Official Title of Study:

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Mavacamten in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy Who Are Eligible for Septal Reduction Therapy

PROTOCOL(S) CV027-006

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CLINICAL STUDY PROTOCOL

Protocol Number:	MYK-461-017 (VALOR-HCM)
Protocol Title:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE MAVACAMTEN IN ADULTS WITH SYMPTOMATIC OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY WHO ARE ELIGIBLE FOR SEPTAL REDUCTION THERAPY**
Indication	Hypertrophic Cardiomyopathy
Study Phase:	Phase 3
Investigative Medicinal Product:	Mavacamten (2.5, 5, 10, 15 mg capsules)
IND Number	121904
EudraCT Number:	Not applicable
US Coordinating Investigator:	[redacted]
Key Sponsor Contacts:	[redacted]
Sponsor:	MyoKardia, Inc. 1000 Sierra Point Parkway Brisbane, CA 94005
Original Protocol Date:	16 December 2019
Amendment 1:	29 June 2020
Amendment 2:	09 November 2020
Amendment 3:	03 August 2021
Amendment 4:	**30 June 2022**

PROTOCOL AMENDMENT
SUMMARY OF CHANGES TABLE

Protocol Amendment 4.0, 30 June 2022
Overall Rationale for the Amendment

This protocol amendment has been developed to clarify dosing and SRT evaluations in the LTE period. Other changes include removing mavacamten washout at Week 128. A summary of the key changes is listed in the table below:

Changes:

Section(s)	Summary of Change	Reason for Change
Synopsis, Objectives and Endpoints, SRT Evaluation, Study Procedures and Treatment; Section 2 Objectives and Endpoints; Section 3.1 Study Procedures and Treatment; Section 7.1 Evaluation for Septal Reduction Therapy Eligibility; Figure 1	Changed the SRT eligibility assessment timepoint from Week 80 to Week 104.	To ensure an SRT evaluation is performed two years from Day 1.
Synopsis, Objectives and Endpoints; Section 2 Objectives and Endpoints	Added 2011 ACCF/AHA HCM Guideline to determine eligibility for SRT	To clarify
Synopsis, Study Procedures and Treatment; 3.1 Overall Design; 5.6 Dose Titration	Clarified the dose titration Weeks for LTE (Weeks 44 to 116).	To clarify
Synopsis, Study Procedures and Treatment; 3.1 Overall Design	Added that the dose titration is possible at unscheduled visits if the participant is symptomatic or clinically indicated and meets criteria with the approval by medical monitor during LTE. Dose up-titration must be at least 12 weeks from last dose up-titration	To clarify
Synopsis, Overall Design, Study Procedures and Treatment; Schedule of Study Assessments, Table 2 MYK-461-017: Schedule of Study	Removed 8-week post-treatment assessments and replaced with a phone call.	No longer needed as washout period data was obtained from a prior study

Assessments (Week 44 through Week 136); Section 3.1.1 Study Procedures and Treatment; Section 3.2 Study Duration: Figure 1 MYK-461-017 Study Schema		
Synopsis, Overall Design; Section 3.2 Study Duration	Clarified study duration	To align with the new EOS definition
Schedule of Study Assessments, Table 2 MYK-461-017: Schedule of Study Assessments (Week 44 through Week 136); Synopsis, Study Procedures and Treatment; Section 3.1.1 Study Procedures and Treatment	Changed from a site visit to a follow up phone call 8 weeks after End of Treatment (EOT)	To assess for AEs and interval procedures and/or concomitant medications (conmeds)
Schedule of Study Assessments, Table 2 MYK-461-017: Schedule of Study Assessments (Week 44 through Week 136); Figure 1 MYK-461-017 Study Schema	Changed the postexercise stress TTE assessment timepoint from Week 80 to Week 104.	To align with the SRT evaluation
Schedule of Study Assessments, Table 2 MYK-461-017: Schedule of Study Assessments (Week 44 through Week 136)	Added a required unscheduled visit for an ECHO if SAE of cardiovascular origin occurs during the LTE period 2-4 weeks after the event.	To assess safety following cardiovascular SAE during the LTE period.
Schedule of Study Assessments, Table 2 MYK-461-017: Schedule of Study Assessments (Week 44 through Week 136)	Added that in LTE, each study visit has a window of +/- 14 days	To provide sites and patients with more flexibility during the LTE period.
Schedule of Study Assessments, Table 2 MYK-461-017: Schedule of Study Assessments (Week 44 through Week 136); Section 7.5.4 Holter Monitor	Added Holter at Week 56 and Week 104.	To assess cardiac rhythm
Section 5.5.3 Background HCM Medication	Added disopyramide as a background cardiomyopathy therapy that may be adjusted or stopped after Week 32	Correction of administrative error

Section 5.6 Dose Titration; Table 8 MYK-461-017 Dose Titration Guidelines (Week 44 to Week 116)	Added post-exercise LVOT >50 mm Hg to Valsalva LVOT >30 mmHg for possible up-titration within the LTE period. Dose up-titration must be at least 12 weeks from last dose up-titration	To allow up-titration in patients with high post-exercise LVOT despite lower Valsalva LVOT
Section 6.1.1 Temporary Treatment Discontinuation	Added provision to notify the Medical Monitor if LVEF is <50% during the LTE.	To ensure appropriate Sponsor oversight
Section 7.2.1 Echocardiography	Added approval by the medical monitor as a requirement for a dose titration and added a requirement for the sites to enter LVEF and LVOT into [redacted] EDC on the day of the ECHO assessment. [redacted] will automatically send ECHO values to IXRS for proper drug dispensation.	To ensure appropriate Sponsor oversight and appropriate dosing and drug dispensation based on current ECHO values.
Section 7.2.2 New York Heart Association Functional Class; Figure 1 MYK-461-017 Study Schema; Schedule of Study Assessments, Table 2 MYK-461-017: Schedule of Study Assessments (Week 44 through Week 136); Figure 1	Removed Week 80 NYHA Functional Class assessment	To align with the SRT eligibility assessment
Section 7.5.2 Physical Examination; Section 7.5.3 Electrocardiograms	Removed body weight assessment and ECG assessment at Week 136	To align with Schedule of Activities

SPONSOR SIGNATORY

DocuSigned by:

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7/5/2022 | 20:55 EDT

Date

Bristol Myers Squibb

COORDINATING INVESTIGATOR SIGNATORY

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LIST OF ABBREVIATIONS

ACCF	American College of Cardiology Foundation
AE	adverse event
AESI	adverse event of special interest
AHA	American Heart Association
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ASA	alcohol septal ablation
AST	aspartate aminotransferase
β-hCG	beta human chorionic gonadotropin
BP	blood pressure
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practice
CI	confidence interval
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
Conmed	Concomitant medication
CPET	cardiopulmonary exercise test or testing
CV	cardiovascular
CYP	cytochrome P450
d	day
DILI	drug-induced liver injury
EC	executive committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
EOT	end of treatment
EQ-5D-5L	EuroQol 5-dimensions 5-level questionnaire
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCM	hypertrophic cardiomyopathy
HCV	hepatitis C virus
HF	heart failure
HIV	human immunodeficiency virus
HR	heart rate
ICD	implantable cardioverter-defibrillator
ICF	informed consent form

ICH	International Council for Harmonization (of Technical Requirements for Pharmaceuticals for Human Use)
ID	identification
IDMC	independent data monitoring committee
IEC	independent ethics committee
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
ITT	intention-to-treat
IXRS	interactive response system
KCCQ-23	Kansas City Cardiomyopathy Questionnaire 23-item version
KCCQ-23, CSS	Kansas City Cardiomyopathy Questionnaire 23-item version, Clinical Summary Score
KCCQ-23, OSS	Kansas City Cardiomyopathy Questionnaire 23-item version, Overall Summary Score
KCCQ-23, TSS	Kansas City Cardiomyopathy Questionnaire 23-item version, Total Summary Score
LAD	left anterior descending (coronary artery)
LTE	long-term extension
LV	left ventricular
LVEF	left ventricular ejection fraction
LVOT	left ventricular outflow tract
MACE	major adverse cardiac event
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect for repeated measurements
n	number
NASH	nonalcoholic steatohepatitis
nHCM	nonobstructive HCM
NIMP	noninvestigational medicinal product
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
oHCM; HOCM	obstructive hypertrophic cardiomyopathy
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PRO	patient-reported outcome
PT	preferred term
PTAE	pretreatment adverse event
QD	once daily
QoL	quality of life
QTc	corrected QT interval
QTcF	QT interval with Fridericia correction
RR	respiratory rate
SAD	single-ascending dose

SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDAC	Statistical Data Analysis Center
SOC	system organ class
SRT	septal reduction therapy
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	terminal half-life
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TTE	transthoracic echocardiography, transthoracic echocardiogram
ULN	upper limit of normal
US	United States
UV	Unscheduled Visit
VAS	visual analog scale

PROTOCOL SUMMARY

Synopsis

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Mavacamten in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy Who Are Eligible for Septal Reduction Therapy

Rationale:

This is a Phase 3 study to evaluate the effect of mavacamten treatment on reducing the number of septal reduction therapy (SRT) procedures performed in subjects with symptomatic obstructive hypertrophic cardiomyopathy (oHCM [also known as HOCM]) who are eligible for SRT based on 2011 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) (ie, guidelines). Data from this study will complement results from the completed MYK-461-004 (PIONEER-HCM) and MYK-461-005 (EXPLORER-HCM) and ongoing MYK-461-007 (EXPLORER-LTE) studies of mavacamten in subjects with symptomatic oHCM and potentially expand the benefit of mavacamten to a population of oHCM patients with severe symptoms refractory to maximal medical therapy.

Objectives and Endpoints: The primary, secondary, exploratory, and pharmacokinetics (PK) objectives and endpoints of the study are as follows:

Objectives	Endpoints
Primary	
To evaluate the effect of mavacamten on the need for SRT in guideline-eligible subjects with oHCM who are referred for SRT	The primary endpoint will be a composite of: 1 Decision to proceed with SRT prior to or at Week 16 2 SRT guideline eligible at Week 16 based on the 2011 ACCF/AHA HCM Guidelines
Secondary	
To evaluate the effect of mavacamten on subject symptoms	Change from baseline to Week 16 in the mavacamten group compared with the placebo group in: • New York Heart Association (NYHA) functional class • Kansas City Cardiomyopathy Questionnaire 23-item version Clinical Summary Score (KCCQ-23, CSS)

To evaluate the effect of mavacamten on cardiac biomarkers	Change from baseline to Week 16 in the mavacamten group compared with the placebo group in N-terminal pro-b-type natriuretic peptide (NT-proBNP) and cardiac troponin
To evaluate the effect of mavacamten on a hemodynamic parameter	Change from baseline to Week 16 in the mavacamten group compared with the placebo group in post-exercise left ventricular outflow tract (LVOT) gradient
Exploratory	
To evaluate the effect of mavacamten on the need for SRT in a long-term follow-up period	At Week 32, 56, 104, and 128, the endpoint is a composite of: 1. Decision to proceed with SRT 2 SRT guideline eligibility based on the 2011 ACCF/AHA HCM Guidelines at each timepoint
To evaluate the effect of mavacamten on the need for SRT as determined by the investigator	The endpoint will be a composite of the outcomes below at Week 16, 32, 56, 104, and 128: 1. Decision to proceed with SRT, 2. SRT eligible based on the Investigator determination as recorded on the SRT evaluation CRF
To evaluate the effect of mavacamten on hemodynamic parameters and cardiac biomarkers and to improve subject activity level and quality of life	Analysis of LVOT gradient at rest and induced by Valsalva, left ventricular ejection fraction (LVEF), left ventricular (LV) filling pressures, left atrium size, cardiac biomarkers, accelerometry, and EuroQol 5-dimensions 5-level (EQ-5D-5L) questionnaire will be performed for: • Change from baseline to Week 16 in the mavacamten group compared with the placebo group
To evaluate the long-term effect of mavacamten on symptoms, hemodynamic parameters, and cardiac biomarkers, subject activity level, and quality of life through Week 128.	Analysis of NYHA functional class, KCCQ-23 (Overall Summary Score [OSS], Total Summary Score [TSS], and individual domain), LVOT gradients, LVEF, LV filling pressures, left atrium

	size, cardiac biomarkers, accelerometry, and EQ-5D-5L throughout Week 128
To evaluate the effects of mavacamten on type and dose of cardiac medications	Change from baseline to Week 16, Week 16 to 32, and Week 32 to Week 128 in HCM standard of care cardiac medications
Safety	
To evaluate the safety of mavacamten for the duration of the study	• Incidence of LVEF < 50% determined by transthoracic echocardiography (TTE) • Incidence and severity of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (SAEs), and laboratory abnormalities • Incidence of SAEs before and after SRT among subjects who undergo SRT • Incidence of major adverse cardiac events (MACE; death, stroke, acute myocardial infarction, heart failure [HF] hospitalization) • Incidence of hospitalizations (due to cardiovascular [CV] and non-CV events) • Incidence of HF events, (including hospitalizations and urgent emergency room/outpatient visits for HF and escalation in HF treatment) • Incidence of atrial fibrillation/flutter (new from screening and recurrent) • Incidence of implantable cardioverter-defibrillator (ICD) therapy and resuscitated cardiac arrest • Incidence of ventricular tachyarrhythmias (includes ventricular tachycardia, ventricular fibrillation, and Torsades de Pointe) • Incidence of adverse events of special interest (AESIs; symptomatic overdose, outcomes of pregnancy, LVEF ≤ 30%)
Pharmacokinetics	
Evaluate plasma concentrations of mavacamten	Summarize mavacamten plasma concentrations from on-treatment sample collection
Overall Design: This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study of males and females ≥ 18 years with oHCM who meet 2011 ACCF/AHA criteria for SRT and have been	

referred for an invasive procedure. After completing screening assessments, eligible subjects will be randomized 1:1 to the mavacamten or placebo treatment groups. Randomization will be stratified by the type of SRT procedure recommended (myectomy or alcohol septal ablation [ASA]) and NYHA functional class.

The study duration will be up to 138 weeks. This includes a 2-week screening period (Week –2), 128 weeks of treatment , and a follow-up phone call at Week 136 (EOS).

There will be 3 dosing periods as follows:

- Placebo-controlled dosing period (Day 1 to Week 16): Subjects will receive double-blind mavacamten or placebo once daily for 16 weeks
- Active-controlled dosing period (Week 16 to Week 32): All subjects will receive mavacamten once daily for 16 weeks. Dose will be blinded.
- Long-term extension (LTE) dosing period (Week 32 to Week 128): All subjects will receive mavacamten once daily for 96 weeks. Dose will be blinded.

Study Drug Dosing

On Day 1, subjects will begin blinded dosing with mavacamten or matching placebo once daily for 16 weeks (placebo-controlled period). After the Week 16 study assessments, subjects in the mavacamten group will continue mavacamten, and subjects in the placebo group will begin dosing with mavacamten, once daily from Weeks 16 to 32 (active-controlled period). During the active-controlled period, mavacamten dose will be blinded. After the Week 32 assessments, all subjects will continue once-daily mavacamten until Week 128 (LTE period). During the LTE period, mavacamten dose will remain blinded. Beginning at Week 16 and throughout the remainder of the study, the placebo group will be referred to as the placebo-to-active group.

SRT Evaluation

At screening, the investigator will confirm the subject's NYHA functional class and eligibility for SRT based on the 2011 ACCF/AHA

At any time during the study, subjects may withdraw from study drug and proceed with SRT at a recognized HCM center after a recommended study drug washout period ≥ 6 weeks. Subjects who discontinue study drug to undergo SRT will undergo end-of-treatment (EOT) assessments within 14 days and will have a telephone follow-up with the study site to assess adverse events (AEs) 8 weeks after treatment discontinuation (or prior to SRT, whichever is earlier). Subjects will be followed every 24 weeks from the date of SRT to Week 128.

At Weeks 16, 32, 56, 104, and 128, subjects will be reevaluated for SRT eligibility by maximal medical therapy, NYHA functional class, and TTE. Every effort should be made to have the **same** investigator who evaluates NYHA at screening also evaluate NYHA at Weeks 16, 32, 56, 104, and 128. At Weeks 16 and 32, maximum LVOT gradient < 50 mmHg or ≥ 50 mmHg will be revealed to the site by the core echocardiography laboratory after the investigator makes the NYHA determination. The investigator will then make a recommendation for SRT (yes or no). The subject must have NYHA Class symptom improvement And maximum LVOT gradient < 50 mmHg to no longer qualify for SRT. Subjects will be required to decide within 48 hours whether to accept the recommendation for SRT or continue study treatment. At Weeks 56, 104, and 128, LVOT < 50 mmHg or ≥ 50 mmHg will be determined by site-read echocardiography.

