring skin patch[m]	X							X			
Randomization		X									
Laboratory											
Hepatitis panel, HIV test	X										
[redacted]				X		X		X		X	X
Coagulation panel	X	X		X		X		X		X	X
Chemistry	X	X		X		X		X		X	X
Hematology	X	X		X		X		X		X	X
Urinalysis	X	X									X

Footnotes and abbreviations are defined on last page of table.

Table 1 Schedule of Study Procedures (continued)

Assessment[a]	Screening[b] Day -28 to Day -1	Day 1	Week 2[c] (telephone call)	Week 4[c]	Week 6[c]	Week 8[c]	Week 10 (telephone call)[c]	Week 12[c]	Week 14 (telephone call)[c]	Week 16[c]/ET	Week 24[c]/EOS
Laboratory (continued)											
hs-cardiac troponin I		X		X		X		X		X	X
NT-proBNP[o]	X[o]	X[o]		X		X		X		X[o]	X
TSH	X										
FSH[p] /Serum pregnancy test (women)[q]	X										
Urine pregnancy test (women)[q]		X		X		X		X		X	X
[redacted]		X									
[redacted]		X									
[redacted]		X								X	X
Symptom Assessments											
[redacted]	X	X		X		X		X		X	X
[redacted]											
[redacted]		X								X	X
[redacted]	X[v]	←	—	—	→		X[w]		X[w]	X[w]	X[w]
[redacted]	X[x]				X		X		X	X	X
[redacted]					X		X		X	X	X
Investigational Medical Product											
IMP QD		←	—	—	—	—	—	—	—	→	
IMP administered at site		X								X	
IMP compliance[y]				X	X	X		X		X	

Abbreviations: AE, adverse event; BP, blood pressure; CPET, cardiopulmonary exercise testing; DNA, deoxyribonucleic acid; ECG, electrocardiogram; eCRF, electronic case report form; EOS, end of study; [redacted]; ET, early termination; FSH, follicle-stimulating hormone; HCM, hypertrophic cardiomyopathy; [redacted], [redacted]; HIV, human immunodeficiency virus; HR, heart rate; hs, high-sensitivity; ICD, implantable cardioverter-defibrillator; ICF, informed consent form; IMP, investigational medicinal product; [redacted]; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; [redacted]; PK, pharmacokinetic; PRO, patient-reported outcomes; QD, once daily; TSH, thyroid-stimulating hormone; TTE, transthoracic echocardiography.

[a] Preferred order of assessments is symptom questionnaires; the following 3 assessments in any order: ECG, vital signs, and TTE; pre-exercise blood draws; exercise test; and post-exercise blood draws.

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

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

[d] Changes in baseline conditions from once the ICF is signed are recorded on the medical history eCRF unless the change is related to a study procedure, which is then considered an AE. All changes that occur after the administration of the IMP are recorded as AEs.

[e] At Screening, ET (if applicable), Week 16 (end of treatment), and Week 24 (end of study), complete vital signs including temperature, HR, respiratory rate, and BP will be obtained. At all other onsite visits except Week 6, only HR and BP are required. If PK sampling is conducted at a visit, vital signs should be collected before PK sampling. Vital signs should be taken with the participant in the same position at all visits. BP should be taken via an automated recorder after the participant rests for at least 5 minutes.

[f] For participants who have ICDs, information including rhythm strips and events will be downloaded from the ICDs.

[g] At Screening, Week 16, and Week 24, a complete physical examination will be conducted, including a neurological examination. At Week 4, Week 8, and Week 12, an abbreviated cardiopulmonary physical examination will be conducted, with other systems assessed as directed by interval history. Physical examinations will also include height (at Screening only) and weight (at all onsite visits at which a physical examination is performed).

[h] 12-lead ECGs will be performed at Screening and all onsite visits except for the Week 6 visit after 10 minutes of rest. Each time an ECG is completed, a 10-second paper ECG will be obtained and maintained in the study participant's source documentation. On Day 1, an ECG will be performed predose.

[i] Resting TTE should be performed prior to post-exercise stress echocardiography or CPET. Instantaneous peak LVOT gradient at rest and provoked peak LVOT gradient (Valsalva maneuver) will be assessed only at Screening.

[j] After a 4-hour fast, participants will undergo a standard symptom-limited exercise test by standardized treadmill or bicycle ergometer. Instantaneous peak LVOT gradient will be assessed immediately post-exercise by TTE.

[k] CPET by standardized treadmill or bicycle ergometer will be performed on both Day 1 and at Week 16/ET prior to dosing. CPET is done after a 4-hour fast. Obtain CPET with study participant in the same position at Week 16 as done on Day 1.

[l] The accelerometer is to be distributed during Screening and at the Week 12 visit and retrieved at the Day 1 and Week 16 visits.

[m] The cardiac monitoring adhesive skin patch is to be applied during Screening and at the Week 12 visit and retrieved at the Day 1 and Week 16 visits.

[n] Blood samples for PK will be collected at all post-Screening onsite visits except for the Day 1 and Week 6 visits. The time of each blood draw will be recorded. At Week 16, a PK sample will be collected before dosing as well as within 2 hours postdose. On other PK sampling days, the PK blood samples can be taken at any time that best facilitates conduct of all scheduled study procedures. The date and time of the last dose of IMP taken prior to the PK sample collection will be recorded.

[o] At Screening, the blood draw for NT-proBNP will occur prior to post-exercise stress echocardiography. At the Day 1 and Week 16 visits, the blood draw for NT-proBNP will be obtained both prior to and immediately after CPET.