An interim analysis will be conducted after 50 subjects have completed the Week 16 visit or terminated early from the study drug to assess efficacy results. The interim analysis will be based on the primary endpoint, SRT eligibility based on the 2011 ACCF/AHA HCM guidelines for SRT.	
Inclusion Criteria:	1. Able to understand and comply with the study procedures, understand the risks involved in the study, and provide written informed consent according to federal, local, and institutional guidelines prior to initiation of any study-specific procedure 2. At least 18 years old at screening 3. Body weight > 45 kg at screening 4. Adequate acoustic windows to enable accurate TTE (refer to the central echocardiography laboratory's manual of operations) 5. Diagnosed with oHCM (unexplained LV hypertrophy with non-dilated ventricular chambers in the absence of other cardiac [e.g. aortic stenosis, hypertension]) or systemic disease. Patient has maximal septal wall thickness ≥ 15 mm or ≥ 13 mm with family history of HCM consistent with current ACCF/AHA 2011. Patient must meet ACCF/AHA 2011 guideline recommendations for invasive SRT therapies as follows: • Clinical criteria: Despite maximally tolerated drug therapy, severe dyspnea or chest pain (NYHA Class III or IV), or for the purposes of the Valor Study, subjects who are NYHA Class II with exertion-induced syncope or near syncope. • Hemodynamic criteria: dynamic LVOT gradient at rest or with provocation (ie, Valsalva or exercise) ≥ 50 mmHg associated with septal hypertrophy of ≥15mm (or ≥13mm with family history of HCM) (read by the core echocardiography laboratory) • Anatomic criteria: targeted anterior septal thickness sufficient to perform the procedure safely and effectively in the judgment of the individual operator 6. Referred or under active consideration within the past 12 months for SRT procedure and willing to have SRT procedure 7. Subjects referred or considered for ASA must have an adequate first septal perforating branch of the left anterior descending (LAD) coronary artery amenable for the Interventionalist to perform the procedure 8. Documented oxygen saturation at rest ≥ 90% at screening 9. Documented LVEF ≥ 60% at screening according to core echocardiography laboratory reading 10. Female subjects not pregnant or lactating and, if sexually active, must either practice true abstinence or use 1 of the following highly effective birth control methods from screening through 4 months after the last dose of study drug: • Estrogen- and progestogen-containing hormonal contraception associated with inhibition of ovulation or progestogen-only hormonal contraception associated with inhibition of ovulation by oral, implantable, or injectable route of administration • Intrauterine device

	• Intrauterine hormone-releasing system • Bilateral tubal occlusion • Female surgically sterile or postmenopausal for 1 year. Permanent sterilization includes hysterectomy, bilateral oophorectomy, bilateral salpingectomy, and/or documented bilateral tubal occlusion. Females are considered postmenopausal if they have had amenorrhea for ≥1 year after cessation of all exogenous hormonal treatments, and follicle stimulating hormone (FSH) levels are in the postmenopausal range. Male partners of female subjects must also use a contraceptive (eg, barrier, condom, or vasectomy) from screening through 4 months after the last dose of study drug.
Exclusion Criteria:	1. Previously participated in a clinical study with mavacamten (individuals who failed screening for a prior mavacamten study may participate) 2. Hypersensitivity to any of the components of the mavacamten formulation 3. Participated in a clinical trial in which the subject received any investigational drug (or currently using an investigational device) within 30 days prior to screening, or at least 5 times the respective elimination half-life (whichever is longer) 4. Known infiltrative or storage disorder causing cardiac hypertrophy that mimics oHCM, such as Fabry disease, amyloidosis, or Noonan syndrome with LV hypertrophy 5. Planned invasive procedure during the first 32 weeks of the study 6. Papillary muscle or mitral valve in need of repair or any other intracardiac procedure planned (however, if need for mitral valve repair is discovered during SRT procedure, the subject will continue to be followed on study) 7. For individuals on beta blockers, calcium channel blockers, or disopyramide, any dose adjustment of these medications < 14 days prior to screening or an anticipated change in regimen during the first 16 weeks of the study 8. Any medical condition that precludes upright exercise stress testing 9. Paroxysmal, intermittent atrial fibrillation with atrial fibrillation present at screening per the investigator's evaluation of the subject's electrocardiogram (ECG) 10. Persistent or permanent atrial fibrillation and subject not on anticoagulation for ≥ 4 weeks prior to screening and/or not adequately rate controlled ≤ 6 months prior to screening 11. Previously treated with invasive septal reduction (surgical myectomy or percutaneous ASA). However, if the subject has a history of a suboptimal or a failed alcohol septal ablation and there is no evidence on site read prescreening echocardiogram of an ASA, the subject may be included after consultation with the MyoKardia or CRO medical monitor. 12. Planned implantable ICD placement or pulse generator change during the first 32 weeks of the study. 13. ECG abnormality considered by the investigator to pose a risk to subject safety (eg, second degree atrioventricular block type II). 14. Acute or serious comorbid condition (e.g. 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 a. Pulmonary disease that limits exercise capacity or systemic arterial oxygen saturation b. History of malignant disease within 10 years prior to screening: • Subjects who have been successfully treated for non-metastatic cutaneous squamous cell or basal cell carcinoma or have been adequately treated for cervical carcinoma in situ or breast ductal carcinoma in situ may be included in the study • Subjects with other malignancies who are cancer-free for more than 10 years prior to screening may be included in the study 15. History or evidence of any other clinically significant disorder, condition, or disease that, in the opinion of the investigator, would pose a risk to subject safety or interfere with study evaluations, procedures, or completion 16. Safety laboratory parameters (chemistry, hematology, coagulation, and urinalysis) outside normal limits (according to the central laboratory reference range) at screening as assessed by the central laboratory; however, a subject with safety laboratory parameters outside the normal limits may be included if all the following criteria are met: a. Safety laboratory parameters outside normal limits are considered by the investigator to be clinically not significant b. If an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) result, the value must be $< 3 \times$ the upper limit of the laboratory reference range c. Body size–adjusted estimated glomerular filtration rate is ≥ 30 mL/min/1.73 m^2 17. Has known moderate or severe aortic valve stenosis or moderate to severe aortic stenosis determined at screening (as read by the echocardiography core laboratory) 18. Positive serologic test at screening for infection with human immunodeficiency virus (HIV); hepatitis C virus (HCV); or hepatitis B virus (HBV), with the exception of hepatitis B s-antibody positive, which is a marker of immunity 19. Known active infection with Covid-19 (PCR+) within 90 days of screening. If subject had a PCR+ test within 6 months of screening, they must have a negative Covid-19 test at screening. 20. Prior treatment with cardiotoxic agents, such as doxorubicin or similar 21. Unable to comply with the study requirements, including the number of required visits to the study site 22. First-degree relative of personnel directly affiliated with the study at the study site, any study vendor, or the study sponsor
Disclosure Statement: This is a parallel group treatment study with 2 treatment groups; subjects and investigators are blinded to treatment and dose for the first 16 weeks of treatment. Mavacamten dose is blinded throughout the study	
Number of Sites: Approximately 20 sites in the North America with experienced CT surgeons with good outcome rates for SRT procedures	

Number of Subjects: Approximately 100 subjects, with 50 subjects in each of 2 treatment groups (mavacamten and placebo)

Study Procedures and Treatment:

Study visits will occur at screening, Day 1, every 4 weeks through Week 32, every 12 weeks thereafter until Week 128 (EOT). Subjects will receive a follow-up phone call 8 weeks later at Week 136 (EOS) to assess for AEs and interval procedure and/or concomitant medications (conmeds). All study visits during the placebo-controlled, active-controlled, and LTE portions of the study (Screening to Week 32 and Week 32 to Week 128) are to take place at the study site. Subjects who prematurely discontinue study drug at any time will attend a treatment discontinuation visit within 14 days of study drug discontinuation and will be followed every 24 weeks thereafter until Week 128. Subjects who discontinue study drug to proceed with SRT will attend a treatment discontinuation visit within 14 days of study drug discontinuation and will be followed every 24 weeks following their SRT procedure until Week 128.

On Day 1, eligible subjects will be randomized in a double-blind manner via an interactive response system (IXRS) to the mavacamten or placebo groups. Randomization will be stratified by the type of SRT procedure recommended (myectomy or ASA) and NYHA functional class. Subjects will begin mavacamten 5 mg or matching placebo once daily by mouth for 16 weeks with subsequent assessments for dose adjustments.

At Weeks 16, 32, 56, 104, and 128, subjects will be reevaluated for SRT eligibility. The investigator will confirm that the subject remains on maximal medical therapy, determine NYHA class, and enter the information in the electronic case report form (eCRF). Every effort should be made to have the **same** investigator who evaluates NYHA at screening also evaluate NYHA at Weeks 16, 32, 56, 104, and 128. Independently, and blinded to the investigator, a TTE will be performed to assess LVOT gradients at rest, provocation, and postexercise. At Weeks 16 and 32, TTE will be read at the core echocardiography laboratory, and a categorical LVOT gradient result (< 50 mmHg or ≥ 50 mmHg) will be reported to the study site by the core laboratory. At Weeks 56, 104, and 128, LVOT < 50 mmHg or ≥ 50 mmHg will be determined by site-read echocardiography. The investigator will remain blinded to the LVOT gradient result until after NYHA results have been entered in the eCRF. Results of medical therapy, NYHA functional class, and LVOT will be reviewed by the investigator, who will determine whether the subject meets criteria for SRT (yes or no). The subject must have NYHA Class symptom improvement And maximum LVOT gradient < 50 mmHg to no longer qualify for SRT. If both criteria have not been met, the answer to SRT eligibility is "yes". The investigator will discuss the recommendation with the subject. If the recommendation is to proceed with SRT, the subject may schedule the SRT at a recommended HCM center to occur after a recommended study drug washout period ≥ 6 weeks, or the subject may decline the recommendation and remain on study drug.

After Week 16 assessments, subjects in the mavacamten treatment group who elect to continue treatment (i.e. do not make a decision to have SRT) will continue once-daily dosing with mavacamten at the dose they had been receiving at Week 16 for an additional 16 weeks; subjects in the placebo group who elect to continue treatment (ie, do not make a decision to have SRT) will begin dosing with mavacamten 5 mg once daily for 16 weeks with subsequent assessments for dose adjustments (placebo-to-active group). During the active-controlled dosing period, mavacamten dose will remain blinded.

After Week 32 assessments, all subjects (mavacamten group and placebo-to-active group) who elect to continue treatment (ie, do not make a decision to have SRT) will continue daily dosing with mavacamten at the dose they had been receiving at Week 32 for an additional 96 weeks to Week 128 (EOT). During the LTE dosing period, mavacamten dose will remain blinded. Subjects will be reevaluated for SRT eligibility at Weeks 56, 104, and 128.

From Week 4 through Week 32, dose may be titrated based on LVEF and LVOT gradient by TTE read at the core echocardiography laboratory and according to dose titration guidelines. Dose may be titrated during the LTE period based on LVEF and LVOT gradient by TTE read at the site electrocardiography laboratory. The last possible dose titration is at Week 116. Dose titration is also possible during the LTE Period at Unscheduled Visits if the participant is symptomatic or clinically indicated and meets titration criteria. In LTE, dose up-titration is permitted only if it has been ≥ 12 weeks from last dose up-titration.

LTE dosing must be approved by the MyoKardia or CRO medical monitor before they are implemented. Throughout the study, all dose adjustments will occur in a blinded manner via the IXRS.

During the placebo-controlled dosing period (Day 1 to Week 16), all subjects will be evaluated for possible down-titration at Week 4 and up-titration at Weeks 8 and 12. Although subjects in the placebo group will be evaluated for dose titration, they will remain on placebo.

During the active-controlled dosing period (Weeks 16 to 32), subjects in the placebo-to-active group, who begin dosing with mavacamten at Week 16, will be evaluated for possible down-titration at Week 20 and up-titration at Weeks 24 and 28.

During the LTE dosing period (Weeks 44 to 116), mavacamten dose may be up-titrated at any scheduled visit after Week 32 if the site-read LVOT gradient with Valsalva maneuver is ≥ 30 mmHg and LVEF is ≥ 50%. Dose titration is also possible during the LTE Period at Unscheduled Visits if the participant is symptomatic or clinically indicated and meets titration criteria. In LTE, dose up-titration is permitted only if it has been ≥ 12 weeks from last dose up-titration. All dose increases during LTE dose titrations must be approved by the MyoKardia or CRO medical monitor before they are implemented. Subjects who have their mavacamten dose increased during the LTE period will attend an unscheduled study visit 4 weeks after the dose increase and then resume the regular study visit schedule.

Safety will be monitored throughout the study.

Dose Titration Safety

Dose may be down-titrated for safety at any time per the titration schedule Table 7 on consultation with the medical monitor.

Criteria for Evaluation:

Efficacy: The primary endpoint will be a composite of 1) the number of subjects who decide to proceed with SRT prior to or at Week 16 and 2) the number of subjects who are SRT eligible per 2011 ACCF/AHA HCM guidelines at Week 16 in the mavacamten group compared with the placebo group.

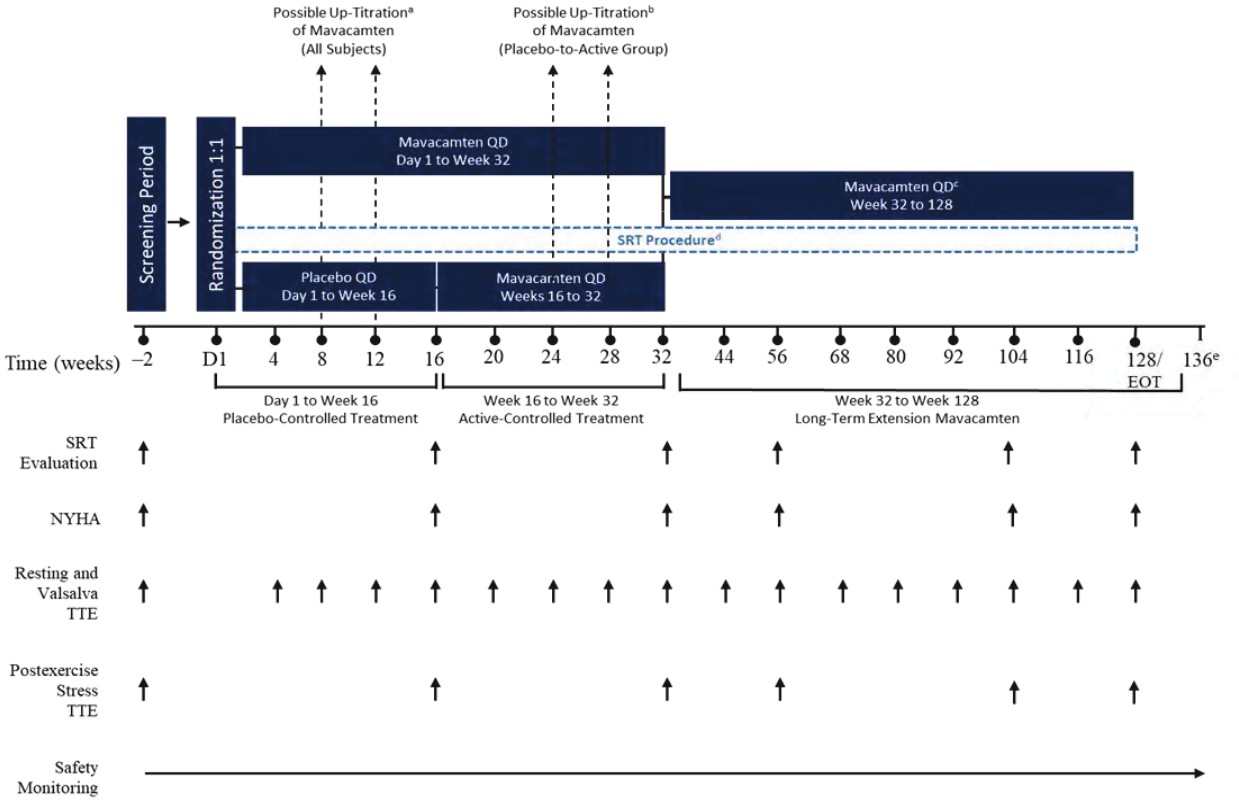
Safety: Safety assessments include monitoring of AEs and concomitant medications, safety laboratory assessments, physical examinations, vital sign measurements, TTEs, cardiac/activity monitoring, and ECGs.

Statistical Methods:

Approximately 100 subjects will be randomized, with 50 subjects in each of the 2 treatment groups. This sample size should provide adequate power to determine the superiority of mavacamten in reducing election of SRT or eligibility for SRT at the end of a 16-week treatment period. The power calculation was derived assuming a true clinically meaningful relative reduction of 50% between subjects in the mavacamten and placebo groups meeting the primary endpoint. It is estimated that 70% of the subjects receiving placebo will meet the endpoint, versus 35% of subjects receiving mavacamten by the end of the 16-week treatment period. The proposed sample size of 50 subjects in each treatment group will provide 95% power at a 2-sided 5% statistical significance level. Subjects who undergo SRT, terminate early, die, or cannot otherwise be assessed for SRT eligibility at the end of the 16-week placebo-controlled treatment period will be classified as eligible for an SRT procedure.
Study Committees: This study includes an Independent Data Monitoring Committee (IDMC) and an Executive Committee (EC).

STUDY SCHEMA

Figure 1: MYK-461-017: Study Schema



EOS = end of study; EOT = end of treatment; NYHA = New York Heart Association (functional classification); QD = once daily; SRT = septal reduction therapy; TTE = transthoracic echocardiogram.

[a] During the placebo-controlled dosing period (Day 1 to Week 16) subjects will be evaluated for possible down-titration at Week 4 and up-titration at Weeks 8 and 12 by independent assessment of TTE by the echocardiography core laboratory and according to dose-titration guidelines. Dose may be down-titrated for safety at any time.

[b] Subjects in the placebo-to-active group, who begin dosing with mavacamten at Week 16, will be evaluated for possible down-titration at Week 20 and up-titration at Weeks 24 and 28. Dose may be down-titrated for safety at any time.

[c] During the long-term extension (LTE) dosing period (Weeks 32 to 128), mavacamten dose may be up-titrated at any scheduled visit after Week 32 if the site-read LVOT gradient with Valsalva maneuver is ≥ 30 mmHg and LVEF is ≥ 50%. All dose increases during LTE dosing must be approved by the MyoKardia or CRO medical monitor before they are implemented. Subjects who have their mavacamten dose increased during the LTE period will attend an unscheduled study visit 4 weeks after the dose increase and then resume the regular study visit schedule. Dose may be down-titrated for safety at any time.

[d] At any time during the study, subjects may withdraw from study drug and proceed with SRT at a recognized HCM center after a recommended study drug washout period ≥ 6 weeks. Subjects who discontinue study drug to undergo SRT will undergo EOT assessments within 14 days and will have a telephone follow-up with the study site to assess adverse events 8 weeks after treatment discontinuation (or prior to SRT, whichever is earlier). Discontinuation due to opting for SRT that occurs before Week 32 will require TTEs to be read by the core lab in a blinded fashion. Subjects will be followed every 24 weeks from the date of SRT to Week 128.

[e] Follow-up phone call to participants will be made 8 weeks after EOT to assess for AEs and interval procedures and/or conmeds.

Schedule of Study Assessments

Table 1: MYK-461-017: Schedule of Study Assessments (Screening through Week 32)

Assessment[a,b]	Screening Days -14 to -1	Placebo-Controlled Dosing Day 1 to Week 16					Active-Controlled Dosing Weeks 16 to 32			
		Day 1	Week 4 (+7 days)	Week 8 (+7 days)	Week 12 (+7 days)	Week 16 (+7 days)	Week 20 (+7 days)	Week 24 (+7 days)	Week 28 (+7 days)	Week 32 (+7 days)
Informed consent	X									
Medical, surgical and HCM history	X									
Randomization		X								
Vital signs[c]	X	X	X	X	X	X	X	X	X	X
Body weight	X		X	X	X	X	X	X	X	X
NYHA functional class[d]	X					X				X
AEs	X	X	X	X	X	X	X	X	X	X
Prior medications	X	X								
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Physical examination[e]	X			X		X		X		X
KCCQ-23, EQ-5D-5L[f]	X		X			X	X			X
Resting and Valsalva TTE[g]	X		X	X	X	X	X	X	X	X
Postexercise stress TTE[g]	X					X				X
Single 12-lead ECG[h]	X		X	X	X	X	X	X	X	X
Holter monitor application[i]	X				X				X	
Accelerometer provided[j]	X				X				X	
ICD download	X[k]					X				X

Table 1: MYK-461-017: Schedule of Study Assessments (Screening through Week 32) (Continued)

Assessment[a,b]	Screening Days -14 to -1	Placebo-Controlled Dosing Day 1 to Week 16					Active-Controlled Dosing Weeks 16 to 32			
		Day 1	Week 4 (+7 days)	Week 8 (+7 days)	Week 12 (+7 days)	Week 16 (+7 days)	Week 20 (+7 days)	Week 24 (+7 days)	Week 28 (+7 days)	Week 32 (+7 days)
PK sample[l]			X	X	X	X	X	X	X	X
Hepatitis/HIV panel	X									
Covid-19 (PCR) test[m]	X									
Optional HCM genotyping[n]			X							
Optional pharmacogenetics[no]			X							
Blood chemistry and coagulation	X			X		X		X		X
Hematology	X					X				X
Cardiac Biomarkers[p]	X			X		X		X		X
Exploratory biomarkers[q]	X			X		X		X		X
Serum pregnancy test or FSH[p]	X									
Urinalysis	X					X				X
Pregnancy test urine (β-hCG)[r]		X	X	X	X	X	X	X	X	X
Study drug dispensed[s]		X	X	X	X	X	X	X	X	X
Once-daily study drug		X	X	X	X	X	X	X	X	X
Dose adjustment based on TTE			X	X	X		X	X	X	
SRT evaluation[t]	X					X				X
Study drug compliance			X	X	X	X	X	X	X	X

Table 1: MYK-461-017: Schedule of Study Assessments (Screening through Week 32) (Continued)

AE = adverse event; β-hCG = beta human chorionic gonadotropin; ECG = electrocardiogram; EQ-5D-5L = EuroQol 5-dimension 5-level questionnaire; FSH = follicle stimulating hormone; FU = follow-up; HCM = hypertrophic cardiomyopathy; HIV = human immunodeficiency virus; ICD = implantable cardioverter-defibrillator; KCCQ-23 = Kansas City Cardiomyopathy Questionnaire (23-item version); NYHA = New York Heart Association; PK = pharmacokinetics; SRT = septal reduction therapy; TTE = transthoracic echocardiogram

[a] Beginning at Week 4, each study visit has a window of +7 days. Regardless of the day within a window that the study visit occurs, the next visit should adhere to the visit schedule based on the Day 1 visit date. Study visits may occur over multiple days.