[p] FSH testing at Screening for postmenopausal women to confirm postmenopausal status.

[q] Pregnancy testing for all females of childbearing potential. Conduct serum test at Screening and a urine pregnancy test at all other visits shown; conduct serum test if a urine test is positive. At Week 20, a urine pregnancy test will be conducted at home.

[r] Separate consent is required for HCM genotyping. Note that if a participant with a prior HCM clinical genotype test that was positive for pathogenic HCM-causing mutation(s) consents to provide their results, then no further genotype assessment will be performed. However, participants who have not been tested, participants who have tested negative for pathogenic HCM-causing mutation(s) on clinical panels, and participants who have a positive HCM genotype result but cannot provide the results or will not consent to provide the results may consent to have blood drawn on Day 1 prior to the first dose of IMP for assessment of HCM genotype.

[s] Participants may also consent separately to have blood drawn prior to dosing on Day 1 for assessment of pharmacogenetics and potentially additional DNA sequencing.

[t] Participants will have blood samples drawn on Day 1 and Week 16 prior to dosing and at Week 24 for potential exploratory biomarker analysis.

- [redacted]
- [redacted]
- [redacted]

[y] All participants will return their IMP dosing containers to the site for capsule counts. Refer to the Pharmacy Manual for details.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

A	peak velocity of late transmitral flow
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
BP	blood pressure
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CI	confidence interval
CPET	cardiopulmonary exercise test or testing
CYP	cytochrome P450
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
E	peak velocity of early diastolic transmitral flow
e'	peak velocity of early diastolic septal and lateral mitral annular motion
EC	ethics committee; refers to an IRB or IEC or equivalent
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
[redacted]	
EOS	end of study
ET	early termination
FDA	The United States Food and Drug Administration
GCP	Good Clinical Practice
HCM	hypertrophic cardiomyopathy
[redacted]	
HR	heart rate
IB	Investigator's Brochure
ICD	implantable cardioverter-defibrillator
ICF	informed consent form
ICH	International Council for Harmonisation

IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
ITT	intention-to-treat
IUD	intrauterine device
IUS	intrauterine system
IXRS	interactive response system
[redacted]	
LV	left ventricular
LVEF	left ventricular ejection fraction
LVOT	left ventricular outflow tract
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
nHCM	non-obstructive hypertrophic cardiomyopathy
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
oHCM	obstructive hypertrophic cardiomyopathy
PD	pharmacodynamic(s)
[redacted]	
[redacted]	
PK	pharmacokinetic(s)
PRO	patient-reported outcomes
PT	preferred term
QD	once daily
QoL	quality of life
QTc	corrected QT interval
QTcF	Fridericia-corrected QT interval
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
TBL	total bilirubin

TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
TTE	transthoracic echocardiography, transthoracic echocardiogram
ULN	upper limit of normal
US	United States
VCO_2	carbon dioxide production
VE	volume expired
VO_2	oxygen uptake

3 STUDY OBJECTIVES

3.1 Objective

The objective of this study is:

- To evaluate the safety and tolerability of a 16-week course of mavacamten in individuals with symptomatic nHCM

[redacted]

4 OVERALL STUDY DESIGN AND PLAN

This is a Phase 2, multicenter, exploratory, randomized, double-blind study to evaluate the safety, tolerability, preliminary efficacy, PD, and PK of 2 target drug concentrations of mavacamten compared with placebo in participants with symptomatic nHCM. Approximately 60 participants with symptomatic nHCM will be enrolled. Participants will be randomized in a 1:1:1 ratio to 1 of 2 active treatment groups or matching placebo group (Figure 1). Randomization will be stratified according to current treatment with beta blocker (yes or no) and type of exercise testing (treadmill or bicycle). Participants will be treated for 16 weeks and then followed up approximately 8 weeks after the last dose of study drug. At Week 6, all participants will undergo blinded dose adjustment based on Week 4 assessments (see Section 2.2 for details). Participants who are treated for their HCM condition (eg, beta blocker or calcium channel blocker) should receive a stable dose of such treatment for at least 2 weeks prior to Screening, and every effort should be made to keep such treatment unchanged (ie, at the same dose) throughout the entire study duration until the EOS visit at Week 24.

During the Screening process, participants will undergo a variety of general, cardiopulmonary, laboratory, [redacted], patient-reported outcomes (PRO), and symptom assessments as detailed in Table 1. Participants will receive their first dose of study drug on Day 1. Participants will then undergo a variety of assessments as noted in Table 1 every 2 weeks through Week 16. Assessments will be conducted at the clinical site at Weeks 4, 6, 8, 12, and 16; assessments will be conducted via telephone call at Weeks 2, 10, and 14. At Week 24, participants will undergo EOS procedures as described in Table 1.

[redacted]

Data from these PRO assessments will not be made available to the investigators and other site personnel throughout the study. Participants will first be informed of this when they fill out the consent form that is required in order to participate in the trial. The form will include information explaining that the PRO information gathered via the device is not shared with their healthcare provider and they should therefore report any concerning symptoms directly to their physician. Participants will then be reminded of this every time they go to complete the assessment on their handheld device. When the participant logs onto his/her handheld device to complete the assessments, a message screen will be shown advising the participant to consult his/her healthcare provider if he/she has any concerning symptoms. The participant will not be able to continue with the PRO assessments until he/she has acknowledged that he/she has read a provided message that any symptoms, health issues, or other concerns he/she is having may need to be discussed with his/her healthcare team.