[b] On study visit days, study drug dosing should be delayed until after study assessments are complete and the study staff instruct the subject to take their daily dose.

[c] Vital signs, including temperature, heart rate (HR), respiratory rate (RR), and blood pressure (BP), will be obtained at screening, Day 1, Week 16, and Week 32 visits. At all other visits, vital signs will include only HR, RR, and BP.

[d] Every effort should be made to have the same investigator evaluate NYHA functional class at screening, Week 16, and Week 32.

[e] At screening, a complete physical examination will be performed, including a neurological examination (gross motor and deep tendon reflexes), height and weight, and assessment of the following: general appearance, skin, head and neck, mouth, lymph nodes, thyroid, abdomen, musculoskeletal, cardiovascular, neurological, and respiratory systems. At all other onsite visits, an abbreviated cardiopulmonary physical examination will be conducted.

[f] At study visits that KCCQ-23 and EQ-5D-5L assessments are collected, they should be completed prior to any other procedure.

[g] Subjects should abstain from food for ≥ 4 hours prior to postexercise stress TTEs at screening, Week 16, Week 32, Week 56, Week 80, and Week 128 (EOT) Any EOT TTE that occurs before Week 32 will be centrally read and remain blinded as an SRT evaluation occurs at this visit. Any EOT TTE that occurs after the Week 32 assessment will have LVEF and LVOT read locally and the ECHO uploaded to the core ECHO lab for complete reading.

[h] Single 12-lead ECGs will be performed prior to dosing and after 10 minutes of rest at screening and all study visits from Week 4 to Week 32. Each time an ECG is completed, a 10-second paper ECG will be obtained and maintained in the subject's source documentation.

[i] A Holter monitor will be applied at screening, Week 12, and Week 28 visits and retrieved at the Day 1, Week 16, and Week 32 visits, respectively. . If a subject has an adverse reaction to the adhesive used for the Holter monitor, the requirement for monitoring may be waived.

[j] A wrist-worn accelerometer will be applied at screening, Week 12, and Week 28 visits and retrieved at the Day 1, Week 16, and Week 32 visits, respectively.

[k] ICD download may be performed at screening or prior to dosing on Day 1.[l] Blood samples for PK should be drawn before subject is dosed at study site

[m] If subject has a history of a positive PCR test within 6 months of Screening, test the subject again

[n] A separate, optional consent form is required for HCM genotyping. If a subject has already been genotyped for HCM, they may consent to provide their results, which will be captured in the electronic case report form. Genetic testing will be done on randomized subjects only and can be done at Week 4 or any visit thereafter.

[o] A separate, optional consent form is required for collection of a blood sample for possible pharmacogenetics analysis. Genetic testing will be done on randomized subjects only and can be done at Week 4 or any visit thereafter.

[p] Blood samples for NT-proBNP, cardiac troponin and exploratory biomarkers will be collected prior to the postexercise stress TTE at screening, Week 16, and Week 32 and prior to dosing at the site at every visit.

[q] FSH testing at screening is for postmenopausal female subjects to confirm postmenopausal status.

[r] Only females of child-bearing potential will be assessed for pregnancy. If a positive result occurs at any time, a serum pregnancy test should be performed.

[s] Study drug dispensing may occur up to 7 days after TTE assessments for dose titration.

[t] Evaluation for SRT may include a cardiopulmonary exercise test (CPET) if CPET is used as standard of care for SRT evaluation by the study site, but it is not required. However, if a site uses CPET for screening SRT evaluation, CPET should be repeated on that subject at all subsequent SRT evaluations.

Table 2: MYK-461-017: Schedule of Study Assessments (Week 44 through Week 136)

Assessment[a,b]	LTE Dosing (Week 32 through 128)								Week 136/ EOS (+ /- 14d)[e]	UV[f]
	Week 44 (+/-14 d)	Week 56 (+ /- 14d)	Week 68 (+ /- 14 d)	Week 80 (+ /- 14 d)	Week 92 (+ /- 14 d)	Week 104 (+ /- 14 d)	Week 116 (+ /- 14 d)	Week 128/EOT[c,d] (+ /- 14 d)		
Vital signs[g]	X	X	X	X	X	X	X	X		X
Body weight	X	X	X	X	X	X	X	X		X
NYHA functional class[h]		X				X		X		X
AEs	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X		X
Physical examination[i]	X		X		X		X	X		X
KCCQ, EQ-5D-5L[j]		X		X		X		X		
Resting and Valsalva TTE	X	X	X	X	X	X	X	X		X
Postexercise stress TTE[k]		X				X		X		
Single 12-lead ECG[l]	X	X		X		X		X		X
Holter[m]		X				X				
ICD download		X		X		X		X		X
PK sample[n]	X	X		X		X		X		X

Table 2: MYK-461-017: Schedule of Study Assessments (Week 44 through Week 136) (Continued)

Assessment[a,b]	LTE Dosing (Week 32 through 128)								Week 136/ EOS (+ /- 14d)[e]	UV[f]
	Week 44 (+/-14 d)	Week 56 (+ /- 14d)	Week 68 (+ /- 14 d)	Week 80 (+ /- 14 d)	Week 92 (+ /- 14 d)	Week 104 (+ /- 14 d)	Week 116 (+ /- 14 d)	Week 128/EOT/[c,d] (+ /- 14 d)		
Blood chemistry and coagulation	X	X		X		X		X		X
Hematology		X		X		X		X		X
Cardiac biomarkers[o]	X	X		X		X		X		X
Exploratory biomarkers[p]	X	X		X		X		X		
Urinalysis		X		X		X		X		X
Pregnancy test urine (β-hCG)[q]	X	X	X	X	X	X	X	X		X
Study drug dispensed	X	X	X	X	X	X	X			X[r]
Once-daily study drug	X	X	X	X	X	X	X	X		
Dose adjustment based on site read TTE[s]	X	X	X	X	X	X	X			
SRT evaluation[t]		X				X		X		
Study drug compliance	X	X	X	X	X	X	X	X		X

Table 2: MYK-461-017: Schedule of Study Assessments (Week 44 through Week 136) (Continued)

AE = adverse event; β-hCG = beta human chorionic gonadotropin; d = day; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; FU = follow up; ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association; PK = pharmacokinetics; TTE = transthoracic echocardiogram; UV = unscheduled visit

[a] Beginning at Week 4,through Week 32 each study visit has a window of +7 days. Regardless of the day within a window that the study visit occurs, the next visit should adhere to the visit schedule based on the Day 1 visit date. Study visits may occur over multiple days. In LTE starting with Week 44 each study visit has a window of +/- 14 days

[b] On study visit days, study drug dosing should be delayed until after study assessments are complete and the study staff instruct the subject to take their daily dose.

[c] Subjects who permanently discontinue study drug prior to Week 128 and are unwilling to remain on study to be evaluated for concomitant medications and clinical assessments will undergo EOT assessments within 14 days of study drug discontinuation and EOS assessments 8 weeks later.

[d] If a subject prematurely discontinues from the study (eg, withdrawal of consent), the medical monitor should be contacted, and EOT assessments should be conducted.

[e] Sites will make a follow-up phone call to participants 8 weeks after EOT to assess for AEs and interval procedure and/or conmeds.

[f] Unscheduled visits may be conducted for assessment of AEs, new or worsening symptoms, physical examinations, vital signs, laboratory tests, ECGs, and TTEs and upon discontinuation of study drug prior to an SRT procedure. All information collected from unscheduled visits will be recorded in the eCRF and included in the clinical database. If an SAE of cardiovascular origin occurs during LTE period, patient to return for unscheduled visit 2-4 weeks after the event for a safety assessment and ECHO (resting Valsalva).

[g] Blood pressure, heart rate, and respiratory rate will be assessed.

[h] Every effort should be made to have the same investigator who evaluated NYHA functional class at screening, Week 16, and Week 32 also evaluate NYHA functional class during LTE: Weeks 56, , 104, and 128 (EOT).

[i] An abbreviated cardiopulmonary physical examination will be conducted.

[j] At study visits that KCCQ-23 and EQ-5D-5L assessments are collected, they should be completed prior to any other procedure.

[k] Subjects should abstain from food for ≥ 4 hours prior to postexercise stress TTEs.

[l] Single 12-lead ECGs will be performed prior to dosing and after 10 minutes of rest from Week 44 to Week 56, Weeks 80, 104, and 128 and unscheduled visits, as applicable. Each time an ECG is completed, a 10 second paper ECG will be obtained and maintained in the subject's source documentation.

[m] Holter will be applied at the visit, worn for 48 hours and the patient will return the Holter to the site.

[n] Blood samples for PK should be drawn before subject is dosed at study site

[o] Blood samples for NT-proBNP, cardiac troponin and exploratory biomarkers will be collected prior to the postexercise stress TTE at screening, Week 104 and Week 128 and prior to dosing at the site at every visit.

[p] Only females of child-bearing potential will be assessed for pregnancy. If a positive result occurs at any time, a serum pregnancy test should be performed.

[q] Study drug may be dispensed if unscheduled visit is to follow up on a temporary discontinuation, and study drug is reintroduced.

[r] Mavacamten dose may be up-titrated at any scheduled visit after Week 32 if the site-read LVOT gradient with Valsalva maneuver is ≥ 30 mmHg and LVEF is ≥ 50%. All dose increases during LTE dosing must be approved by the MyoKardia or CRO medical monitor before they are implemented. Subjects who have their mavacamten dose increased during the LTE period will attend an unscheduled study visit 4 weeks after the dose increase and then resume the regular study visit schedule.

[s] Evaluation for SRT may include a CPET if CPET is used as standard of care for SRT evaluation by the study site, but it is not required. However, if a site uses CPET for screening SRT evaluation, CPET should be repeated on that subject at all subsequent SRT evaluations.

Schedule of Follow-Up Assessments After Septal Reduction Therapy

Table 3: MYK-461-017: Schedule of Assessments Following Septal Reduction Therapy

	Weeks After SRT			
Assessments[a]	**24 (± 7 Days)**	**48 (± 7 Days)**	**72 (± 7 Days)**	**96 (± 7 Days)**
Postoperative follow-up[b]	X			
Vital signs[c]	X	X	X	X
AEs	X	X	X	X
Concomitant medications	X	X	X	X
Physical examination[d]	X	X	X	X
Resting and Valsalva TTE	X	X	X	X
NYHA functional class	X	X	X	X
KCCQ-23[e]	X	X	X	X
EQ-5D-5L[e]	X	X	X	X

AE = adverse event; EQ-5D-5L = EuroQol 5-dimension 5-level questionnaire; KCCQ-23 = Kansas City Cardiomyopathy Questionnaire (23-item version); NYHA = New York Heart Association; SRT = septal reduction therapy; TTE = transthoracic echocardiogram

[a] Subjects who discontinue study drug to undergo SRT will undergo end of treatment assessments (as outlined in Table 2) within 14 days and will have a telephone follow-up with the study site to assess adverse events 8 weeks after treatment discontinuation (or prior to SRT, whichever is earlier). Any EOT TTE that occurs before Week 32 will be centrally read and remain blinded as an SRT evaluation occurs at this visit. Subjects will be followed every 24 weeks from the date of SRT to Week 128.

[b] At the first visit after SRT, the following information should be collected: date of SRT, procedure type (myectomy or alcohol septal ablation), dates of hospitalization, any complications, need for pacemaker, periprocedure adverse events

[c] Blood pressure, heart rate, and respiratory rate will be assessed

[d] An abbreviated cardiopulmonary physical examination will be conducted.

[e] KCCQ-23 and EQ-5D-5L should be completed prior to any other procedure.

Schedule of Follow-Up Assessments for Subjects Who Remain on Study Following Discontinuation of Study Drug

Table 4: MYK-461-017: Schedule of Assessments Following Discontinuation of Study Drug

Assessments[a]	Weeks After Discontinuation of Study Drug			
	24 (± 7 Days)	48 (± 7 Days)	72 (± 7 Days)	96 (± 7 Days)
AEs	X	X	X	X
Concomitant medications	X	X	X	X
Vital signs[b]	X	X	X	X
Physical examination[c]	X	X	X	X
Single 12-lead ECG	X	X	X	X
ICD download	X	X	X	X
Resting and Valsalva TTE	X	X	X	X
NYHA functional class	X	X	X	X
KCCQ-23[d]	X	X	X	X
EQ-5D-5L[d]	X	X	X	X
SRT evaluation[e]	X	X	X	X

AE = adverse event; ECG = electrocardiogram; EQ-5D-5L = EuroQol 5-dimension 5-level questionnaire; ICD = implantable cardioverter-defibrillator; KCCQ-23 = Kansas City Cardiomyopathy Questionnaire (23-item version); NYHA = New York Heart Association; SRT = septal reduction therapy; TTE = transthoracic echocardiogram

[a] Subjects who permanently discontinue treatment prior to Week 128 will undergo end of treatment assessments (as outlined in Table 2) within 14 days of study drug discontinuation and will be followed every 24 weeks thereafter until Week 128.

[b] Blood pressure, heart rate, and respiratory rate will be assessed.

[c] An abbreviated cardiopulmonary physical examination will be conducted.

[d] KCCQ-23 and EQ-5D-5L should be completed prior to any other procedure.

[e] Evaluation for SRT after discontinuation of study drug should be based on NYHA functional class, maximal medical therapy, and resting and Valsalva TTE. A postexercise TTE is not required.

1. INTRODUCTION

1.1. Background

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder defined by left ventricular (LV) hypertrophy that cannot be explained by another cardiac or systemic disease. HCM is a chronic, progressive disease of the cardiomyocyte, largely of the cardiac sarcomere, with a diverse clinical presentation and course. A defining feature of HCM is myocardial hypercontractility accompanied by reduced LV compliance, which is reflected clinically as reduced ventricular chamber size, often supranormal ejection fraction, and diastolic dysfunction. HCM can be familial and is the most common genetic disease of the myocardium. Point mutations in one of the structural genes of the sarcomere can be documented in approximately 40% of affected individuals overall and in about 60% of those with a family history of clinical disease Hershberger et al. (2009); (Gersh et al. 2011; Maron, Maron, and Semsarian 2012; Alfares et al. 2015). Mutations in cardiac myosin and other sarcomere proteins appear to increase net power generation by the sarcomere (Chuan et al. 2012; Sommese et al. 2013; Sung J 2012), consistent with the generally hypercontractile state and impaired compliance of the myocardium observed clinically in HCM.

HCM is a global disease, with a prevalence of approximately 1:500 reported across geographic regions (Maron et al. 1995). HCM can present at any age, although prevalence increases with age. It is a chronic disease that can progress to the point at which patients develop debilitating symptoms and cardiac dysfunction. The most prevalent burden of morbidity for patients with HCM is exertional dyspnea, which limits daily activity and can be debilitating. Patients with HCM are at increased risk for adverse clinical events, including overt heart failure (HF) prompting hospitalization; atrial fibrillation, causing both worsening of exertional symptoms and an increased risk for stroke; syncope; malignant ventricular arrhythmias; and sudden cardiac death, one of the most common nontraumatic causes of death in young adults and sometimes the first manifestation of HCM (Ho et al. 2002; Gersh et al. 2011; Ho 2012). Mortality due to HCM is 4 times higher than in the general population.

HCM is categorized as obstructive (ie, oHCM [also known as HOCM]) or nonobstructive (nHCM) based on the presence or absence of LV outflow tract (LVOT) obstruction. The presence of LVOT obstruction is associated with more severe symptoms and greater risk of heart failure and cardiovascular (CV) death (Maron et al. 2003). The most prevalent burden of morbidity for patients with HCM is exertional dyspnea, which limits daily activities and can be debilitating. Current treatment guidelines for HCM include the use of beta blockers, calcium channel blockers, and disopyramide (Gersh et al. 2011). However, despite treatment, symptoms and disease burden persist for many patients, and therapeutic options are limited.

Patients with oHCM with severe drug-refractory symptoms may be referred for septal reduction therapy (SRT; ie, myectomy or alcohol septal ablation [ASA]). While these procedures can be effective in reducing or eliminating LVOT obstruction, thereby alleviating symptoms, they are invasive, associated with risk, and should be performed only by experienced operators in centers of excellence with high-volume SRT performance as defined in the 2011 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines (Gersh et al.

2011). Performance of myectomy at lower-volume centers has been associated with worse outcomes, including higher mortality, longer length of stay, and higher costs (Kim et al. 2016). Following myectomy, nearly all patients develop a left bundle branch block, and patients with right bundle branch block prior to surgery are at increased risk for complete heart block after surgery. ASA has been associated with postprocedural arrhythmias, coronary artery dissection, pericardial effusion, and large myocardial infarction resulting from escape of ethanol from the target vessel to another coronary vessel (usually the left anterior descending [LAD] artery), as well as a higher incidence of heart block requiring implantation of a permanent pacemaker (Nishimura and Ommen 2010). Thus, there is an unmet need for noninvasive alternatives to SRT for drug-refractory, symptomatic oHCM patients.

Mavacamten is a small-molecule allosteric inhibitor of cardiac myosin that reversibly inhibits its binding to actin, thereby relieving systolic hypercontractility and improving ventricular compliance. MyoKardia, Inc. is developing mavacamten for the treatment of adults with symptomatic oHCM to reduce ventricular filling pressures, improve symptoms, and increase exercise capacity.

Mavacamten has been well tolerated in Phase 1 and 2 studies in healthy subjects and subjects with HCM. In the Phase 2 study MYK-461-004 (PIONEER-HCM), in which subjects with symptomatic oHCM received up to 20 mg mavacamten once daily for 12 weeks, marked reductions in LVOT gradients were observed that were associated with improved exercise tolerance, improved New York Heart Association (NYHA) functional class, and a decrease in dyspnea symptom score.

1.1.1. Clinical Studies

To date, 15 clinical studies have been initiated to investigate the safety and tolerability of mavacamten. As of 31 October 2019, clinical conduct has been completed for 9 studies as follows:

- Study MYK-461-002, a single ascending dose (SAD) study in 48 healthy subjects
- Study MYK-461-003, a multiple ascending dose (MAD) study in 60 healthy subjects
- Study MYK-461-009, a drug-interaction study with verapamil in 25 healthy subjects
- Study MYK-461-010, a drug-interaction study with an oral contraceptive in 13 healthy women
- Study MYK-461-011, an ethnobridging pharmacokinetics (PK) study in 20 Japanese and 8 Caucasian subjects
- Study MYK-461-012, an intrinsic factor PK study in 8 cytochrome P450 (CYP)2C19 poor metabolizers and 8 CYP2C19 normal metabolizers
- Study MYK-461-013, a single-dose, mass balance study in 6 healthy subjects
- Study MYK-461-001, a SAD study in 15 subjects with HCM
- Study MYK-461-004 (PIONEER-HCM), a Phase 2 study in patients with oHCM

In total, 210 patients with HCM or healthy subjects were enrolled across the completed studies, 188 of whom were exposed to at least 1 dose of mavacamten.