[redacted]

4.1 Study Duration

The expected study duration is approximately 28 weeks: up to 4 weeks for Screening and 24 weeks (± 7 days) for study conduct, including the 8-week posttreatment follow-up period.

4.2 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will meet at regular intervals to review study data. The role of the IDMC will be to act in an advisory capacity to the Sponsor with respect to safeguarding the interest of study participants, assessing interim safety data, and advising the Sponsor and investigators on important emerging study conduct issues. The IDMC may formulate recommendations in relation to the evaluation procedures and methodologies being employed to survey and detect potential safety signals. Meeting frequency and membership is described in the IDMC Charter.

5 SELECTION AND WITHDRAWAL OF STUDY POPULATION

5.1 General Study Population and Clinical Sites

Approximately 60 participants with symptomatic nHCM are expected to enroll in this study at up to 35 clinical sites in the US.

5.2 Inclusion Criteria

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

1. Able to understand and comply with the study procedures, including cardiopulmonary exercise testing (CPET), 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
2. Is at least 18 years old at Screening
3. Body weight is greater than 45 kg at Screening
4. Diagnosed with nHCM (hypertrophied and non-dilated left ventricle in absence of systemic or other known cause) consistent with current American College of Cardiology Foundation/American Heart Association and European Society of Cardiology guidelines, ie, the participant must meet at least 1 of the 2 following criteria at the time of Screening:
   - LV wall thickness ≥ 15 mm, or
   - LV wall thickness ≥ 13 mm with a positive family history of HCM
5. Has documented LVEF ≥ 55% at the Screening visit as determined by the echocardiography central laboratory
6. Has adequate acoustic windows to enable accurate transthoracic echocardiograms (TTEs)
7. LVOT peak gradient at rest AND during Valsalva AND post-exercise < 30 mmHg as determined by the echocardiography central laboratory
8. If intracavitary gradient is present and distinctly measurable from the LVOT gradient, then maximal intracavitary gradient at rest AND during Valsalva AND post-exercise < 30 mmHg as determined by the echocardiography central laboratory
9. Has NYHA Class II or III symptoms at Screening
10. Has an elevated NT-proBNP at rest (> 300 pg/mL) at Screening
11. Has safety laboratory parameters (chemistry, hematology, coagulation, and urinalysis) 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

12. Female participants must not be pregnant or lactating and, if sexually active, must be using one of the following acceptable birth control methods from the Screening visit through 3 months after the last dose of study drug. Hormonal contraceptives are not considered highly effective contraception for this study because it is unknown if mavacamten reduces the effectiveness of hormonal contraceptives.
    - Double-barrier method (eg, male using a condom and female using a diaphragm or cervical cap)
    - Barrier plus nonhormonal contraception (eg, male using a condom and female using a nonhormonal intrauterine device [IUD] or nonhormonal intrauterine system [IUS])
    - Female is surgically sterile for 6 months or postmenopausal for 2 years. 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 2 years or more following cessation of all exogenous hormonal treatments and follicle-stimulating hormone levels are in the postmenopausal range
13. Male participants with sexual partners must agree to use condoms for the duration of the study and for 3 months after the last dose of study medication in order to prevent passing mavacamten to the partner in the ejaculate

5.3 Exclusion Criteria

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

1. Previously participated in a clinical study with mavacamten
2. Hypersensitivity to mavacamten or any of the components of the mavacamten formulation
3. Participated in a clinical trial where the participant received any investigational drug (or is currently using an investigational device) within 30 days prior to Screening or 5 times the respective elimination half-life (whichever is longer)
4. Has a known infiltrative or storage disorder causing cardiac hypertrophy that mimics nHCM, such as Fabry disease, amyloidosis, or Noonan syndrome with LV hypertrophy
5. Has any medical condition that precludes upright exercise stress testing
6. Has a history of syncope or a history of sustained ventricular tachyarrhythmia with exercise within the past 6 months
7. Has a history of resuscitated sudden cardiac arrest at any time or known appropriate implantable cardioverter defibrillator (ICD) discharge within 6 months prior to Screening
8. Has paroxysmal, intermittent atrial fibrillation with atrial fibrillation present per the investigator's evaluation of the participant's electrocardiogram (ECG) at the time of Screening
9. Has persistent or permanent atrial fibrillation not on anticoagulation for at least 4 weeks prior to Screening and/or is not adequately rate-controlled within 6 months prior to

Screening (note: patients with persistent or permanent atrial fibrillation who are anticoagulated and adequately rate-controlled are allowed)