Additionally, as of 31 October 2019, more than 400 subjects have been enrolled across 5 ongoing studies of mavacamten:

- Study MYK-461-005 (EXPLORER-HCM), a Phase 3, multinational, randomized, double-blind, placebo-controlled study in subjects with symptomatic oHCM
- Study MYK-461-006 (MAVERICK-HCM), a Phase 2 randomized, placebo-controlled, concentration-guided exploratory study in subjects with symptomatic nHCM
- Study MYK-461-008 (PIONEER-OLE), an open-label extension study in subjects with symptomatic oHCM who were previously enrolled in Study MYK-461 PIONEER-HCM study
- Study MYK-461-007 (MAVA-LTE), an open-label extension study in subjects with symptomatic HCM who were previously enrolled in Studies MYK-461-006 (MAVERICK-HCM) or MYK-461-005 (EXPLORER-HCM) studies
- Study MYK-461-014, a 3-period cross-over study in healthy subjects to assess the relative bioavailability of the initial capsule formulation and the final commercial formulation of mavacamten, and the effect of food on the final commercial formulation
- Study MYK-461-015, an intrinsic factor study to assess the effect of mild and moderate hepatic impairment on the PK of mavacamten

Oral doses of mavacamten up to 96 mg (single doses administered in 8 even aliquots every 15 minutes) and 18.5 mg once daily (28-day course) have been well tolerated. Once-daily doses of 25 mg were well tolerated clinically in healthy subjects up to 25 days, after which time dosing was suspended because stopping criteria were met (left ventricular ejection fraction [LVEF] relative decrease by ≥ 20%). The predefined stopping criterion for dose escalation (reduction in LVEF by ≥ 20%) was satisfied in both the single-dose Study MYK-461-001 at 144 mg and in the 28-day multidose study (Study MYK-461-003) at 25 mg daily. Please refer to the Investigator's Brochure (IB) for details of safety outcomes.

Preliminary efficacy was demonstrated in a 21-patient study, in which subjects with oHCM received open label mavacamten at doses ranging from 2 to 20 mg for 12 weeks (Study MYK 461-004; PIONEER-HCM). This 2-part study demonstrated a marked reduction in LVOT gradient to levels considered clinically insignificant at plasma mavacamten concentrations ≥ 350 ng/mL with LVEF remaining essentially within normal range at concentrations of up to 1000 ng/mL. The gradient reduction was accompanied by the resolution of systolic anterior motion of the mitral valve in all but 2 subjects (9 of 11 subjects [82%]) in Part A. The study also demonstrated an improvement in NYHA functional class and dyspnea score, a decrease in N-terminal pro b-type natriuretic peptide (NT-proBNP) levels and a trend toward improved exercise tolerance as measured by peak O_2 consumption on cardiopulmonary exercise testing (CPET). Lastly, there was a trend toward improved diastolic function as measured by echocardiographic criteria. Overall, mavacamten was well tolerated; there was one SAE of atrial fibrillation in a patient with a history of atrial fibrillation.

In the EXPLORER-HCM (MYK-461-005) phase 3, randomized, double-blind, placebo-controlled study, patients with oHCM were assigned (1:1) to receive mavacamten (starting at 5 mg) or

placebo for 30 weeks (Ho et al.2020b). Treatment with mavacamten was superior to placebo across the primary endpoint and all secondary endpoints in a study population with 92% of subjects on either beta-blocker or non-dihydropyridine calcium channel blocker therapy. Subjects treated with mavacamten demonstrated twice the response rate of those in the placebo group on the composite functional primary endpoint (36.6% vs 17.2%), with a highly statistically significant between-group difference (19.4% [95% CI: 8.67, 30.13], p = 0.0005). Additionally, 20.3% of subjects treated with mavacamten met the criteria of ≥ 3.0 mL/kg/min increase in pVO_2 and ≥ 1 NYHA class improvement compared with 7.8% of subjects on placebo. Mavacamten treatment was also effective in reducing LVOT gradients and improving symptoms, exercise performance, and health status, as shown by significant improvement in all secondary endpoints (Olivotto et al. 2020).

In the MAVERICK-HCM (MYK-461-006) phase 2, randomized, double-blind, placebo-controlled study, patients with nHCM were assigned to received mavacamten (starting at 5 mg) or placebo for 16 weeks. This was the first therapeutic study to demonstrate a substantial reduction of NT-proBNP in nHCM patients. Although this dose-ranging, exploratory study was underpowered to detect clinical benefit as reflected by pVO_2 or NYHA class, the rapid and sustained dose-dependent reduction in NT-proBNP with mavacamten treatment suggests physiological benefit (Ho et al. 2020a).

The preliminary safety of mavacamten has been evaluated for single and multiple doses in healthy subjects and subjects with HCM. Overall, mavacamten appears to be generally well tolerated with little evidence for off-target toxicity.

Treatment with mavacamten was well tolerated in the EXPLORER-HCM (MYK-461-005) study through 30 weeks of treatment. Overall, treatment-emergent adverse events (TEAEs) were higher in the mavacamten group compared with the placebo group during the on-treatment (Day 1 to Week 30) period (87.8% vs 78.9%) and treatment-emergent (Day 1 to Week 38) period (87.8% and 81.3%). It is notable that the TEAE rate did not increase in the mavacamten group with 8 weeks of additional observation during study drug washout. The proportion of subjects in the mavacamten group with treatment discontinuations due to TEAEs was 1.6% (2 of 123 subjects). No subjects in the placebo group discontinued treatment due to TEAEs, however one subject discontinued due to experiencing sudden death. SAEs were balanced between treatment groups; on-treatment rates of SAEs were 8.1% in the mavacamten group versus 8.6% in the placebo group, and rates of treatment-emergent SAEs were 11.4% and 9.4%, respectively (Olivotto et al. 2020). On-treatment LVEF reductions of <50% were observed in 7 mavacamten and 2 placebo subjects; three of seven were during the 30 weeks and four were at the end of treatment (week 30 visit). After a temporary study drug discontinuation, the three subjects who had LVEF reductions of <50% during treatment restarted drug on a lower dose and completed the study. No off-target signals were identified.

Treatment with mavacamten was well tolerated in the MAVERICK-HCM (MYK-461-006) study (Ho et al. 2020a). The majority of TEAEs were mild or moderate in severity, with few severe TEAEs and no fatal adverse events (AEs). The types of TEAEs reported were similar for the mavacamten and placebo groups and were representative of the underlying disease. The incidence of SAEs was low, and the only SAE reported for > 1 subject was atrial fibrillation. There were 6 SAEs in 4 patients receiving mavacamtent: 2 in cadiac disorder system organ class (SOC); 1 in musculoskeletal & connective tisse disorders; 1 in psychiatric disorders;1 in renal &

urinary disorders No fatal TEAEs were reported. Five subjects (2 subjects in the 200 ng/mL group and 3 subjects in the 500 ng/mL group) discontinued treatment due to meeting the protocol-specified stopping criteria of LVEF ≤ 45% and/or heart failure with systolic dysfunction. In all five cases, LVEF was returned/returning to baseline by end of washout. No off-target signals were identified.

Systolic dysfunction, drug-drug interactions with CYP-2C19 inhibitors, teratogenicity, and prolonged corrected QT interval (QTc) have been identified as important risks.

The PK profile of mavacamten is characterized by a biphasic profile with a rapid absorption (time to reach maximum concentration [t_{max}] generally between 1 and 2 h) and a long terminal half-life ($t_{1/2}$) with a mean of 6 to 9 days in CYP2C19 extensive metabolizers. In CYP2C19 poor metabolizers, $t_{1/2}$ is up to 21 days and the exposure is increased up to approximately 4-fold compared with extensive metabolizers. The exposure is slightly greater than dose proportional starting at doses of 12.5 mg. At steady-state, the peak-to-trough plasma concentration ratio with once-daily dosing is very low (1.5 to 1). Clearance and volume of distribution have not been determined in humans as they require intravenous administration; however, data are consistent with a low clearance and high volume of distribution demonstrated nonclinically. Four metabolites have been detected in human plasma from the multiple ascending dose clinical trial (MYK-461-003). The exposure of the most abundant metabolite in human plasma was less than 5% of the exposure of mavacamten, and the other metabolites had exposure less than 1% of the exposure of mavacamten. The available data thus far indicate that approximately 75% of the metabolism occurs through CYP2C19, 16% through 3A4/5 and the rest through CYP2C9. Less than 1% of the administered drug is found unchanged in the urine. Pilot data indicate a food effect of less than 15% reduction in exposure when mavacamten was administered after a high fat meal vs. the fasted state. In most cases, the between-subject variability (coefficient of variation) for exposure is moderate (in the 30 to 60% range).

A drug interaction study with the moderate CYP3A4 inhibitor, verapamil, which is frequently used in the treatment of oHCM, revealed no changes in AUC and a 50% increase in maximum plasma concentration (C_{max}) after a single dose of mavacamten. These changes are not considered clinically significant, especially in light of the proposed dosing strategy of starting every patient on a low dose of mavacamten and increasing the dose as needed. An ethnobridging study indicated no important PK differences between Japanese and Caucasian subjects.

Because of the potential for mavacamten to cause induction of CYP3A4, a drug-drug interaction study was conducted with a typical oral contraceptive consisting of ethinyl estradiol and norethindrone (Ortho-Novum®), which was administered before and after a 17-day course of mavacamten (25 mg on Days 1 and 2, followed by 15 mg daily for 15 days). Mavacamten did not decrease the exposure to either ethinyl estradiol or norethindrone, thus ruling out a drug interaction with oral contraceptives.

1.2. Rationale for the Study

There is no approved medical alternative to invasive SRT for drug refractory symptomatic oHCM patients. Mavacamten's profile of myosin inhibition is predicted to reduce dynamic LVOT obstruction in individuals with oHCM by reducing systolic hypercontractility and dynamic obstruction in the near term and may reduce ventricular hypertrophy with long-term treatment. Therefore, mavacamten may provide an additional pharmacologic therapy to comply

with guideline-recommended maximal medical therapy prior to considering an invasive SRT procedure and reduce the need for myectomy or ASA procedures.

Study MYK-461-017 (VALOR-HCM) is a Phase 3, double-blind, placebo-controlled, randomized study of subjects with drug-refractory, symptomatic oHCM who are eligible for SRT according to 2011 ACCF/AHA guidelines (Gersh et al. 2011;). The study is designed to investigate the percentage of guideline-eligible subjects referred for SRT at study entry who decide to undergo SRT or remain guideline-eligible for SRT after 16 weeks of treatment with mavacamten compared with placebo.

After 16 weeks of placebo-controlled treatment, subjects in the placebo group will begin 16 weeks of dosing with mavacamten (active-controlled period), providing them access to the potential benefits of mavacamten.

After Week 32, all subjects will have the opportunity to receive mavacamten for 96 additional weeks until Week 128 (end of treatment [EOT]). During this long-term extension (LTE) period, NYHA functional class, resting and Valsalva transthoracic echocardiograph (TTE) parameters, SRT guideline eligibility criteria, and safety of mavacamten will be assessed to determine long-term outcomes of subjects receiving mavacamten.

Data from this study will complement results from the completed MYK-461-004 (PIONEER-HCM) study and the MYK-461-005 (EXPLORER-HCM) study of mavacamten to a population oHCM patients with severe symptoms refractory to maximal medical therapy.

1.3. Justification for Dose Selection

Clinical, nonclinical, and PK modeling studies have shown that mavacamten 5 mg once daily is a safe starting dose and that the dose in individual subjects can be titrated up to 15 mg based on TTE profile, while maintaining LVEF ≥ 50%. Therefore, the mavacamten starting dose in this study is 5 mg once daily with up-titration to a maximum of 15 mg once daily based on LVEF and LVOT measured by TTE (Section 5.6). Formal evaluation for mavacamten dose titration will occur 4 weeks (down-titration) and 8 and 12 weeks (up-titration) after beginning mavacamten dosing. No formal mavacamten dose titrations will be conducted during the LTE period, and any dose increases during that time must be approved by the MyoKardia or CRO medical monitor before they are implemented.

Dose may be down-titrated for safety at any time (see Table 7) on consultation with the medical monitor.

Throughout the study, mavacamten dose will be blinded and dose titrations will be performed in a blinded manner using an interactive response system (IXRS).

1.4. Benefit/Risk Assessment

The potential clinical benefit of mavacamten in this study is to provide a noninvasive therapeutic alternative to SRT and its related morbidities in subjects with treatment-refractory, symptomatic oHCM.

Available nonclinical and clinical data to date indicate that the primary risk of mavacamten use is its exaggerated on-target effect of reduction in cardiac contractility (ie, reduced LVEF), which could result in the development of signs or symptoms of systolic heart failure. The highest

mavacamten dose allowed in the current study is 15 mg once daily, which is within the range of doses that were well tolerated in the MAD study in healthy subjects (Study MYK-461-003) and doses that were tolerated in subjects with symptomatic oHCM who received a 30-week course of mavacamten in Study MYK-461-005 (EXPLORER-HCM).

Other potential risks of mavacamten use include teratogenicity (observed in animal studies only), drug-drug interactions with use of drugs metabolized by the CYP2C19 pathway and QTc prolongation (observed in animal species and healthy volunteers). No QTc prolongations were observed in the Phase 212-week study of subjects with oHCM (MYK-461-004), in the Phase 2 nHCM (MYK-461-006) subjects at the 16-week (end of treatment) analysis, or in the Phase 3 oHCM (MYK-461-005) subjects at the 30-week (end of treatment) analysis. Study inclusion/exclusion criteria and monitoring during the study will mitigate for these risks.

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 definition and management of overdose definitions and management, see Section 5.9.

2. OBJECTIVES AND ENDPOINTS

Table 5 summarizes the primary, secondary, exploratory, PK, and safety objectives and endpoints of the study.

Table 5: MYK-461-017: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the effect of mavacamten on the need for SRT in guideline-eligible subjects with oHCM who are referred for SRT	The primary endpoint will be a composite of: 1. Decision to proceed with SRT prior to or at Week 16 2. SRT guideline eligible at Week 16 based on the 2011 ACCF/AHA HCM Guidelines
Secondary	
To evaluate the effect of mavacamten on subject symptoms	Change from baseline to Week 16 in the mavacamten group compared with the placebo group in: • NYHA functional class • Kansas City Cardiomyopathy Questionnaire 23-item version (KCCQ-23, CSS)
To evaluate the effect of mavacamten on cardiac biomarkers	Change from baseline to Week 16 in the mavacamten group compared with the placebo group in NT-proBNP and cardiac troponin

Table 5: MYK-461-017: Objectives and Endpoints (Continued)

Objectives	Endpoints
To evaluate the effect of mavacamten on a hemodynamic parameter	Change from baseline to Week 16 in the mavacamten group compared with the placebo group in post-exercise LVOT gradient
Exploratory	
To evaluate the effect of mavacamten on the need for SRT in a long-term follow-up period	At Week 32, 56, 104, and 128, the endpoint is a composite of: 1. Decision to proceed with SRT, 2 SRT guideline eligibility based on the 2011 ACCF/AHA HCM Guidelines at each timepoint
To evaluate the effect of mavacamten on the need for SRT as determined by the investigator	The endpoint will be a composite of the outcomes below at Week 16, 32, 56, 104, and 128: 1. Decision to proceed with SRT 2. SRT eligible based on the Investigator determination as recorded on the SRT evaluation CRF
To evaluate the effect of mavacamten on hemodynamic parameters and cardiac biomarkers and to improve subject activity level and quality of life (QoL)	Analysis of left ventricular outflow tract (LVOT) gradient at rest and induced by Valsalva, LVEF, LV filling pressures, left atrium size, cardiac biomarkers, accelerometry, and EuroQol 5-dimensions 5-level (EQ-5D-5L) questionnaire will be performed for: • Change from baseline to Week 16 in the mavacamten group compared with the placebo group
To evaluate the long-term effect of mavacamten on symptoms, hemodynamic parameters, cardiac biomarkers, subject activity level, and quality of life through Week 128.	Analysis of NYHA functional class, KCCQ-23 (Overall Summary Score [OSS], Total Summary Score [TSS], and individual domain), LVOT gradients, LVEF, LV filling pressures, left atrium size, cardiac biomarkers, accelerometry, and EQ-5D-5L, throughout Week 128

Table 5: MYK-461-017: Objectives and Endpoints (Continued)

Objectives	Endpoints
To evaluate the effects of mavacamten on type and dose of cardiac medications	Change from baseline to Week 16, Week 16 to 32, and Week 32 to Week 128 in HCM standard of care cardiac medications
Safety	
To evaluate the safety of mavacamten for the duration of the study	• Incidence of LVEF < 50% determined by TTE • Incidence and severity of TEAEs, treatment-emergent SAEs, and laboratory abnormalities • Incidence of SAEs before and after SRT among subjects who undergo SRT Incidence of major adverse cardiac events (MACE; death, stroke, acute myocardial infarction, heart failure hospitalization) • Incidence of hospitalizations (due to CV and non-CV events) • Incidence of HF events, (including hospitalizations and urgent emergency room/outpatient visits for HF and escalation in HF treatment) • Incidence of atrial fibrillation/flutter (new from screening and recurrent) • Incidence of implantable cardioverter-defibrillator (ICD) therapy and resuscitated cardiac arrest • Incidence of ventricular tachyarrhythmias (includes ventricular tachycardia, ventricular fibrillation, and Torsades de Pointe) • Incidence of adverse events of special interest (AESIs; symptomatic overdose, outcomes of pregnancy, LVEF ≤ 30%)
Pharmacokinetics	
Evaluate plasma concentrations of mavacamten	Summarize mavacamten plasma concentrations from on-treatment sample collection

3. STUDY DESIGN

3.1. Overall Design

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study of males and females ≥ 18 years with oHCM who meet 2011 ACCF/AHA criteria for SRT and have been referred for an SRT procedure. (Desai et al, 2021)

There will be 3 dosing periods as follows:

- Placebo-controlled dosing period (Day 1 to Week 16): Subjects will receive double-blind mavacamten or placebo once daily for 16 weeks
- Active-controlled dosing period (Week 16 to Week 32): All subjects will receive mavacamten once daily for 16 weeks. Dose will be blinded.
- LTE dosing period (Week 32 to Week 128): All subjects will receive mavacamten once daily for 96 weeks. Dose will be blinded.

After completing screening assessments, eligible subjects will be randomized in a 1:1 ratio to 1 of 2 treatment groups as follows:

- Mavacamten: One 2.5, 5, 10, or 15 mg capsule once daily for 128 weeks
- Placebo: One placebo-to-match mavacamten capsule once daily for 16 weeks and then switch to mavacamten (placebo-to-active) one 2.5, 5, 10, or 15 mg mavacamten capsule once daily for 112 weeks (Week 16 to Week 128)

Randomization will be stratified by the type of SRT procedure recommended (myectomy or ASA) and NYHA functional class.

At screening, the investigator will confirm that the subject is willing to have an SRT procedure and meets 2011 ACCF/AHA SRT eligibility criteria.

At any time during the study, subjects may withdraw from study drug and proceed with SRT at a recognized HCM center after a recommended study drug washout period ≥ 6 weeks. Subjects who discontinue study drug to undergo SRT will undergo EOT assessments as outlined in Table 2 within 14 days and will have a telephone follow-up with the study site to assess AEs 8 weeks after treatment discontinuation (or prior to SRT, whichever is earlier). Subjects will be followed every 24 weeks from the date of SRT to Week 128 as outlined in Table 3.

At Weeks 16 and 32, 56, 104, and 128, subjects will be reevaluated for SRT eligibility, and the investigator will make a guideline-based recommendation for SRT (yes or no). Subjects will be required to decide within 48 hours whether to accept the recommendation for SRT or continue on study treatment.