10. Is currently treated with disopyramide or ranolazine (within 14 days prior to Screening) or treatment with disopyramide or ranolazine is planned during the study
11. For participants on beta blocker, verapamil, or diltiazem, any dose adjustment < 14 days before Screening (see Section 7.7.2)
12. Currently treated or planned treatment during the study with a combination of beta blocker and verapamil or a combination of beta blocker and diltiazem
13. Has been treated with invasive septal reduction (surgical myectomy or percutaneous alcohol septal ablation) within 6 months prior to Screening (note: if a participant has had prior septal reduction therapy, the diagnostic wall thickness criteria and all other eligibility criteria must be met at time of Screening)
14. Documented history of resting or post-exercise LVOT or intracavity gradient > 30 mmHg unless subsequently treated by septal reduction therapy
15. QTcF > 480 ms or any other ECG abnormality considered by the investigator to pose a risk to participant safety (eg, second-degree atrioventricular block type II)
16. Has documented obstructive coronary artery disease (> 70% stenosis in one or more epicardial coronary arteries) or myocardial infarction within the past 6 months
17. Has known moderate or severe (as per the investigator's judgment) aortic valve stenosis at Screening
18. Has any acute or serious comorbid condition (eg, major infection or hematologic, renal, metabolic, gastrointestinal, or endocrine dysfunction) that, in the judgment of the investigator, could lead to premature termination of study participation or interfere with the measurement or interpretation of the efficacy and safety assessments in the study
19. Has pulmonary disease that limits exercise capacity or systemic arterial oxygen saturation
20. Positive serologic test at Screening for infection with human immunodeficiency virus, hepatitis C virus, or hepatitis B virus
21. History of clinically significant malignant disease within 10 years of Screening:
    - Participants who have been successfully treated for nonmetastatic cutaneous squamous cell or basal cell carcinoma or have been adequately treated for cervical carcinoma in situ can be included in the study
    - Participants with other malignancies who are cancer-free for more than 10 years before Screening can be included in the study
22. History or evidence of any other clinically significant disorder, condition, or disease (with the exception of those outlined above) that, in the opinion of the investigator or the medical monitor, would pose a risk to participant safety or interfere with the study evaluation, procedures, or completion
23. Currently taking, or has taken within 14 days prior to Screening, a CYP 2C19 inhibitor (eg, omeprazole), a strong CYP 3A4 inhibitor, or St. John's Wort (see APPENDIX 2 for more details)
24. Prior treatment with cardiotoxic agents such as doxorubicin or similar (see APPENDIX 2)

25. Unable to comply with the study requirements, including the number of required visits to the clinical site
26. Employed by, or a relative of someone employed by MyoKardia, the investigator, or his/her staff or family

5.4 Screening and Enrollment

An informed consent form (ICF) must be signed and dated by the participant before any study-specific tests or procedures may be performed.

Each participant will be assigned a unique identification number when informed consent has been obtained. The identification number will be assigned based on information obtained from an interactive response system (IXRS). Participants will be considered enrolled once an identification number has been assigned. The identification number will be used to identify the participant throughout the study and should appear on all study-related documentation. Numbers will not include identifiable information. The investigator will ensure that informed consent is obtained from each participant before any study-specific procedures are performed.

Participants that fail to meet all inclusion criteria or present with an exclusion criterion may be re-screened. Refer to the Study Reference Manual for re-screening criteria and procedures.

6 RANDOMIZATION AND BLINDING PROCEDURES

6.1 Randomization

Participants who meet the inclusion/exclusion criteria will be randomized via an IXRS to 1 of 3 groups in a 1:1:1 ratio: 2 active treatment groups and 1 matching placebo group. Randomization will be stratified according to current treatment with beta blocker (yes or no) and type of exercise testing (treadmill or bicycle).

6.2 Study Blinding

Participants will be randomized to 1 of 3 groups via the IXRS. All participants receive either 5 mg mavacamten or matching placebo from Day 1 to Week 6. Blinded dose adjustment (2.5, 5, 10, or 15 mg mavacamten or placebo) via the IXRS will begin at Week 6 based on PK measurements at Week 4. Study drug administration will occur in a double-blind manner via the IXRS such that the investigator, site staff, the pharmacist, and the participant will not know which study drug is being administered.

In addition, the Sponsor, the central and core laboratories, and clinical site monitors will be blinded to assigned treatment. Echocardiography results (eg, LVEF) performed at clinic visits will be blinded to the investigator and study staff. The 4 different doses of mavacamten and matching placebo will be identical in appearance in order to preserve the blind. Study drug (2.5, 5, 10, or 15 mg mavacamten or matching placebo) will be labeled with a unique identifying number that will be assigned to a participant through the IXRS.

The pharmacovigilance team will be unblinded for suspected unexpected serious adverse reaction (SUSAR) reporting. The IDMC may also review unblinded safety and efficacy data.

6.3 Methods for Unblinding

Unblinding by the investigator independently of the Sponsor also may occur if an AE or toxicity necessitates identification of the medication for the welfare of the participant. Please refer to the IXRS Manual for the unblinding process and contact information.

7 STUDY TREATMENT

Study drug is defined as mavacamten or placebo.

All randomized study participants will receive either mavacamten (5 mg from Day 1 to Week 6 and one of a range of doses [2.5, 5, 10, or 15 mg] from Week 6 to Week 16) or matching placebo (Day 1 to Week 16) in a double-blind manner.

7.1 Formulation, Packaging, and Labeling of Study Drug

Mavacamten capsules and matching placebo have the same appearance. The study drug 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 4 strengths: 2.5, 5, 10, and 15 mg.

Mavacamten active and placebo 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.

The mavacamten active and placebo 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 via the IXRS 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 physician. Participants should be instructed to take the study drug under fasting conditions (≥ 8 hours) at approximately the same time every day (± 4 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.

7.3 Treatment Compliance

Compliance with study drug will be monitored by capsule count at Weeks 4, 6, 8, 12, and 16 (Table 1). Refer to the Pharmacy Manual for details.

7.4 Hepatotoxicity Stopping and Rechallenge Rules

Participants with abnormal hepatic laboratory values (eg, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL], or international normalized ratio) or signs/symptoms of hepatitis may meet the criteria for withholding of 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 FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009).