From Week 4 through Week 32, mavacamten dose may be titrated based on LVEF and LVOT gradient by TTE results read at the core echocardiography laboratory and according to the dose titration guidelines (Section 5.6). Dose may be titrated during the LTE period based on LVEF and LVOT gradient by TTE read at the site electrocardiography laboratory. The last possible dose titration is at Week 116. Dose titration is possible at Unscheduled Visits if the participant is symptomatic or clinically indicated and meets titration criteria (Section 5.6). During LTE, dose up-titration must be at least 12 weeks from last dose up-titration. LTE dosing must be approved by the

MyoKardia or CRO medical monitor before they are implemented. Throughout the study, all dose adjustments will occur in a blinded manner via the IXRS.

During the placebo-controlled dosing period (Day 1 to Week 16), subjects will be evaluated for possible down-titration at Week 4 and up-titration at Weeks 8 and 12. During the active-controlled dosing period (Weeks 16 to 32), subjects in the placebo-to-active group, who begin dosing with mavacamten at Week 16, will be evaluated for possible down-titration at Week 20 and up-titration at Weeks 24 and 28. During the LTE dosing period (Weeks 44to 116), mavacamten dose may be up-titrated at any scheduled visit after Week 32 if the site-read LVOT gradient with Valsalva maneuver is ≥ 30 mmHg and LVEF is ≥ 50%. All dose increases during LTE dosing must be approved by the MyoKardia or CRO medical monitor before they are implemented.

Dose may be down-titrated for safety at any time per titration schedule (Table 7) on consultation with the medical monitor. See Section 5.6.

A formal interim analysis will be conducted after 50 subjects have completed the Week 16 study visit or terminated early from the study drug to assess efficacy and safety results. The Independent Data Monitoring Committee (IDMC) may recommend early stopping for statistically significant efficacy (p-value less than 0.001) of the guideline based SRT primary endpoint. If early stopping is suggested, the subjects that are randomized to placebo and in the placebo-controlled period will skip the remainder of the placebo-controlled period and continue to week 16 visit to begin mavacamten in the active-controlled period.

3.1.1. Study Procedures and Treatment

Research study visits will occur at screening, Day 1, every 4 weeks through Week 32, every 12 weeks thereafter until Week 128 (EOT). Subjects will receive a follow-up phone call 8 weeks later at Week 136 (EOS) visit to assess for AEs and interval procedure and/or concomitant medications (conmeds). Subjects who prematurely discontinue study drug at any time prior to Week 128 (except for SRT) will undergo EOT assessments as outlined in Table 2 within 14 days of study drug discontinuation and will be followed every 24 weeks thereafter until Week 128 as outlined in Table 4.

A variety of general, cardiopulmonary, laboratory, biomarker, patient-reported outcome (PRO), and symptom assessments will be performed at screening, Day 1, and all subsequent study visits as outlined in Table 1 and Table 2 and described in Section 7.

On Day 1, subjects will begin placebo-controlled dosing with mavacamten 5 mg or placebo once daily for 16 weeks.

At Week 16, subjects will be reevaluated for SRT eligibility as described in Section 7.1. After the Week 16 assessments, subjects in the mavacamten treatment group who elect to continue treatment (ie, do not make a decision to have SRT) will continue once-daily dosing with mavacamten at the dose they had been receiving at Week 16 for an additional 16 weeks to Week 32; subjects in the placebo group who elect to continue treatment will begin dosing with mavacamten 5 mg once daily for 16 weeks to Week 32 (placebo-to-active group).

At Week 32, subjects will again be evaluated for SRT eligibility. After the Week 32 assessments, all subjects who elect to continue study treatment (ie, do not make a decision to have SRT) will

continue once-daily dosing with mavacamten at the dose they had been receiving at Week 32 for an additional 96 weeks to Week 128 (EOT).

At Weeks 56, 104, and 128, subjects will again be evaluated for SRT eligibility. Subjects who elect to continue study treatment (ie, do not make a decision to have SRT) at Week 104 will continue once-daily dosing with mavacamten at the dose they had been receiving at each SRT assessment until Week 128 (EOT).

3.2. Study Duration

The study duration will be up to 138 weeks. This includes a 2-week screening period (Week –2), 16 weeks of placebo-controlled treatment (Day 1 to Week 16), 16 weeks of active-controlled treatment (Weeks 16 to 32), 96 weeks of LTE mavacamten (Weeks 32 to 128), and a follow-up phone call at Week 136 (EOS). The follow-up phone call will be made to assess for AEs and interval procedure and/or conmeds.

3.3. Study Committees

This study includes an executive committee (EC) and an IDMC.

3.3.1. Executive Committee

The EC will play an active role in providing scientific guidance and advice to the sponsor related to the design, conduct, results analysis, and publication strategy for the MYK-461-017 (VALOR-HCM) study. The EC will be composed of members who are experts in CV disease, including HCM, with relevant clinical, surgical, and methodological expertise. All EC members will remain blinded to treatment assignments until Week 32. Meeting frequency, membership, and specific responsibilities will be further described in the EC Charter.

3.3.2. Independent Data Monitoring Committee

An IDMC will meet at regular intervals to review ongoing study data. The role of the IDMC will be to act in an advisory capacity to the sponsor and the EC with respect to safeguarding the interest of study subjects, assessing interim unblinded safety and efficacy data, and advising the sponsor and EC on important emerging study conduct issues. An interim efficacy analysis will occur after 50 subjects complete Week 16 or terminated early from the study drug. The results will be reviewed by the IDMC and will inform the Chairperson of the EC of recommendation to continue the study as planned or stop the study early. The IDMC may formulate recommendations in relation to the evaluation procedures and methodologies being used to survey and detect potential safety signals. Meeting frequency, membership, and conduct will be described in the IDMC Charter.

4. STUDY POPULATION

Approximately 100 subjects ≥ 18 years old with symptomatic oHCM who meet 2011 ACCF/AHA criteria for SRT, are willing to have an SRT procedure, and are referred or under active consideration for SRT within the past 12 months who meet all the inclusion criteria and none of the exclusion criteria will be enrolled.

4.1. Inclusion Criteria

1. Able to understand and comply with the study procedures, understand the risks involved in the study, and provide written informed consent according to federal, local, and institutional guidelines prior to initiation of any study-specific procedure
2. At least 18 years old at screening
3. Body weight > 45 kg at screening
4. Adequate acoustic windows to enable accurate TTE (refer to the central echocardiography laboratory's manual of operations)
5. Diagnosed with oHCM (unexplained LV hypertrophy with nondilated ventricular chambers in the absence of other cardiac [eg. aortic stenosis, hypertension]) or systemic disease. Patient has maximal septal wall thickness ≥ 15 mm or ≥ 13 mm with family history of HCM consistent with current ACCF/AHA 2011 guidelines. Patient must meet ACCF/AHA 2011 guideline recommendations for invasive SRT therapies as follows:
   - Clinical criteria: Despite maximally tolerated drug therapy severe dyspnea or chest pain (NYHA Class III or IV) or for the purposes of the Valor Study, subjects who are NYHA Class II with exertion-induced syncope or near syncope
   - Hemodynamic criteria: dynamic LVOT gradient at rest or with provocation (ie, Valsalva or exercise) ≥ 50 mmHg associated with septal hypertrophy of ≥15mm (or ≥13mm with family history of HCM) (read by the core echocardiography laboratory)
   - Anatomic criteria: targeted anterior septal thickness sufficient to perform the procedure safely and effectively in the judgment of the individual operator
6. Referred or under active consideration within the past 12 months for SRT procedure and willing to have SRT procedure
7. Subjects referred or considered for ASA must have an adequate first septal perforating branch of left anterior descending (LAD) coronary artery, amenable for the interventionalist to perform the procedure
8. Documented oxygen saturation at rest ≥ 90% at screening
9. Documented LVEF ≥ 60% at screening according to core echocardiography laboratory reading
10. Female subjects not pregnant or lactating and, if sexually active, must either practice true abstinence or use 1 of the following highly effective birth control methods from screening through 4 months after the last dose of study drug:
    - Estrogen- and progestogen-containing hormonal contraception associated with inhibition of ovulation or progestogen-only hormonal contraception associated with inhibition of ovulation by oral, implantable, or injectable route of administration
    - Intrauterine device
    - Intrauterine hormone-releasing system
    - Bilateral tubal occlusion

- Female surgically sterile or postmenopausal for 1 year. Permanent sterilization includes hysterectomy, bilateral oophorectomy, bilateral salpingectomy, and/or documented bilateral tubal occlusion. Females are considered postmenopausal if they have had amenorrhea for ≥1 year after cessation of all exogenous hormonal treatments, and follicle stimulating hormone (FSH) levels are in the postmenopausal range.

Male partners of female subjects must also use a contraceptive (eg, barrier, condom, or vasectomy) from screening through 4 months after the last dose of study drug.

4.2. Exclusion Criteria

1. Previously participated in a clinical study with mavacamten (individuals who failed screening for a prior mavacamten study may participate)
2. Hypersensitivity to any of the components of the mavacamten formulation
3. Participated in a clinical trial in which the subject received any investigational drug (or currently using an investigational device) within 30 days prior to screening, or at least 5 times the respective elimination half-life (whichever is longer)
4. Known infiltrative or storage disorder causing cardiac hypertrophy that mimics oHCM, such as Fabry disease, amyloidosis, or Noonan syndrome with LV hypertrophy
5. Planned invasive procedure during the first 32 weeks of the study
6. Papillary muscle or mitral valve in need of repair or any other intracardiac procedure planned (however, if need for mitral valve repair is discovered during SRT procedure, the subject will continue to be followed on study)
7. For individuals on beta blockers, calcium channel blockers, or disopyramide, any dose adjustment of these medications < 14 days prior to screening or an anticipated change in regimen during the first 16 weeks of the study
8. Any medical condition that precludes upright exercise stress testing
9. Paroxysmal, intermittent atrial fibrillation with atrial fibrillation present at screening per the investigator's evaluation of the subject's electrocardiogram (ECG)
10. Persistent or permanent atrial fibrillation and subject not on anticoagulation for ≥ 4 weeks prior to screening and/or not adequately rate controlled ≤ 6 months prior to screening
11. Previously treated with invasive septal reduction (surgical myectomy or percutaneous ASA). However, if the subject has a history of a suboptimal or a failed alcohol septal ablation and there is no evidence on site read prescreening echocardiogram of an ASA, the subject may be included after consultation with the MyoKardia or CRO medical monitor.
12. Planned ICD placement or pulse generator change during the first 32 weeks of the study.
13. ECG abnormality considered by the investigator to pose a risk to subject safety (eg, second degree atrioventricular block type II)

14. 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
    a. Pulmonary disease that limits exercise capacity or systemic arterial oxygen saturation
    b. History of malignant disease within 10 years prior to screening:
        - Subjects who have been successfully treated for nonmetastatic cutaneous squamous cell or basal cell carcinoma or have been adequately treated for cervical carcinoma in situ or breast ductal carcinoma in situ may be included in the study
        - Subjects with other malignancies who are cancer-free for more than 10 years prior to screening may be included in the study
15. History or evidence of any other clinically significant disorder, condition, or disease that, in the opinion of the investigator, would pose a risk to subject safety or interfere with study evaluations, procedures, or completion
16. Safety laboratory parameters (chemistry, hematology, coagulation, and urinalysis) outside normal limits (according to the central laboratory reference range) at screening as assessed by the central laboratory; however, a subject with safety laboratory parameters outside the normal limits may be included if all the following criteria are met:
    a. Safety laboratory parameters outside normal limits are considered by the investigator to be clinically not significant
    b. If an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) result, the value must be $< 3 \times$ the upper limit of the laboratory reference range
    c. Body size–adjusted estimated glomerular filtration rate is ≥ 30 mL/min/1.73 m^2
17. Has known moderate or severe aortic valve stenosis or moderate to severe aortic stenosis determined at screening (as read by the echocardiography core laboratory)
18. Positive serologic test at screening for infection with human immunodeficiency virus (HIV); hepatitis C virus (HCV); or hepatitis B virus (HBV), with the exception of HBV s-antibody positive which is a marker of immunity
19. Known active infection with Covid-19 (PCR+) within 90 days of screening. If subject had a PCR+ test within 6 months of screening, they must have a negative Covid-19 test at screening.
20. Prior treatment with cardiotoxic agents, such as doxorubicin or similar
21. Unable to comply with the study requirements, including the number of required visits to the study site
22. First-degree relative of personnel directly affiliated with the study at the study site, any study vendor, or the study sponsor

4.3. Subject Restrictions During this Study

The following restrictions apply for the specified times during the study period. If a subject does not comply with these restrictions, they may be excluded from the study or withdrawn from the study medication.

- Starting at screening, subjects will be required to abstain from blood or plasma donation until 4 months after the final study visit
- Starting 72 hours prior to the first dose through Week 32, subjects should not engage in unaccustomed intensive exercise except during protocol-specified exercise tests,
- Subjects will be asked to abstain from biotin supplements from 14 days prior to screening through EOS visit.
- Starting on Day 1 until EOS, subjects will be asked to abstain from grapefruit or grapefruit juice, Seville oranges and quinine (eg, tonic water)

4.4. Screening and Enrollment

An informed consent form (ICF) must be signed and dated by a prospective subject before any study-specific procedures or assessments may be performed.

Each subject will be assigned a unique identification (ID) number when informed consent has been obtained. This ID number will be used to identify the subject throughout the study and should appear on all study-related documentation.

Subjects will undergo screening assessments as outlined in Table 1. The following screening assessments may be repeated, if done so within the 2-week screening window: blood tests, ECG, and TTE. Repeat assessments are allowed if central core laboratories require a repeat submission for quality and to better assess inclusion/exclusion values.

Subjects who fail to meet all enrollment criteria may be re-screened. The MyoKardia or CRO Medical Monitor should be contacted to discuss the specific situation and to gain approval for rescreening. Upon rescreening, the subject will be issued a new ID number, and all screening assessments must be repeated. Refer to the Study Reference Manual for rescreening criteria and procedures.

5. STUDY TREATMENT

5.1. Study Treatments Administered

The study treatments administered in this study are mavacamten and placebo-to-match mavacamten. Mavacamten is supplied as 2.5, 5, 10, and 15 mg capsules. Mavacamten capsules of all strengths are identical in appearance. Placebo-to-match mavacamten is supplied as a single capsule to match all mavacamten strengths and is identical in appearance to mavacamten capsules.

Subjects will receive mavacamten (2.5, 5, 10, or 15 mg capsule) or 1 placebo-to-match mavacamten capsule once daily for 16 weeks (Day 1 to Week 16) in a double-blind manner. Beginning Week 16, all subjects (ie, mavacamten group and placebo-to-active group) will

receive mavacamten once daily through Week 128 (EOT). During the study, there is an opportunity for mavacamten dose titration as described in Section 5.6.

Table 6 provides an overview of the study treatments.

Table 6: MYK-461-017: Study Treatments

	Treatment Group	
	Mavacamten	**Placebo**
Name of Study Treatment	Mavacamten	Placebo
Type	Study drug	Placebo
Dose Formulation	Capsules	Capsules
Unit Dose Strength	2.5, 5, 10, and 15 mg	Placebo capsule matching all mavacamten strengths
Dosage Level	2.5, 5, 10, or 15 mg once daily	Placebo once daily
Route of Administration	Oral	
IMP and NIMP	Mavacamten	Placebo
Sourcing	Sponsor	
Packaging and Labeling	See Section 5.2.1	
Current/Former Name	Mavacamten	Not applicable

IMP = investigational medicinal product; NIMP = noninvestigational medicinal product

5.2. Study Drug Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions were maintained during transit for all study drug received and that any discrepancies are reported and resolved before use of the study drug.

Only subjects randomized into the study may receive study drug, and only authorized study staff may supply or administer study drug. All study drug must be stored in a secure and monitored area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator/designee is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). Further guidance and information for the final disposition of unused study drug are provided in the Pharmacy Manual.

5.2.1. Formulation, Packaging, and Labeling of Study Drug

Mavacamten capsules are provided as size 2, blue opaque capsules printed with a yellow band on the body and a black band on the cap. Each capsule contains white to off-white powder.

Mavacamten capsules are supplied in 2.5, 5, 10, and 15 mg strengths. Mavacamten capsules of all strengths are identical in appearance. Matching placebo capsules are identical in appearance to mavacamten capsules.

Mavacamten and matching placebo capsules are manufactured according to current Good Manufacturing Practice (cGMP) regulations. They are supplied in high-density polyethylene bottles with induction seals and child-resistant caps with 30 capsules in each bottle. All bottles are labeled according to applicable local regulatory guidelines.

Mavacamten and placebo capsules must be stored at 36°F to 77°F (2°C to 25°C) in the packaging supplied by MyoKardia.

5.2.2. Direct-to-Subject Study Drug Shipment (At Selected Sites)

In certain circumstances, it may be necessary to ship study drug directly to a subject. When study drug is shipped directly to the subject, a qualified individual who is contracted by the sponsor will open the package of study drug, review TempTale® (Sensitech, Inc., Beverly, MA, USA) monitoring data, and confirm receipt. Study sites should contact subjects by telephone to confirm study drug delivery. Refer to the Pharmacy Manual for details.

5.3. Randomization and Blinding

5.3.1. Randomization

Eligible subjects will be randomized via an IXRS in a 1:1 ratio to receive double-blind treatment with mavacamten or matching placebo. Randomization will be stratified by the type of SRT recommended (myectomy or ASA) and NYHA functional class.

5.3.2. Study Treatment Blinding

During the placebo-controlled treatment period (Day 1 to Week 16), study drug and dose will be blinded; and during the active-controlled treatment period (Week 16 to Week 32) and the LTE treatment period (Week 32 to 128) mavacamten dose will be blinded.

Sites and investigators will not be actively adjusting doses. All dose adjustments will occur in a double-blind manner via IXRS, and all subjects, whether receiving mavacamten or matching placebo, will undergo assessments that could lead to a dose adjustment. Throughout the study, all study drug (mavacamten 2.5, 5, 10, or 15 mg and placebo-to-match mavacamten) will be dosed as a single capsule once daily.

All subjects will receive blinded mavacamten or matching placebo from Day 1 to Week 16. Study drug will be dispensed in a double-blind manner via the IXRS such that the investigator, site staff, the pharmacist, and the subject will not know which study drug is being administered. The sponsor, central and core laboratories, and clinical site monitors will also be blinded to assigned treatment. In addition, 1 or more sham temporary dose discontinuations for subjects in the placebo group may be performed by the IXRS to maintain the study blind during placebo-controlled dosing (Day 1 to Week 16).

Echocardiography results will be transferred to the IXRS by the core echocardiography laboratory to allow for dose adjustments and dose discontinuations to be managed in a blinded manner. If a study team member uploads the echocardiography image to the core laboratory, he or she must not have access to the echocardiography results or interpretation. Study center personnel who are not associated with the study who review echocardiograms for safety will have knowledge of the echocardiography results (see Study Reference Manual). However, they

will not share results with the study staff unless there is a safety finding of LVEF ≤ 30%. After Week 32, echocardiograms will be site read (Section 7.2.1) and PI and study staff will have knowledge of LVEF and LVOT gradients.

The pharmacovigilance team will be unblinded to study treatment for reporting of suspected unexpected serious adverse reactions (SUSARs). The IDMC will also review unblinded safety data.

5.3.3. Methods for Unblinding Study Treatment

All efforts should be made to keep subjects blinded to treatment assignment. However, subjects may be unblinded to treatment assignment upon request from the investigator and agreement by the sponsor if knowledge of treatment assignment will impact future treatments or clinical care of the subject. Unblinding by the investigator independent of the study sponsor also may occur if an AE or toxicity necessitates identification of the study treatment for the welfare of the subject. Refer to the [redacted] Interactive Web Response System Manual for the unblinding process and contact information. In the case of emergency unblinding by the principal investigator, the MyoKardia or CRO medical monitor should be notified at the time of the unblinding.

The sponsor may choose to unblind mavacamten dose after at least 100 subjects have completed the Week 16 study visit or terminated early from the study drug. The sponsor may also unblind if IDMC recommends early stopping after interim analysis.

Inadvertent Study team or patient knowledge of the echocardiography results does not constitute true treatment unblinding.

5.4. Study Drug Administration and Schedule

Study drug will be supplied to subjects via the IXRS in 30-count high-density polyethylene bottles that are appropriately labeled. Subjects will be instructed to store study drug in a cool, dry place.

Subjects will take study drug as directed by the investigator/designee. Subjects should be instructed to take the study drug at approximately the same time every day. Study drug should be taken with approximately 8 ounces of water. Subjects should never take > 1 dose of study drug within an 8-hour period. On study visit days, study drug dosing should be delayed until after study assessments are complete and the study staff instruct the subject to take their daily dose.

5.4.1. Treatment Compliance

Subject compliance with study drug dosing will be monitored by capsule count at all study visits from Week 4 through the EOS treatment. Refer to the Pharmacy Manual for details.

5.5. Prior and Concomitant Medications

Any medication or vaccine, including over-the-counter or prescription medicines, vitamins, and/or herbal supplements a subject is taking will be monitored at all study visits from screening until the end of the study and documented on the appropriate electronic case report form (eCRF), including start/stop dates, dose, route of administration, and indication.

5.5.1. Prior Medication

At the time of providing signed informed consent, subjects will be asked about medication use during the previous 30 days, including prescription and nonprescription medications, herbal medications, vitamins, and minerals. These will be reported as prior medications in electronic data capture (EDC). Any prohibited medication and restricted food items must be discontinued for ≥ 14 days before screening may proceed. Any medication stopped on or after signing of the ICF and prior to Day 1 will also be reported as prior medications.

5.5.2. Concomitant medication

Any medications taken at Day 1 or started after Day1 will be reported as concomitant medications.

5.5.3. Background HCM Medication

Background HCM medications (eg, beta blocker, verapamil, diltiazem, or disopyramide) are allowed during the study. Subjects should be on optimal tolerated HCM medication as determined by the investigator and informed by HCM treatment guidelines (Gersh et al. 2011). The treatment should be well tolerated for at least 2 weeks prior to screening and should be maintained through Week 32. Investigators are encouraged not to change background HCM medications from Day 1 to Week 32; however, investigators should manage subjects appropriately using their clinical judgment. After Week 32, investigators should manage background HCM medications as clinically appropriate. Background cardiomyopathy therapy (eg, beta blocker, verapamil, diltiazem, or disopyramide) may be adjusted or stopped after Week 32 as determined by the investigator in conjunction with the MyoKardia Medical Monitor. Any change in HCM medications must be entered into the eCRF with the rationale for the change.

5.5.4. Prohibited Medication

Medications that are prohibited during the study are outlined in Appendix 2. Prior or concomitant treatment with cardiotoxic agents, such as doxorubicin or similar, is prohibited. Drugs metabolized by CYP2C19 pathway (moderate and potent inhibitors) and by the CYP3A4 pathway (potent inhibitors) are prohibited. Use of St. John's Wort is prohibited from 14 days prior to screening through the end of the study. Biotin supplements are prohibited from 14 days prior to screening through the end of the study. Multivitamins which contain biotin should be taken >24 hours prior to clinical visits.

The MyoKardia or CRO medical monitor should be contacted for any questions regarding prior or concomitant medications.

5.6. Dose Titration

During the study, dose may be titrated based on LVEF and LVOT by TTE and according to dose titration guidelines. Dose adjustments will occur in a blinded manner via the IXRS.

During the placebo-controlled dosing period (Day 1 to Week 16), subjects will be evaluated for possible down-titration at Week 4 and up-titration at Weeks 8 and 12. Although subjects in the placebo group will be evaluated for dose titration, they will remain on placebo (refer to Section 5.1).

During the active-controlled dosing period (Weeks 16 to 32.), subjects in the placebo-to-active group, who begin dosing with mavacamten at Week 16, will be evaluated for possible down-titration at Week 20 and up-titration at Weeks 24 and 28.

During the LTE dosing period (Weeks 44 to 116), mavacamten dose may be up- titrated at any scheduled visit after Week 32 if the LVEF is ≥ 50% and the site-read LVOT gradient with Valsalva maneuver is ≥ 30 mmHg **or** the post-exercise LVOT is ≥50 mmHg Principal Investigators have the discretion to do a post-exercise ECHO at scheduled visits which are not SRT visits. All dose increases during LTE dosing must be approved by the MyoKardia or CRO medical monitor before they are implemented. Subjects who have their mavacamten dose increased during the LTE period will attend an unscheduled study visit 4 weeks after the dose increase and then resume the regular study visit schedule.

Dose may be down-titrated for safety at any time in consultation with the medical monitor.

Table 7 and Table 8 provides guidelines for dose titration. Procedures for temporary and permanent discontinuation of study drug based on dose-titration guidelines are outlined in Section 6.1.1.and Section 6.1.2.1.

Table 7: MYK-461-017: Dose Titration Guidelines (Screening to Week 32)

	LVEF ≥ 50%					
	Mavacamten Group Placebo-Controlled Dosing Period (Day 1 to Week 16)			**Placebo-to-Active Group Active-Controlled Dosing Period (Week 16 to Week 32)**		
	Study Week			**Study Week**		
	4	**8**	**12**	**20**	**24**	**28**
Valsalva LVOT ≥ 30 mmHg	Remain on 5 mg	Increase dose 2.5mg to 5mg 5 mg to 10 mg	Increase dose 2.5 mg to 5 mg 5 mg to 10 mg 10 mg to 15 mg[a]	Remain on 5 mg	Increase dose 2.5mg to 5mg 5 mg to 10 mg	Increase dose 2.5 mg to 5 mg 5 mg to 10 mg 10 mg to 15 mg[a]
Valsalva LVOT < 30 mmHg	Decrease dose 5 mg to 2.5 mg	Dose remains unchanged	Dose remains unchanged	Decrease dose 5 mg to 2.5 mg	Dose remains unchanged	Dose remains unchanged
LVOT not applicable	**LVEF < 50%**					
	If at any time LVEF < 50%, discontinue mavacamten 2 to 4 weeks until follow-up visit If at follow-up[b] LVEF ≥ 50%, resume at 1 step decreased dose: 15 mg to 10 mg 10 mg to 5 mg 5 mg to 2.5 mg 2.5 mg to a retrial of 2.5mg. If LVEF again falls to < 50%, mavacamten will be permanently discontinued. Placebo to placebo					
	LVEF ≤ 30%					
	If at any time LVEF ≤ 30%, permanently discontinue mavacamten					

LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract.
[a] 15 mg once daily is the maximum allowable dose of mavacamten.
[b] Follow-up visit will be an unscheduled visit.

Table 8: MYK-461-017: Dose Titration Guidelines (Week 44 to Week 116)

	LVEF ≥ 50%						
	Mavacamten Group Placebo-Controlled Dosing Period (Week 44 to Week 116)						
	Study Week[a]						
	44	**56**	**68**	**80**	**92**	**104**	**116**
Valsalva LVOT ≥ 30 mmHg or post-exercise LVOT ≥ 30 mmHg	Increase dose 2.5 mg to 5 mg 5 mg to 10 mg 10 mg to 15 mg[b]						
LVOT not applicable	**LVEF < 50%**						
	If at any time LVEF < 50%, discontinue mavacamten 2 to 4 weeks until follow-up visit If at follow-up[c] LVEF ≥ 50%, resume at 1 step decreased dose: 15 mg to 10 mg 10 mg to 5 mg 5 mg to 2.5 mg 2.5 mg to a retrial of 2.5mg. If LVEF again falls to < 50%, mavacamten will be permanently discontinued. Placebo to placebo						
	LVEF ≤ 30%						
	If at any time LVEF ≤ 30%, permanently discontinue mavacamten						

LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract.

[a] Dose titration can occur at any scheduled **and unscheduled visit** during the LTE except W128. Dose up-titration must be at least 12 weeks from last dose up-titration

[b] 15 mg once daily is the maximum allowable dose of mavacamten.

[c] Follow-up visit will be an unscheduled visit.

5.7. Hepatotoxicity Stopping and Rechallenge Rules

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

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

Mavacamten should be discontinued permanently and the subject 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 INR > 1.5

AND increased AST or ALT, if the baseline value was < ULN and AST or ALT elevation is > 3 × ULN

AND no other cause for the combination of laboratory abnormalities is immediately apparent. Important potential causes for abnormal AST/ALT or TBL values include, but are not limited to, the following:

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

If an alternative cause for hepatotoxicity is identified, or less stringent conditions develop 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 the subject population and/or the severity of the hepatotoxicity or event, as deemed appropriate for the safety of the subject.

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

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

- AST or ALT > 8 × ULN at any time
- AST or ALT > 5 × ULN and < 8 × ULN for ≥ 2 weeks
- AST or ALT > 5 × ULN and < 8 × ULN and unable to adhere to enhanced monitoring schedule
- ALT or AST > 3 × ULN and (TBL > 2 × ULN or INR > 1.5)
- ALT or AST > 3 × ULN and 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%).
- TBL > 3 × ULN at any time
- ALP > 8 × ULN at any time

Mavacamten should be withheld pending an investigation into alternative causes of DILI. If mavacamten is withheld, the subject should be followed according to recommendations for possible DILI (Appendix 3). 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 5.7.3).

5.7.3. Criteria for Rechallenge of Mavacamten After Potential Hepatotoxicity

The decision to rechallenge a subject should be discussed and unanimously agreed upon by the investigator, the IDMC, and the sponsor.

If signs or symptoms recur with rechallenge, then mavacamten will be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.1.2.1) should never be rechallenged.

5.8. Management of Exaggerated Pharmacologic Effect (Systolic Dysfunction)

If during the treatment period a subject has a resting LVEF ≤ 30%, it will be communicated to the investigator and sponsor that a study drug stopping criterion has been met. Upon receipt of this information, the study site/investigator will contact the subject by telephone and instruct the subject to discontinue study drug. Appropriate care of systolic dysfunction will be determined by the treating medical personnel. Subjects who prematurely discontinue study drug will undergo EOT assessments as outlined in Table 2 within 14 days of study drug discontinuation and will be followed regularly until clinically stable and LVEF returns close to subject's baseline on study entry.

5.9. 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 subject. An overdose may be symptomatic or asymptomatic. Only symptomatic overdoses should be reported as AEs.

In the event of symptomatic overdose or in the presence of significant symptoms and/or clinical compromise, the investigator should contact the MyoKardia or CRO medical monitor, and no further study drug should be administered until further notice (see guidelines for temporary study drug discontinuation in Section 6.1.1). The subject should be closely monitored clinically for AEs/SAEs, with supportive measures undertaken as clinically indicated. If necessary, corrective measures, as described in the 2013 American College of Cardiology Foundation/American Heart Association Guideline for the Management of Heart Failure (Yancy et al. 2013) and in the 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (Ponikowski et al. 2016), should be implemented. Reintroduction of study drug must be approved by the MyoKardia or CRO medical monitor.

5.9.1. Reporting and Follow-Up of Overdose

Symptomatic overdose is an adverse event of special interest (AESI) as defined in Section 8.1.4. If a subject should experience symptomatic overdose, the investigator will report the symptomatic overdose to the medical monitor and complete the required information in the EDC system within 24 hours of study staff becoming aware of the overdose. Follow-up on the subject's condition will be conducted by the investigator and study staff.

6. TREATMENT DISCONTINUATION AND SUBJECT WITHDRAWAL

6.1. Treatment Discontinuation

6.1.1. Temporary Treatment Discontinuation

Temporary treatment discontinuation

- Will be implemented when a predefined safety threshold has been met
- 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 (Section 6.1.2.1).

If during evaluation for dose titration LVEF > 30% but < 50% (ie, 31-49%) is measured at the core echocardiography laboratory-the investigator will be promptly notified, and study drug will be discontinued for 2 to 4 weeks until a follow-up visit is conducted. If at follow-up LVEF ≥ 50% is measured, study drug may be resumed at a dose that is 1 step decreased from the dose being taken when study drug was discontinued as follows (and outlined in Table 7):

- If dose at discontinuation was 15 mg, resume at 10 mg
- If dose at discontinuation was 10 mg, resume at 5 mg
- If dose at discontinuation was 5 mg, resume at 2.5 mg

- If dose at discontinuation was 2.5 mg, 1 retrial of 2.5 mg is allowed. If LVEF again falls to ≤ 50%, mavacamten will be permanently discontinued (see Section 6.1.2).
- If dose at discontinuation was placebo, resume placebo.

During the LTE (W44-128) if site read LVEF is <50% immediately notify the sponsor or CRO Medical Monitor. The site read values should be recorded in EDC the day the echocardiogram is performed. The patient should be instructed to hold study drug and return for an unscheduled visit in 2 to 4 weeks. If at follow-up LVEF ≥ 50% is measured, study drug may be resumed at a dose that is 1 step decreased from the dose being taken when study drug was discontinued (as outlined in Table 7).

In the case of temporary study drug 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 discontinuations should be recorded in the eCRF.

6.1.2. 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 the treatment discontinuation permanent. The investigator should make every effort to contact the medical monitoring team before considering any treatment discontinuation permanent. Every effort should be made to collect important safety data if feasible and the study subject agrees.

There may be situations in which it is necessary for a subject to permanently discontinue study drug. In all cases, subjects should be encouraged to discuss stopping study drug with the investigator/designee so that questions can be addressed, and concomitant therapy can be adjusted if needed. Investigators should contact the medical monitor prior to permanent study drug discontinuation to discuss the situation. If study drug is permanently discontinued prior to Week 128, the subject will undergo EOT assessments as outlined in Table 2 within 14 days of study drug discontinuation and remain on study to be evaluated for concomitant medications and clinical assessments every 24 weeks through Week 128, as outlined in Table 4. If the subject is unwilling or unable to be followed for the duration of the study, they will undergo EOT assessments within 14 days of study drug discontinuation and EOS assessments 8 weeks later as outlined in Table 2.

Subjects who discontinue study drug to undergo SRT will undergo EOT assessments as outlined in Table 2 within 14 days and will have a telephone follow-up with the study site to assess AEs 8 weeks after treatment discontinuation (or prior to SRT, whichever is earlier). Subjects will be followed every 24 weeks from the date of SRT to Week 128 as outlined in Table 3.

All permanent treatment discontinuations should be recorded in the eCRF.

6.1.2.1. Criteria for Permanent Treatment Discontinuation

Study drug will be permanently discontinued in the event of any of the following:

- Pregnancy
- LVEF < 50% following a retrial of 2.5 mg after a temporary discontinuation for LVEF< 50%
- LVEF ≤ 30%. Subjects should return to the clinic within 14 days of stopping study drug and be followed regularly until clinically stable and LVEF returns close to subject's baseline on study entry.
- 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 subject's safety or well being
- All the criteria are met for possible DILI (Section 5.7.1)
- Subject requests to discontinue study drug
- Sponsor requests that the subject permanently discontinue study drug

6.2. Withdrawal from Study

6.2.1. Withdrawal of Consent for Ongoing Study Participation

Subjects may withdraw from the study 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 and from withdrawal of consent for non-subject contact follow-up (eg, medical records check).

Subject withdrawal from the study prior to completion is expected to be uncommon, occurring only if the subject explicitly withdraws consent for participation. The subject may withdraw consent verbally or in writing (preferably in writing). If consent is withdrawn verbally, the study site should document it appropriately, and if the subject or the subject's representative refuses or is physically unavailable, the site should document and sign the reason for the subject's failure to withdraw consent in writing. At the time of discontinuing from the study, the subject should discontinue study drug, the medical monitor should be contacted, and EOT assessments should be conducted as outlined in Table 2.

Subjects who withdraw from the study should be explicitly asked about the reason and the contribution of any possible AE that led to their decision, and any AE information provided should be documented.

All study withdrawals should be recorded by the investigator in the appropriate eCRF and in the subject's medical records. The date of the withdrawal and the reason for the withdrawal should be documented. Subjects who withdraw from the study may not be rerandomized into the study, and their subject ID numbers may not be reused.

6.2.2. Lost to Follow-Up

A subject will be considered potentially lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site. Site personnel are expected to make ongoing, diligent attempts to contact subjects who fail to return for a scheduled visit or are otherwise unable to be followed-up by the site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject by phone; e-mail; text message; and if necessary, by letter and/or certified mail; to reschedule the visit. All efforts to contact the subject should be documented in the subject's medical source record. In any circumstance, every effort should be made to document subject outcome, if possible.

The statistical analysis plan (SAP) will specify how subjects who are lost to follow-up will be considered for analyses.

7. STUDY PROCEDURES

The schedule of study procedures is summarized in Table 1 and Table 2 and described in the following sections. The investigator is responsible for ensuring that all staff involved in the study are familiar and comply with the content of this section.

All study visits and assessments from Screening through Week 32 must be done at the site. Under certain circumstances (such as a Pandemic) the site may choose to contract with a community-based facility (with sponsor's approval, by the CRO, or by the sponsor) for study visits at Weeks 4, 8, and 12. Refer to the Study Reference Manual for details. Study Visits during the LTE (Week 32 through EOS) should take place at the study site.

On study visit days, study drug dosing should be delayed until after study assessments are complete and the study staff instructs the subject to take their daily dose. Blood samples will be collected for mavacamten plasma concentration assessments at all post Day- 1 visits (Table 1 and Table 2) prior to dosing. For assessments that require subjects to be in a semirecumbent or supine position, assessments should be conducted with subjects in that same position at all time points.

At the investigator's discretion, unscheduled visits may be conducted for assessment of AEs, new or worsening symptoms, physical examinations, vital signs, laboratory tests, ECGs, and TTEs. ECGs and TTEs conducted at unscheduled visits will be sent to the respective core laboratory for central reading. From Day1 through Week 32, investigator and study staff will remain blinded to results of TTE at unscheduled visits unless there are safety findings as specified in Section 5.3.2. All information collected from unscheduled visits will be recorded on the eCRF and included in the clinical database.

7.1. Evaluation for Septal Reduction Therapy Eligibility

All randomized subjects will meet the 2011 ACCF for SRT:

- Clinical criteria: Despite maximally tolerated drug therapy severe dyspnea or chest pain (NYHA Class III or IV) or for the purposes of the Valor Study, subjects who are NYHA Class II with exertion-induced syncope or near syncope.

- Hemodynamic criteria: Dynamic LVOT gradient at rest or with provocation (ie, Valsalva or exercise) ≥ 50 mmHg associated with septal hypertrophy
- Anatomic criteria: Targeted anterior septal thickness sufficient to perform the procedure safely and effectively in the judgment of the individual operator

Subjects referred or considered for ASA must have an adequate first septal perforating branch of LAD coronary artery amenable to the interventionalist to perform the procedure.

At screening, the investigator will confirm the subject's NYHA and eligibility for SRT based on the 2011 ACCF/AHA. Every effort should be made to have the **same** investigator who evaluates NYHA at screening also evaluate NYHA at Weeks 16, 32, 56, 104, and 128.