7.4.1 Criteria for Permanent Withholding of Study Drug Due to Potential Hepatotoxicity

Study drug 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 gallbladder 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 Study Drug Due to Potential Hepatotoxicity

For participants who do not meet the criteria for permanent withholding of study medication outlined above, study drug 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

Study drug 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 Study Drug After Potential Hepatotoxicity

The decision to rechallenge the participant should be discussed and unanimously agreed by the investigator, IDMC, and Sponsor.

If signs or symptoms recur with rechallenge, then study drug 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), Higher Than Expected Plasma Concentration, or Excessive QT Prolongation

If during the treatment period a participant has a resting LVEF ≤ 45%, plasma drug concentration ≥ 1000 ng/mL, or QTcF ≥ 500 ms (as determined by the echocardiography central laboratory, PK analysis laboratory, or ECG core laboratory, respectively), it will be communicated to the investigator and Sponsor that a stopping criterion has been met. Upon receipt of this information, the study site/investigator will contact the participant by

telephone and instruct the participant to discontinue study drug and return for the next scheduled onsite study visit or within 2 weeks, whichever is earlier. After the participant discontinues study drug, the participant will be encouraged to undergo early termination (ET) and EOS assessments (see Section 10.1.4). To maintain the study blind, a participant in either of the other 2 treatment groups may be randomly selected via the IXRS to similarly discontinue study drug.

If a participant experiences heart failure related to systolic dysfunction, no further study drug should be administered and administration of therapeutic doses of a β-adrenergic agonist (eg, 5 to 10 µg/kg/min dobutamine infusion) should be considered. Additional supportive measures, eg, intravenous volume supplementation and/or the use of arterial vasoconstrictor agents (α-adrenergic agonists) could complement the use of a β-adrenergic agonist. Aside from this specific advice regarding the role of a β-adrenergic agonist, appropriate care will be determined by the treating medical personnel.

New or worsening heart failure associated with systolic dysfunction is one of the criteria for permanent treatment discontinuation (Section 10.1.3) and should be subsequently managed as described in Section 10.1.2 and Section 10.1.4.

7.5.1 Management of Double-blind Treatment in the Case of LVEF ≤ 30% at Study Site

Results of TTE performed by study site sonographers at each scheduled visit following randomization should be kept blinded to the investigator and other study site personnel. An exception may occur if LVEF ≤ 30% is measured at the site. Under these circumstances, the sonographer should review and re-measure the findings with at least one other nonstudy professional qualified in echocardiography assessment who is not the investigator (eg, echocardiography laboratory director, other experienced sonographer, or nonstudy cardiologist). If the result is confirmed (LVEF ≤ 30%), then the investigator will be immediately notified and study drug will be discontinued.

LVEF ≤ 30%, as measured by local site sonography, is one of the criteria for permanent treatment discontinuation (Section 10.1.3). As this finding will lead to the investigator being unblinded, it should be subsequently managed as described in Section 10.1.2 and Section 10.1.4.

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.

In the event of suspected overdose, the investigator should contact the medical monitor. No further study drug should be administered. The participant should be closely monitored clinically for AEs/SAEs, with supportive measures undertaken as clinically indicated. If necessary, corrective measures such as initiation of inotropic support with adrenergic agents,

levosimendan, and/or PDE III inhibitors and other supportive measures, as described in the 2013 American College of Cardiology Foundation/American Heart Association Guideline for the Management of Heart Failure ([redacted]) and in the 2016 European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure ([redacted] should be implemented.

7.6.1 Reporting and Follow-up of Overdose

If a participant should experience an overdose, the investigator will report the overdose to the medical monitor 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.

[redacted]

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 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

Women of childbearing potential must use appropriate methods of birth control as listed in Section 8.2.3. Women of nonchildbearing potential are defined as women 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. Women are considered postmenopausal if they have had amenorrhea for at least 2 years or more following cessation of all exogenous hormonal treatments and follicle-stimulating hormone levels are in the postmenopausal range.

8.2.2 Restrictions for Male Participants

Male participants with sexual partners should use condoms for the duration of the study and for 3 months after the last dose of study drug in order to prevent passing mavacamten to the partner in the ejaculate.

Male participants should be advised not to donate sperm for 3 months after the last dose of study drug.

8.2.3 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 3 months after the last dose of study drug, participants should practice true abstinence or use effective means of contraception as follows:

- Double-barrier method (eg, male using a condom and female using a diaphragm or cervical cap)
- Barrier (eg, male using a condom) plus nonhormonal contraception (female using a nonhormonal IUD or IUS)
- Female is surgically sterile or postmenopausal as defined in Section 8.2.1.

8.2.4 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 3 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. The participant will be asked to provide information on the outcome of the pregnancy, including 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 1 of this document. 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.

[redacted]

[redacted]

[redacted]

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).

9.3.2 Physical Examination

At selected visits, a complete physical examination will be conducted including a neurological examination (gross motor and deep tendon reflexes), height (Screening only) 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.

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 at Screening and at all onsite study visits except the Week 6 visit. All ECG data will be sent to a central cardiac laboratory.

On Day 1, ECG will be performed predose

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 Cardiac Monitoring Skin Patch

At 2 time points during the study, participants will wear a small device to collect HR and rhythm data (Table 1). The self-contained device attaches to the skin using medical adhesive and contains surface electrodes, internal electronics to capture a continuous single lead ECG waveform, an accelerometer to capture physical activity, sufficient solid state memory to

store data over multiple days, and a battery to power the device. Two sequential patches will be worn for approximately 7 days (14 days total). Following a period of data collection, the device will be transported to a core laboratory where the continuous ECG waveforms and activity record stored on the device will be uploaded for analysis. The analysis will provide full disclosure capabilities for HR, heart rhythm, and physical activity over the period during which the device was properly applied and functioning. The device will be used to explore the pattern of HR and heart rhythm before and during treatment with study drug.