At Weeks 16, 32, 56, 104, and 128, subjects will be reevaluated for SRT eligibility. The investigator will confirm that the subject remains on maximal medical therapy, determine NYHA class, and enter the information in the eCRF. Independently, and blinded to the investigator, a TTE will be performed to assess LVOT gradients at rest, Valsalva provocation, and post-exercise. At Weeks 16 and 32, the TTE will be read at the core echocardiography laboratory, and the maximum LVOT result (< 50 mmHg or ≥ 50 mmHg) will be reported to the study site by the core laboratory via email notification from EDC. The investigator will remain blinded to the LVOT gradient result until after NYHA results have been entered in the eCRF. At Weeks 56, 104, and 128, LVOT < 50 mmHg or ≥ 50 mmHg will be determined by site-read echocardiography, but not reported to the principal investigator until after the principal investigator has determined subject's NYHA class.

The derivation for the primary endpoint in the primary analysis will use the 2011 ACCF/AHA guideline eligibility criteria and subject's decision to withdraw to proceed to SRT. This is further described in Section 9.3.5.1.

Results of medical therapy, NYHA functional class, and LVOT will be reviewed by the investigator, who will determine SRT eligibility (yes or no) based on clinical judgment. The investigator recommendation recorded in the CRF will be used as an exploratory analysis.

The investigator will enter the SRT recommendation in the eCRF and will discuss the recommendation with the subject. Subjects will be required to decide within 48 hours whether to accept the recommendation for SRT or continue on study treatment. The subject's decision will be entered in the eCRF. If the decision is to proceed with SRT, the subject may schedule the SRT procedure at a recognized HCM center to occur after a recommended study drug washout period ≥ 6 weeks. Subjects who discontinue study drug to undergo SRT will undergo EOT assessments as outlined in Table 2 within 14 days and will have a telephone follow-up with the study site to assess AEs 8 weeks after treatment discontinuation (or prior to SRT, whichever is earlier). Subjects will be followed at the site every 24 weeks from the date of SRT to Week 128 as outlined in Table 3.

If at Weeks 16 and 32, LVOT gradient is < 50% and NYHA functional class remains Class III or IV, it is recommended that investigator evaluate the subject for a cause other than oHCM for the subject's symptoms.

7.2. Efficacy and Pharmacodynamics Assessments

7.2.1. Echocardiography

All echocardiography data will be sent to the core echocardiography laboratory throughout the study; echocardiography results will be transmitted to the IXRS to maintain dose blinding. Through the Week 32 visit, TTEs may be performed prior to a scheduled study visit so that the core laboratory data will be available in the IXRS at the time of the study visit. There will be a firewall between the sonographer and the investigator and study staff; the sonographer will not communicate directly with the investigator or study staff unless the LVEF is ≤ 30%. Through Week 32, if LVEF ≤ 30% is measured, the sonographer should review and re-measure the findings with at least one other non-study professional qualified in echocardiography assessment who is not the investigator (eg, echocardiography laboratory director, another experienced sonographer, or non-study cardiologist). If LVEF is ≤ 30%, the sonographer will communicate the result directly to the investigator. The investigator will instruct the subject to discontinue the study drug. Site will report AESI within 24 hours.

After Week 32 through the end of the study, TTEs will be read locally, and each individual site will determine if the subject needs a dose titration in consultation with the medical monitor. If dose titration is required, approval from the medical monitor must be obtained. In addition, the site will answer the dose titration questions in IXRS. Site read TTEs will be uploaded to the core echocardiography laboratory for a complete read of hemodynamic parameters. After Week 32, when echocardiography is site read, if LVEF ≤ 30% is measured at the site the sonographer should review and re-measure the findings with at least one other professional qualified in echocardiography assessment (eg, the investigator, echocardiography laboratory director, another experienced sonographer, or cardiologist). If LVEF is ≤ 30%, the sonographer will communicate the result directly to the investigator. The investigator will instruct the subject to discontinue the study drug. Site will enter LVEF and LVOT value into [redacted] EDC on the day the echocardiogram was performed in order to determine proper dose dispensation. Site must enter LVEF and LVOT values within [redacted] EDC *prior* to registering and requesting drug dispensation via IXRS. Site will report AESI within 24 hours.

7.2.1.1. Resting Transthoracic Echocardiography

TTE will be performed at every study visit as outlined in Table 1 and Table 2. Through Week 32, the core echocardiography laboratory will determine instantaneous peak LVOT gradient at rest and provoked peak LVOT gradient (Valsalva maneuver). LVEF fraction (2--dimensional) and LVEF shortening will be evaluated, along with a variety of other echocardiographic measures, including measures of diastolic function.

7.2.1.2. Postexercise Stress Echocardiography

Subjects will undergo standard postexercise stress TTEs as outlined in Table 1 and Table 2. Subjects should abstain from food for ≥ 4 hours prior to postexercise stress TTEs.

The echocardiography laboratory will determine instantaneous peak LVOT immediately postexercise. Any concomitant medication or standard therapies for the treatment of HCM should be taken as prescribed on the day of the exercise test. The postexercise stress TTE should

be performed after the resting and Valsalva TTE. Refer to the Study Reference Manual/Manual of Operations for details.

7.2.2. New York Heart Association Functional Class

The NYHA functional classification of heart failure assigns subjects to 1 of 4 categories based on the subject's symptoms as outlined in Table 9. Every effort should be made to have the **same** investigator who evaluates NYHA at screening, Week 16, and Week 32 also evaluate NYHA functional class during LTE: Weeks 56, 104, and 128 (EOT).

Table 9: New York Heart Association Functional Classification of Heart Failure

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

Source: American Heart Association's Classes of Heart Failure https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure.

7.3. Pharmacokinetic, Pharmacogenetic, and Biomarker Assessments

7.3.1. Pharmacokinetics Assessments

Blood samples will be collected for mavacamten plasma concentration assessments at all study visits beginning at Week 4 as outlined in Table 1 and Table 2. Unscheduled or additional PK samples may be collected if appropriate in the opinion of the investigator and/or sponsor.

7.3.2. Exploratory Biomarker Assessments

Subjects will have blood samples drawn for potential exploratory biomarker analysis (eg, proteomic analysis related to disease activity, metabolic pathways, efficacy measures, or safety measures) as outlined in Table 1 and Table 2.

7.3.3. HCM Genotyping

For subjects who provide separate, specific consent, a blood sample will be collected at Week 4 or any visit thereafter for assessment of HCM genotype and potentially additional DNA sequencing. If a subject with a prior clinical genotype test that was positive for genetic mutation associated with HCM consents to provide the results, no additional genotype assessment will be performed.

7.3.4. Pharmacogenetic Assessments

For subjects who provide separate, specific consent, a blood sample will be collected at Week 4 or any visit thereafter for pharmacogenetic samples that will be stored for potential future analysis of genetic biomarkers of efficacy, safety, pharmacodynamics (PD), or PK parameters as

determined by future studies using clinically meaningful endpoints, through DNA sequencing or other genetic testing.

7.3.5. Cardiac Biomarkers

Blood samples will be collected to evaluate cardiac biomarker concentrations as outlined in Table 1 and Table 2. For efficacy, dedicated serum tubes will be collected and concentrations of NT-proBNP and cardiac troponin will be evaluated in a blinded manner. All blood draws for cardiac biomarkers must be drawn at rest and prior to exercise. Serum concentrations of NT-proBNP and cardiac troponin obtained through Safety Laboratory Assessments will be included in the data package provided for the periodic IDMC meetings.

Unscheduled or additional blood samples may be collected if appropriate in the opinion of the investigator (eg, for medical management of heart failure) and/or sponsor. Whenever possible, discussion with the medical monitor is encouraged.

7.3.6. Wrist-Worn Accelerometer

A battery-operated wrist-worn accelerometer will be provided to subjects at screening, Week 12, and Week 28 to record step counts as outlined in Table 1. Accelerometer data will be retrieved at the Day 1, Week 16, and Week 32 visits, respectively. Refer to the study-specific manual for instructions on using the accelerometer.

7.4. Patient-Reported Outcomes

At on-treatment study visits, PRO assessments should be completed prior to any other study procedure and any meaningful discussion about the study or study treatment with investigative site staff.

7.4.1. Kansas City Cardiomyopathy Questionnaire

The KCCQ-23 is a 23-item, self-administered questionnaire that measures the impact of a subject's cardiovascular disease or its treatment on 6 distinct domains using a 2-week recall period: symptoms/signs, physical limitation, QoL, social limitations, self-efficacy, and symptom stability (Green et al. 2000). In addition to the individual domains, summary scores can be calculated from the KCCQ-23: the overall summary score (OSS) which includes the total symptom, physical limitation, social limitation, and QoL scores and the clinical summary score (CSS) which combines the total symptom and physical limitation scores. Scores range from 0 to 100, with higher scores reflecting better health status. The KCCQ-23 will be completed by subjects at study visits as outlined in Table 1 and Table 2. The KCCQ-23, CSS will be evaluated as a secondary endpoint. The KCCQ-23: OSS, TSS and individual domains will be evaluated as exploratory endpoints.

7.4.2. EuroQol 5-Dimensions 5-Level Questionnaire

The EQ-5D-5L questionnaire is a generic PRO instrument that measures health status and health-related QoL. There are 2 components to the EQ-5D-5L: (1) a health utility index score derived from 5 items addressing mobility, self-care, usual activities, pain/discomfort, and anxiety/depression "today") and (2) a current ("right now") general health status score derived from a single visual analog scale (VAS) ranging from 0 to 100. The items contributing to the

EQ-5D-5L health utility index score each have the same 5-point response scale (1 = no problem, 2 = slight problems, 3 = moderate problems, 4 = severe problems, 5 = very severe problems). The VAS is anchored with "best imaginable health state" and "worst imaginable health state." The EQ-5D-5L is critical for acceptance by many health technology assessment bodies for coverage decisions. The EQ-5D-5L will be completed by subjects at study visits as outlined in in Table 1 and Table 2.

7.5. Safety Assessments

Safety will be assessed throughout the study as outlined in Table 1 and Table 2. Safety assessments include medical history, physical examinations, ECGs, TTEs, Holter monitor, vital signs, observed and subject reported- AEs, pregnancy testing, and safety laboratory results.

7.5.1. History

A complete medical and surgical history will be conducted at screening, including evaluation of the following (past or present): 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). An HCM--specific medical and surgical history will also be obtained. All cardiovascular drugs currently used by the subject should be included on the HCM-specific medical history form (eg. beta blockers or calcium channel blockers taken for hypertension).

7.5.2. Physical Examination

At screening, a complete physical examination will be conducted, including a neurological examination (gross motor and deep tendon reflexes), height and body 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. Subjects will be required to remove their shoes and wear clothing as specified by the clinical site.

Body weight will be measured at screening and Weeks 4, 8, 12, 16, 20, 24, 28, 32, 44, 56, 68, 80, 92, 104, 116, and 128 (EOT)) as body weight is required on days TTE is performed.

7.5.3. Electrocardiograms

Single 12-lead ECGs will be performed prior to dosing and after 10 minutes of rest at screening, all study visits from Week 4 to Week 56, and Weeks 80, 104, and 128 as outlined in Table 1 and Table 2 using an ECG machine that automatically calculates the heart rate (HR) and measures PR, QRS, QT, and QT interval with Fridericia correction (QTcF) intervals.

All ECG data will be sent to a central ECG laboratory.

The investigator will interpret the ECG results as normal, abnormal without clinical significance, or abnormal with clinical significance. The investigator will correlate any abnormal findings with the subject's clinical, laboratory, and medical history data to determine the clinical importance of the finding.

7.5.4. Holter Monitor

A battery operated Holter monitor will be applied at screening, Week 12, Week 28, Week 56 and Week 104 to record cardiac activity during 48 hours as outlined in Table 1. Holter data will be retrieved at the Day 1, Week 16, and Week 32 visits, respectively. For Weeks 56 and 104, the holter monitor will be applied on the patient at the visit, worn for 48 hours and the patient will return the holter to the site for data collection. Refer to the study-specific manual for instructions on applying and retrieving Holter monitors. If a subject has an adverse reaction to the adhesive used for the Holter monitor, the requirement for monitoring may be waived.

7.5.5. Vital Signs

Vital signs, including temperature, HR, respiratory rate (RR), and blood pressure (BP), will be obtained at screening, Day 1, Week 16, and Week 32. At all other visits, vital signs will include only HR, RR, and BP. Vital signs should be taken with the subject in the same position at all visits. BP should be taken via an automated recorder after the subject rests for at least 5 minutes.

7.5.6. Clinical Laboratory Evaluations

Appendix 1 outlines the hematology, coagulation, chemistry, and urinalysis parameters to be assessed according to the schedule in in Table 1 and Table 2.

7.5.7. Pregnancy Testing

Serum pregnancy testing will be performed centrally at screening for all female subjects of childbearing potential. In addition, urine pregnancy testing either in clinic will be conducted on Day 1, and every 4 weeks through Week 32 and then every 12 weeks until the end of the study. Confirmatory serum testing will be performed locally if any urine test is positive.

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

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

Hospitalization or procedural intervention for endpoint events (myectomy, septal ablation) will not be captured as SAEs, but will be recorded on specialized eCRFs that will be part of the documentation provided to the IDMC for their periodic review.

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

8.1.1. Pretreatment Adverse Events

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

8.1.2. Adverse Events

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

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

- Preplanned medical or surgeries or procedures
  - Preplanned surgeries or procedures that were scheduled prior to signing of informed consent are not considered PTAEs or AEs. However, if a planned

procedure is performed early (eg, as an emergency) due to worsening of a preexisting condition, the worsening of the condition should be captured appropriately as a PTAE or AE.

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

The following should not be recorded as PTAEs or AEs:

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

8.1.3. Serious Adverse Event

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

- Results in death
- Is immediately life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital abnormality or birth defect

- Is an important medical event that may not result in death, be life-threatening, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it may require medical or surgical intervention to prevent any of the outcomes listed above

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

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

SAEs are required to be reported by the investigator to the sponsor within 24 hours after learning of the event.

8.1.4. Adverse Events of Special Interest

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

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

8.2. Collection and Reporting of Adverse Events

8.2.1. Pretreatment Adverse Events and Adverse Events Collection Periods

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

Collection of TEAEs (as defined in Section 9.3.6) will commence at the time the subject receives the first dose of study drug. Routine collection of TEAEs will continue until the end of the study. Assessments of the relationship of AEs to study drug will be captured for TEAEs and not PTAEs.

8.2.2. Pretreatment Adverse Events and Adverse Events Reporting Periods

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

All subject experiencing PTAEs or TEAEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to screening levels or until there is a satisfactory

explanation for the changes observed. All PTAEs and TEAEs will be documented in the PTAE/AE page of the eCRF, whether or not the investigator concluded that the event is related to the study drug. The information to be documented for each event is described in the following sections.

8.2.2.1. Event description

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

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

8.2.2.2. Start Date/Time and Stop Date/Time

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

8.2.2.3. Relationship to Study Drug (Suspected Adverse Reactions)

The investigator will assess causality by answering either “related” or “not related” to the question “Is there a reasonable possibility that the event may have been caused by the investigational medicinal product (IMP)/study medication?”

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

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

8.2.2.4. Severity/Intensity

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

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

8.2.2.5. Seriousness

A PTAE or TEAE that meets any of the criteria for an SAE outlined in Section 8.1.3 will be recorded as an SAE, along with the criteria that were met.

It is important to distinguish between seriousness (PTAE or AE compared with SAE) and severity/intensity (mild, moderate, severe, life-threatening, or fatal) of AEs as outlined in Section 8.1.3.

8.2.2.6. Outcome

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

8.2.3. Reporting of Serious Adverse Events

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

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

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

Spontaneously reported SAEs after completion of the study should be promptly reported by the investigator to the sponsor.

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs, SAEs, and AESIs, will be followed until resolution, stabilization, the event is otherwise explained, or the subject is considered lost to follow-up at the end of the study.

8.3. Safety Reporting to Investigators, Institutional Review Boards, Independent Ethics Committees, and Regulatory Authorities

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.

Investigational new drug (IND) safety reports/SUSARs are SAEs that qualify for mandatory expedited reporting to regulatory authorities when the SAE is suspected to be caused by the study drug and is considered unexpected (ie, not defined as expected in the current IB, clinical study protocol, or approved labeling for marketed products). In this case, MyoKardia/designee will report to the relevant regulatory authority(ies) and forward a formal notification describing the IND safety report/SUSAR to investigators, according to regulatory requirement. Each investigator must then notify his/her ethics committee IRB/IEC of the SUSAR as required by local regulatory authorities and in accordance with their IRB/IEC policy.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4. Pregnancy

8.4.1. Avoidance of Pregnancy

Female subjects of childbearing potential must use appropriate methods of contraception as listed in the inclusion criteria (Section 4.1). Female subjects of nonchildbearing potential are defined as those who are permanently (surgically) sterilized or are postmenopausal. Permanent sterilization includes hysterectomy, bilateral oophorectomy, and bilateral tubal occlusion or ligation. Female subjects are considered postmenopausal if they have had amenorrhea for at least 1 year or more following cessation of all exogenous hormonal treatments and FSH levels are in the postmenopausal range.

8.4.2. Reporting and Follow-up of Pregnancies

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

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

9.1.1. Sample Size Determination

Approximately 100 subjects will be randomized, with 50 subjects in each of the 2 treatment groups. This sample size should provide adequate power to determine the superiority of mavacamten in reducing eligibility for SRT procedures at the end of a 16-week treatment period. The power calculation was derived assuming a true clinically meaningful relative reduction of 50% between subjects in the mavacamten and placebo groups meeting the primary endpoint. It is estimated that 70% of the subjects receiving placebo will meet the endpoint versus 35% of subjects receiving mavacamten by the end of the 16-week treatment period. The proposed

sample size of 50 subjects in each treatment group will provide 95% power at a 2-sided 5% statistical significance level. Subjects who undergo SRT, terminate early, die, or cannot otherwise be assessed for SRT eligibility at the end of the 16-week placebo-controlled treatment period will be classified as eligible for an SRT procedure.

9.2. Populations for Analyses

Four analysis populations are defined in this study:

- Intention-to-Treat (ITT) Population: all randomized subjects regardless of whether they receive study drug, with analyses conducted according to the randomized treatment assignment
- Safety Analysis Population: all randomized subjects who receive at least 1 dose of study drug, with analyses conducted by actual treatment received
- PK Analysis Population: all randomized subjects who receive at least 1 dose of mavacamten and have at least 1 detectable mavacamten plasma drug concentration

9.3. Statistical Analyses

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

9.3.1. General Considerations

Descriptive summary statistics for continuous variables will include the number of subjects, mean, standard deviation (SD) or standard error, median, minimum, and maximum. Nominal categorical variables will be summarized using counts and percentages.

9.3.2. Subject Disposition

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

9.3.3. Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will be summarized descriptively.

9.3.4. 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. Adjusted duration will also be derived by taking protocol-defined interruptions into account.

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

Treatment exposure and compliance will be summarized descriptively (number [n], mean, SD, median, minimum, and maximum). The compliance of subjects with compliance < 80% and those with compliance > 100% will be summarized.

9.3.5. Efficacy Analyses

All efficacy analyses will be performed on the ITT population. An alpha spending strategy will be used to control the family-wise Type 1 error rate at 5% level for testing the primary and secondary efficacy endpoints. The details of this strategy will be provided in the SAP.