9.3.5 Vital Signs

Vital signs, including temperature, HR, respiratory rate, and blood pressure (BP), will be obtained at Screening, ET (if applicable), Week 16 (end of treatment), and Week 24 (EOS). At all other onsite visits except Week 6, only HR and BP are required. If PK sampling is conducted at a visit, vital signs should be collected before PK sampling. Vital signs should be taken with the participant in the same position at all visits. BP should be taken via an automated recorder after the participant rests for at least 5 minutes.

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

9.3.6 Other Safety Assessments

Refer to Section 11.2.2 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 72 hours prior to the first dose until the final follow-up visit, participants should not engage in unaccustomed intensive exercise except during protocol-specified exercise tests
- Starting at Screening, participants will be required to abstain from blood or plasma donation until 3 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 1. 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, 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 (± 7 days). If an evaluation is missed, reschedule and perform it as close as possible to the original date.

10 TREATMENT DISCONTINUATION AND WITHDRAWAL FROM STUDY

In general, every effort should be made to keep a participant on double-blind treatment for as long as possible during the study unless a safety concern arises. Treatment discontinuation may either be temporary or permanent, and if treatment discontinuation is permanent, the degree to which a study participant withdraws can vary (see Section 10.1.4). Each of these circumstances is described below.

10.1 Treatment Discontinuation

10.1.1 Temporary Treatment Discontinuation

Temporary treatment discontinuation may be considered by the investigator in the case of an AE/SAE or for another reason.

As a general rule, any discontinuation of study drug should be initially considered temporary unless permanent treatment discontinuation is mandated by the protocol (see Section 10.1.3).

In the case of discontinuation for an AE/SAE, the investigator should make a best effort to resume study drug as soon as practically possible, assuming there are no safety concerns (ie, the investigator is satisfied that in his or her medical judgment, the study drug is unlikely to be responsible for the event concerned).

All temporary treatment interruptions should be recorded in the eCRF.

10.1.2 Permanent Treatment Discontinuation

After a temporary treatment discontinuation, if a safety concern has not resolved or stabilized or the investigator suspects that study drug is responsible, the investigator may consider a treatment discontinuation as permanent. The investigator should make a best effort to contact the monitoring team before considering any treatment discontinuation as permanent. Permanent treatment discontinuation should be considered a last resort. Every effort should be made to collect important safety data if feasible and the study participant agrees.

In all cases, participants should be encouraged to discuss stopping study drug with the investigator or the investigator's designee so that questions can be addressed, concomitant therapy can be adjusted if needed, and a follow-up assessment be arranged.

Any permanent treatment discontinuation should be recorded in the eCRF.

10.1.3 Criteria for Permanent Treatment Discontinuation

The following reasons will lead to permanent treatment discontinuation:

- Safety threshold being met (see Section 7.5)

- Pregnancy
- New or worsening heart failure associated with systolic dysfunction
- Any breaking of the study blind requested by the investigator
- Continued administration of study drug is considered by the investigator to be detrimental to the participant's safety or well-being
- If all the criteria are met for possible DILI (see Section 7.4.1)
- The participant requests to discontinue study drug
- The Sponsor requests that the participant permanently discontinues study drug

10.1.4 Management of Participants After Permanent Treatment Discontinuation

If a participant permanently discontinues treatment prior to Week 16 (end of treatment), the participant will be asked to undergo an ET visit as soon as possible after stopping study drug, undergoing the procedures normally planned for the Week 16 visit, including CPET. Subsequently, every effort will be made to have the participant return to the site at the times corresponding to his or her remaining scheduled visits (ie, until the end of the study at Week 24), or through the recovery or stabilization of any AE to be followed as specified in this protocol, whichever comes last.

Under circumstances of permanent treatment discontinuation, study participants can:

- Withdraw from treatment (permanent treatment discontinuation) and agree to participate in the 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 (see Section 10.2)

In case of difficulties to comply and return for all study visits through Week 24, every effort should be made to have the participant return for as many study visits as possible, especially the Week 16 visit with CPET.

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 his/her 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).

10.2 Withdrawal from Study

10.2.1 Withdrawal of Consent for Ongoing Study Participation

Participants may withdraw from the study before study completion if they decide to do so, at any time and for any reason. Withdrawal of consent for treatment (permanent treatment discontinuation) described above 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).

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 any 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 eCRF and in the participant's medical records when considered as confirmed. The date of the withdrawal and the reason should be documented.

The statistical analysis plan (SAP) will specify how these participants lost to follow-up will be considered for their primary endpoints.

Participants who have withdrawn from the study cannot be re-randomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.2.2 Replacement of Participants Who Withdraw from the Study

Participants who withdraw from the study after receiving an initial dose of treatment will not be replaced. If a participant withdraws after randomization and before dosing, that participant may be replaced. The replacement participant will undergo the same stratification procedure as a new participant; no special replacement randomization schedule is necessary.

11 EVALUATION, RECORDING, AND REPORTING OF ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Event

An AE is any untoward medical occurrence or the deterioration of a pre-existing medical condition (other than the condition that is being treated by the study) associated with the use of a study medication in humans, whether or not it is considered related to the study medication. An AE (also referred to as an adverse experience) can therefore be any unfavorable and unintended sign (eg, tachycardia, enlarged liver, clinically important abnormal laboratory result or diagnostic procedure), participant-reported symptom (eg, nausea, chest pain), or evidence of any disease activity temporally associated with the use of a study medication, whether or not related to the study medication.

In clinical studies, an AE can include an undesirable medical condition occurring at any time after the participant has signed informed consent, including run-in or washout periods, even if no specific treatment has been administered.

Preexisting medical conditions (other than natural progression of the disease being studied) judged by the investigator or participant to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period will be reported as AEs or SAEs as appropriate.

Imaging-based assessments of a decrease in contractility are not considered AEs unless associated with symptoms or signs of clinical concern on the part of the investigator. Such events should be categorized as an AE defined in terms of those symptoms or signs.

An AE or SAE can also be a complication that occurs as a result of protocol-mandated procedures (eg, invasive procedures such as biopsies).

For MyoKardia to collect additional information about clinically important laboratory results or diagnostic tests (eg, blood, ECG, imaging), at a minimum, the following abnormalities should be captured on the AE eCRF:

- Any test result that meets the definition of an SAE (see Section 11.1.2)
- Any clinically important test abnormality that suggests a disease and/or organ toxicity is worsening or is new (eg, > 3 × deviation from the upper or lower limit of the analyzing laboratory reference range, or as otherwise specified in the protocol)
- Any test abnormality that requires the participant to have study medication discontinued or interrupted in the clinical judgment of the investigator

- Any test abnormality that requires the participant to receive specific corrective therapy, close observation, more frequent follow-up assessment, or further diagnostic investigation

The term AE is used generally to include any AE whether serious or nonserious.

11.1.1.1 Events That Do Not Meet the Definition of Adverse Event

Events that do not meet the definition of AE include the following:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, 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
- Medical or surgical procedure (eg, endoscopy, appendectomy, device implantation): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen

11.1.2 Serious Adverse Event

An SAE is an AE that fulfills one or more of the following criteria in the opinion of the investigator or MyoKardia:

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

11.2 Adverse Event Reporting and Descriptions

11.2.1 Reporting Period and Follow-up

11.2.1.1 Adverse Events

AEs will be assessed from the time the participant provides informed consent through the duration of the study. Preexisting medical conditions that increase in severity from the first dose of study medication will be reported as AEs. Preexisting medical conditions that increase in severity after providing informed consent but before the first dose of study medication will be reported as medical history.

Any AEs that are unresolved at the participant's last visit in the study will be followed by the investigator until resolved or stabilized and are considered irreversible, or the participant has died.

MyoKardia retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

11.2.1.2 Serious Adverse Events

All SAEs occurring during the treatment-emergent period (defined as the period from the first administration of study drug to 56 days [8 weeks] after the last administration of study drug) regardless of causality will be reported by the investigator or designee to MyoKardia or its designee within 24 hours of knowledge of the event. All follow-up information for previously reported SAEs will also be reported to MyoKardia or its designee within 24 hours of knowledge. SAEs occurring after informed consent is signed but before the first dose of study drug is administered will be reported as SAEs only if they are considered related to the protocol or study procedure.

SAE reporting instructions are provided in the Study Reference Manual.

11.2.1.3 Adverse Events of Special Interest

Overdose, pregnancy, and LVEF ≤ 30% (as determined by local site−read echocardiogram) are considered adverse events of special interest (AESIs). Pregnancy includes the pregnancy of a female participant or the pregnancy of a partner of a male participant during the study up to 3 months after the last dose of study drug.

If an AESI occurs, this event must be reported to MyoKardia within 24 hours of knowledge of the event. A pregnancy will be followed until the final outcome, and a live birth will be followed for 6 months after the birth.

11.2.2 Recording and Assessing Adverse Events

11.2.2.1 Description

All AEs spontaneously reported by the participant or reported in response to the open question from the study personnel "Have you had any health problems since you were last asked?", or revealed by observation will be collected and recorded in the eCRF.

When collecting AEs 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. If the cause of death is unknown, "found dead" is an acceptable description.

11.2.2.2 Relationship to Study Treatment

The investigator should assess causality by answering either "yes" or "no" to the question "Is there a reasonable possibility that the event may have been caused by the investigational medicinal product [IMP]/study medication?"

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

- Challenge/rechallenge: Did the event abate after study medication was reduced or interrupted? 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

11.2.2.3 Severity

Severity can be assessed as follows:

- 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)

It is important to distinguish between category (AE vs SAE) and intensity (mild, moderate, or severe) of AEs.

Severity is a measure of intensity, whereas seriousness is defined by the criteria in Section 11.1.2.

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.

11.3 Suspected Unexpected Serious Adverse Reactions (SUSARs)

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 may be required per regulatory requirements to unblind the participant to determine treatment assignment. Only specified MyoKardia pharmacovigilance staff members or designees will have access to the unblinded information in order to meet regulatory requirements and report to the relevant regulatory authority(ies). A blinded report describing the SUSAR will be sent to all investigators. Each investigator must then notify his/her ethic committee (EC) of the blinded SUSAR as required by local regulatory authorities and in accordance with their EC policy.

12 STATISTICAL METHODS

12.1 Determination of Sample Size

This study will include a total of approximately 60 participants, or approximately 20 participants per treatment group. Such a sample size will be sufficient to obtain sound variability estimates while yielding reasonable effect size estimates for future planning purposes.

12.2 Study Endpoints

12.2.1 Safety Endpoints

- Frequency and severity of treatment-emergent AEs, AESIs, and SAEs; laboratory abnormalities; vital signs; and cardiac rhythm abnormalities

[redacted]

[redacted]

12.3 Statistical Analysis

Before database lock, final SAPs for clinical data and PK data will be prepared that contain full details of all planned analyses. The analyses presented here represent an outline of the intended methodology.

12.3.1 Analysis Populations

Four analysis populations are defined in this study:

- Intention-to-treat (ITT) Population: all randomized participants regardless of whether they receive study drug, with analyses conducted according to the randomized treatment assignment
- Safety Analysis Population: all randomized participants who receive at least 1 dose of study drug, with analyses conducted by actual treatment received
- PK Analysis Population: all randomized 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 randomized 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

12.3.2 General Considerations

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 analyzed as if they were continuously scaled. Confidence intervals at 95% and first and third quartiles may be presented as well.

12.3.3 Participant Disposition

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

12.3.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively. Treatment groups may be simultaneously compared to confirm that the randomization process generated 3 homogeneous groups prior to treatment.

12.3.5 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 and above-planned and under-planned dosing percentages will be summarized descriptively (number [n], mean, SD, median, minimum, and maximum). The 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, as well as the number and percentage of participants with 0, (0, 20%), and > 20% under-planned dosing administrations.

[redacted]

[redacted]

12.3.8 Safety Analyses

All safety analyses will be performed on the Safety 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.

12.3.8.1 Adverse Events

AEs will be mapped to system organ classes and preferred terms 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 one treatment-emergent AE (TEAE) by system organ class (SOC) and preferred term (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.

Adverse event 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

The following deaths summaries will be generated:

- Number and percent of participants who died by study period (TEAE, on-study) summarized on the safety population by treatment received
- Death in non-randomized participants or randomized and not treated participants
- TEAE leading to death (death as an outcome on the AE eCRF page as reported by the investigator) by primary SOC and PT showing number and percent of participants

Pregnancy

The following pregnancy summaries will be generated:

- Number of participants or partners of participants who became pregnant summarized by treatment received
- Outcomes of the pregnancies and analysis of the outcomes

- TEAE experienced during the pregnancy by primary SOC and PT showing the number and percent of participants

Overdose

The following summaries for reports of overdose will be generated:

- Number of participants who experienced overdose summarized by treatment received
- Analysis of the cause and occurrence of the overdose
- TEAE experienced during the overdose by primary SOC, high-level group term, high-level term, and PT showing the number and percent of participants

12.3.8.2 12-lead Electrocardiogram

The RR, PR, QRS, and QT intervals will be measured and read by a central laboratory. HR will be calculated as 60/(RR × 1000) (with RR expressed in msec) 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 msec):

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 msec, > 480 msec, and > 500 msec will be tabulated for all participants. Participants with QTc values > 500 msec 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 msec and > 60 msec 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% CI of the relationship. Predictions at selected concentration values will be computed within the model.

12.3.8.3 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, 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).

12.3.8.4 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.

12.3.8.5 Other Safety Analyses

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

12.3.9 Interim Analysis

No interim analysis is planned.

[redacted]

[redacted].

13 STUDY COMPLIANCE AND ETHICAL CONSIDERATIONS

13.1 Compliance Statement

This study will be conducted in accordance with the International Council for Harmonisation (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.

13.2 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.

13.3 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 11.3)
- 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.

14 ADMINISTRATIVE PROCEDURES

14.1 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

14.1.1 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.

[redacted]

14.1.3 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.

14.1.4 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 11.3), as appropriate. The investigator(s) must forward this documentation to the EC as described in Section 11.3.

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.

14.1.5 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).

14.1.6 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.

14.2 Investigator's Responsibilities

14.2.1 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.

14.2.2 Study Drug 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.

14.2.3 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.

14.2.4 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 clinical site's policy does not permit direct access to the electronic medical records.

14.2.5 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.

14.2.6 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 last 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing application 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.

14.2.7 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.

14.2.8 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 FDA 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.

14.3 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.

14.4 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 change 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.

15 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.

16 ADMINISTRATIVE CONSIDERATIONS

16.1 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, CPET, and echocardiographic data from digital equipment used by clinical site personnel to collect participant data
- IXRS to dispense IMP and transfer data in double-blind manner
- Electronic clinical outcomes assessment equipment to allow participants to complete questionnaires

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 as outlined in the SAP

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.

16.2 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.

17 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.

[redacted]

[redacted]

APPENDIX 1 LABORATORY ASSESSMENTS

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

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

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] Urine microscopy will be performed if there is a significant abnormality in the dipstick.

[b] 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 nonsafety laboratory parameters will be measured at Screening:

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

[redacted]

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 eCRF (eg, Adverse Event eCRF) 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 11.1.2.

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 (PK) 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 non-alcoholic 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 eCRFs.

APPENDIX 4 INVESTIGATOR'S SIGNATURE

I have read and understood the contents of the clinical protocol, MYK-461-006, A Randomized, Double-blind, Placebo-controlled, Concentration-guided, Exploratory Study of Mavacamten (MYK-461) in Patients with Symptomatic Non-obstructive Hypertrophic Cardiomyopathy (nHCM) and Preserved Left Ventricular Ejection Fraction, 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: _____