9.3.5.1. Primary Efficacy Endpoint Analyses

The primary endpoint will be a composite of:

1. Decision to proceed with SRT prior to or at Week 16
2. SRT guideline eligible at Week 16 based on the 2011 ACCF/AHA HCM Guidelines

The decision to proceed with SRT is based on the patient's decision as recorded on the CRF. The SRT guideline eligibility will be derived using the NYHA class and LVOT gradient assessments at Week 16 per the 2011 ACCF/AHA guideline clinical and hemodynamic criterion below:

- Clinical criteria: NYHA Class III or IV or for the purposes of the Valor Study, subjects who are NYHA Class II with exertion-induced syncope or near syncope.

  and

- Hemodynamic criteria: dynamic LVOT gradient at rest or with provocation (i.e. Valsalva or exercise) ≥ 50 mmHg

The comparison of the proportions of subjects who meet the primary efficacy endpoint between the mavacamten and placebo treatment groups will be performed using the Cochran-Mantel-Haenszel (CMH) test for stratified categorical data. Early dropouts or subjects whose response status cannot be assessed at the end of the 16-week dosing period will be classified as SRT eligible. Detailed statistical analysis strategies will be documented in the SAP.

Further details regarding the primary endpoint derivation and analysis will be provided in the SAP.

9.3.5.2. Secondary Efficacy Endpoints Analyses

The secondary efficacy endpoints are as follows:

- Change from baseline to Week 16 in the mavacamten group compared with the placebo group in
  - NYHA functional class
  - KCCQ-23, CSS
- Change from baseline to Week 16 in the mavacamten group compared with the placebo group in NT-proBNP and cardiac troponin
- Change from baseline to Week 16 in the mavacamten group compared with the placebo group in post exercise LVOT gradient

The general analytical approach for the secondary efficacy endpoints are as follows:

- To minimize false positive among the secondary endpoints, appropriate Type 1 error control methods will be used. Additional details will be specified in the SAP.
- Categorical endpoints will be analyzed by comparing the respective proportions of the 2 treatment groups using CMH tests.
- Continuous variables will be analyzed by analysis of covariance (ANCOVA) or mixed-effect for repeated measurements (MMRM) evaluating the treatment group differences.

Specific details will be provided in the SAP.

9.3.5.3. Exploratory Efficacy Endpoints Analyses

Analyses for exploratory efficacy endpoints, including investigator SRT evaluation, hemodynamic parameters, subject symptoms, PRO assessments, cardiac biomarkers and medications, and subject activity monitoring will be specified in the SAP.

The general analytical approach for the exploratory efficacy endpoints includes descriptive summaries (e.g. N, mean, SD, 95% CIs, and percentage) and between-group comparisons for placebo-controlled period as following:

- Categorical endpoints will be analyzed by the CMH test, taking stratification factors into account
- Continuous variables will be analyzed by an ANCOVA or MMRM model comparing between-group means

Detailed analysis methodology for each endpoint will be specified in the SAP.

9.3.5.4. Pharmacokinetics Analyses

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

9.3.6. Safety Analyses

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

- The safety analysis performed for the placebo-controlled period will focus on comparing the mavacamten and placebo, and data will be summarized by the treatment received. The analysis performed for the active-controlled and LTE period will focus on assessing the long-term safety of mavacamten treatment.
- The baseline value is defined generally as the last available value before the first administration of study drug of analysis interest
- 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; 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 dose of study drug to the last dose of study drug + 56 days.

9.3.6.1. Adverse Events

AEs will be mapped to SOC and preferred terms (PTs) using Medical Dictionary for Regulatory Activities (MedDRA) Version 23. 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 drug. AEs with onset during the treatment-emergent period (i.e. TEAEs) or with an onset before the first dose of study drug that increase in severity or become serious during the treatment-emergent period, will be considered TEAEs.

AE incidence tables will present the number (n) and percentage (%) of subjects experiencing at least one TEAE by SOC, and preferred term (PT) in alphabetical order for each treatment group. Multiple occurrences of the same event in the same subject will be counted only once within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

AE incidence tables will be provided by treatment group for TEAEs, including all TEAEs, all treatment-emergent SAEs, all treatment-emergent treatment-related AEs, all treatment-emergent treatment-related SAEs, TEAEs by severity, and all TEAEs leading to permanent treatment discontinuation.

9.3.6.1.1. Death

All deaths will be listed for the event time relative to the first study dose and the relevant AE descriptions, if applicable.

9.3.6.1.2. Pregnancy Outcome

An adverse pregnancy outcome will be considered as TEAE if the pregnancy is confirmed during the TEAE period, and will be summarized for the percentage of adverse outcomes among all pregnancy events.

9.3.6.1.3. Overdose

The following summaries for reports of symptomatic overdose will be generated:

- Number of subjects who experienced symptomatic overdose summarized by treatment received
- Analysis of the cause and occurrence of the symptomatic overdose
- TEAE experienced during the symptomatic overdose by primary SOC, and PT showing the number and percent of subjects sorted by internationally agreed order of SOC and alphabetic order of PT

9.3.6.2. 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.

9.3.6.2.1. 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:

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

9.3.6.2.2. 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 subject. For each time point of measurement, the changes from baseline will be summarized using descriptive statistics.

9.3.6.2.3. Categorical Analysis

The number and percentage of subjects with any postdose QTcF values of > 450 msec, > 480 msec, > 500 msec, > 520 msec, and > 550 msec will be tabulated for all subjects. Subjects with QTc values > 500 msec will be listed with corresponding baseline values, ΔQTcF, and baseline and treatment HR. The incidence count and percentage of subjects with ΔQTcF increase from baseline of > 30 msec and > 60 msec will be tabulated.

9.3.6.2.4. Morphology Findings

ECG morphologies for each subject will be listed.

9.3.6.2.5. Concentration-QTc Analyses

A concentration-QTc regression analysis, based on data collected from the ECG recordings after drug administration and concentration values for each subject at each matching time point, will be performed. 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.

9.3.6.3. Laboratory Data

The summary statistics (including number of subjects, mean, median, SD, minimum and maximum) of all laboratory variables (laboratory values and changes from baseline), will be calculated at all baseline and postbaseline time points and presented by treatment group.

Listings of subjects with laboratory values that are outside of the reference range will be produced.

9.3.6.3.1. 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 compared with 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 number and percentage of subjects with elevated liver function tests (based on safety laboratory data) during the TEAE period 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). Potential Hy's law cases will be investigated by summarizing the number of subjects with elevated ALT or AST (> 3 x ULN) and with elevated TBL (> 2 x ULN) where transaminase elevation coincides with or precedes bilirubin elevation.

9.3.6.4. Vital Signs Data

The summary statistics (including number, mean, median, SD, minimum and maximum) of all vital signs variables (values and changes from baseline), will be calculated at all baseline and postbaseline time points and presented by treatment group.

Listings of subjects with vital signs values that are outside of the reference range will be produced.

9.3.6.5. Other Safety Analyses

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

9.3.7. Exploratory Analyses

Additional exploratory analyses may be performed. Detailed planned exploratory analyses will be specified in the SAP.

9.3.8. Pharmacokinetics Analyses

Plasma concentrations of mavacamten will be determined and summarized using descriptive statistics.

9.4. Interim Analysis

An independent Statistical Data Analysis Center (SDAC) will provide statistical and data support for the IDMC. A formal interim analysis will be conducted by the SDAC after 50 subjects have completed the Week 16 study visit or terminated early from the study drug to assess efficacy results. A p-value less than 0.001 is considered statistical significance for the primary endpoint analysis in the interim analysis. SAP will be finalized prior to conducting the interim analysis.

9.5. Independent Data Monitoring Committee

The roles and responsibilities of the IDMC are described in Section 3.3.2.

10. STUDY COMPLIANCE AND ETHICAL CONSIDERATIONS

10.1. Compliance Statement

This study will be conducted in accordance with the ICH GCP Guidelines; US Title 21 Code of Federal Regulations (CFR) Parts 11, 50, 54, 56, and 312; the European Union; 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.

10.2. 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 subject is aware of potential benefits and risks. Potential subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Subjects, or a legal guardian if the subject is unable to, must give informed consent in writing.

Prior to participation in any study-related procedures, subjects must sign and date an IRB/IEC-approved written ICF in a language the potential subject can understand. The informed consent process must be conducted and documented in the source document (including the date), and the form must be signed before the subject 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 subject. Before informed consent is obtained, the investigator should provide the potential subject 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 subject. The written ICF should be signed and personally dated by the subject and by the person who conducts the informed consent discussion. All subjects will receive a copy of their signed and dated ICF.

10.3. Ethics Committee

The IRB/IEC must review and, if appropriate, approve the following documents, as applicable:

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

The IRB/IEC approval must be in writing, clearly identifying the study (by protocol date and/or version); the documents reviewed, including informed consent; and the date of the review. The

investigator has the responsibility to provide MyoKardia with the written IRB/IEC approval prior to initiating any study-related procedures.

The investigator also has the responsibility to inform the IRB/IEC of the following according to the IRB/IEC policy:

- All SUSARs (as described in Section 8.3)
- Any new information that may adversely affect the safety of the subjects or the conduct of the study
- Protocol deviations
- A synopsis of the clinical study report upon study completion

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

11. ADMINISTRATIVE PROCEDURES

11.1. 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 subjects' 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 a regulatory agency or health authority to terminate the study
- Unsatisfactory subject enrollment with regard to quality or quantity
- Significant or numerous deviations from study protocol requirements, such as failures to perform required evaluations on subjects, 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

11.1.1. Subject 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 subject.

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

Subjects 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.

11.1.2. Study Supplies

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

- Mavacamten active capsules in 4 strengths (2.5 mg, 5 mg, 10 mg, and 15 mg) and placebo capsules in 30-count bottles
- Cardiac/activity monitoring devices, including Holter monitors, accelerometers, and ECG machines
- Supplies for laboratory assessments
- Study Reference Manual
- Laboratory Manual
- Pharmacy Manual
- IXRS Manual
- IB

11.1.3. Investigator Training

All clinical sites will have a center-specific study initiation meeting to ensure the center staff understand the protocol, study requirements and procedures, and data capture processes. This training will take place before the first subject 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 study team members are adequately trained, and the training is documented.

11.1.4. Ongoing Communication of Safety Information During the Study

MyoKardia will provide investigators with documentation of SAEs from this study and other studies that are related to mavacamten and are unexpected (refer to Section 8.3), as appropriate. Investigators must forward this documentation to the IRB/IEC as described in Section 8.3.

MyoKardia will also notify investigators of 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 subjects, affect the conduct of the study, or alter the IRB/IEC opinion regarding continuation of the study.

11.1.5. Study Monitoring

MyoKardia and a contracted clinical research organization 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 laws, rules and regulations. The clinical site monitor will also assess proper eCRF completion and source document retention. The investigators and clinical site staff are expected to provide adequate space for monitoring visits and allocate sufficient time to permit adequate review of the study's progress. The investigators will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections, providing direct access to source data/documents and study-related facilities (eg, pharmacy, diagnostic laboratories).

11.1.6. Study Auditing and Inspecting

MyoKardia may audit the study conduct, compliance with the protocol, and accuracy of the data at1 or more study centers.

The investigators/institutions will permit study-related monitoring, audits, and inspections by MyoKardia, IRBs/IECs, government regulatory authorities, and MyoKardia quality assurance personnel/designees by providing direct access to source data/documents after appropriate notification from MyoKardia.

11.2. Investigator Responsibilities

11.2.1. Screening Log

The investigator must keep a record that lists all subjects who signed an ICF and the reason for noninclusion if the potential subject does not ultimately enroll and receive study drug. Screening procedures are described in Section 4.4.

11.2.2. Mavacamten Accountability

The investigator must ensure that the study drug at the investigational site is kept secured and accounted for with access limited to only those individuals authorized by the investigator. The investigator/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 available for inspection by the site monitor and/or auditor. Only those sites with institutional, local, state, or federal restrictions on the destruction of material will be allowed to return study drug to the depot. No study drug may be destroyed or returned to the depot until the clinical site monitor has verified the accuracy of the study drug records at the clinical site.

11.2.3. Reporting and Recording of Study Data

Data will be captured and compiled using procedures developed by MyoKardia/designee. 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 in the eCRF will result in data queries that require resolution by the investigator/designee. Corrections to the eCRF, including the reason for the change, will be automatically documented through the EDC system's audit trail.

Subject 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 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 in the eCRF must match the source documents.

An eCRF must be completed for all screened subjects. 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 subject.

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

11.2.4. 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 subject:

- Subject identification and contact information (name, date of birth, sex, address, phone)
- Documentation verifying subject 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 subject's medical records in the event that a clinical site's policy does not permit direct access to the electronic medical records.

A subject's medical records must be obtained by the principal investigator to support documentation of any SAEs. The principal investigator is responsible for summarizing the pertinent aspects of the SAE (including discharge summaries, diagnostic procedures, laboratory data, interventions) and updating the SAE eCRF with this information.

11.2.5. Subject Identification Information

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

11.2.6. 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 subjects (eg, subject identification code list and all source documents), all original signed ICFs, copies of all eCRFs, original laboratory reports, detailed records of study medication disposition, and all essential documents for the conduct of a clinical study. To comply with international regulations, the records should be retained by the investigator for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing 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.

11.2.7. 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/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 subjects without prior IRB/IEC approval. Immediately after the implemented deviation or change, the investigator must submit a report explaining the reasons for the protocol deviation to the IRB/IEC and MyoKardia, if required. The MyoKardia or CRO medical monitor will notify the study monitor of the decision.

11.2.8. 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 accordance with the purposes outlined in the ICF.

11.3. Clinical Trial Insurance

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

11.4. 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, 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 IRB/IEC and the appropriate regulatory authorities before implementation, as appropriate. Local requirements should be followed for revised protocols.

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

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

12. 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.

13. ADMINISTRATIVE CONSIDERATIONS

13.1. Use of Computerized Systems

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

- EDC system to capture protocol-required subject data: clinical sites will enter data from source documents into eCRFs for each study visit using a web-based interface. Study monitors and data management personnel will use the EDC system to review data and generate queries and reports as needed
- Cardiac clinical data management systems will be used to analyze ECG, Holter monitoring, and accelerometry data from digital equipment used by clinical site personnel to collect subject data
- IXRS to dispense study drug and transfer data in a blinded manner

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.

13.2. 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 requirements. These include, but are not limited to, the protocol, eCRFs, AE reports, subject source data (original records or certified copies), correspondence with health authorities and IRB/IEC, ICFs, 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 subject'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 subject's eCRF will be maintained by the investigator.

14. PUBLICATION

The data and results of the Study will be published as outlined in the agreement between the investigator/institution and MyoKardia regarding the conduct of the clinical study (the "Clinical Study Agreement"), and as applicable, described further in the Executive Committee Charter.

15. REFERENCES

Alfares, A. A., M. A. Kelly, G. McDermott, B. H. Funke, M. S. Lebo, S. B. Baxter, J. Shen, H. M. McLaughlin, E. H. Clark, L. J. Babb, S. W. Cox, S. R. DePalma, C. Y. Ho, J. G. Seidman, C. E. Seidman, and H. L. Rehm. 2015. 'Results of clinical genetic testing of 2,912 probands with hypertrophic cardiomyopathy: expanded panels offer limited additional sensitivity', *Genet Med*, 17: 880-8.

Chuan, P., S. Sivaramakrishnan, E. A. Ashley, and J. A. Spudich. 2012. 'Cell-intrinsic functional effects of the alpha-cardiac myosin Arg-403-Gln mutation in familial hypertrophic cardiomyopathy', *Biophys J*, 102: 2782-90.

Desai, MY, Wolski K, Owens A, et al. 2021. Study design and rationale of VALOR-HCM: Evaluation of mavacamten in adults with symptomatic obstructive hypertrophic cardiomyopathy who are eligible for septal reduction therapy. *Am Heart J.* 239:80-89

Gersh, B. J., B. J. Maron, R. O. Bonow, J. A. Dearani, M. A. Fifer, M. S. Link, S. S. Naidu, R. A. Nishimura, S. R. Ommen, H. Rakowski, C. E. Seidman, J. A. Towbin, J. E. Udelson, C. W. Yancy, Guidelines American College of Cardiology Foundation/American Heart Association Task Force on Practice, Surgery American Association for Thoracic, Echocardiography American Society of, Cardiology American Society of Nuclear, America Heart Failure Society of, Society Heart Rhythm, Angiography Society for Cardiovascular, Interventions, and Surgeons Society of Thoracic. 2011. '2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines', *Circulation*, 124: 2761-96.

Green, C. P., C. B. Porter, D. R. Bresnahan, and J. A. Spertus. 2000. 'Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure', *J Am Coll Cardiol*, 35: 1245-55.

Hershberger, R. E., J. Cowan, A. Morales, and J. D. Siegfried. 2009. 'Progress with genetic cardiomyopathies: screening, counseling, and testing in dilated, hypertrophic, and arrhythmogenic right ventricular dysplasia/cardiomyopathy', *Circ Heart Fail*, 2: 253-61.

Ho, C. Y. 2012. 'Hypertrophic cardiomyopathy in 2012', *Circulation*, 125: 1432-8.

Ho, C. Y., N. K. Sweitzer, B. McDonough, B. J. Maron, S. A. Casey, J. G. Seidman, C. E. Seidman, and S. D. Solomon. 2002. 'Assessment of diastolic function with Doppler tissue imaging to predict genotype in preclinical hypertrophic cardiomyopathy', *Circulation*, 105: 2992-7.

Kim, L. K., R. V. Swaminathan, P. Looser, R. M. Minutello, S. C. Wong, G. Bergman, S. S. Naidu, C. L. Gade, K. Charitakis, H. S. Singh, and D. N. Feldman. 2016. 'Hospital Volume Outcomes After Septal Myectomy and Alcohol Septal Ablation for Treatment of Obstructive Hypertrophic Cardiomyopathy: US Nationwide Inpatient Database, 2003-2011', *JAMA Cardiol*, 1: 324-32.

Maron, B. J., J. M. Gardin, J. M. Flack, S. S. Gidding, T. T. Kurosaki, and D. E. Bild. 1995. 'Prevalence of hypertrophic cardiomyopathy in a general population of young adults.

Echocardiographic analysis of 4111 subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults', *Circulation*, 92: 785-9.

Maron, B. J., M. S. Maron, and C. Semsarian. 2012. 'Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives', *J Am Coll Cardiol*, 60: 705-15.

Maron, M. S., I. Olivotto, S. Betocchi, S. A. Casey, J. R. Lesser, M. A. Losi, F. Cecchi, and B. J. Maron. 2003. 'Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy', *N Engl J Med*, 348: 295-303.

Nishimura, R. A., and S. R. Ommen. 2010. 'Septal reduction therapy for obstructive hypertrophic cardiomyopathy and sudden death: what statistics cannot tell you', *Circ Cardiovasc Interv*, 3: 91-3.

Ponikowski, P., A. A. Voors, S. D. Anker, H. Bueno, J. G. F. Cleland, A. J. S. Coats, V. Falk, J. R. Gonzalez-Juanatey, V. P. Harjola, E. A. Jankowska, M. Jessup, C. Linde, P. Nihoyannopoulos, J. T. Parissis, B. Pieske, J. P. Riley, G. M. C. Rosano, L. M. Ruilope, F. Ruschitzka, F. H. Rutten, P. van der Meer, and E. S. C. Scientific Document Group. 2016. '2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC', *Eur Heart J*, 37: 2129-200.

Sommese, R. F., J. Sung, S. Nag, S. Sutton, J. C. Deacon, E. Choe, L. A. Leinwand, K. Ruppel, and J. A. Spudich. 2013. 'Molecular consequences of the R453C hypertrophic cardiomyopathy mutation on human beta-cardiac myosin motor function', *Proc Natl Acad Sci U S A*, 110: 12607-12.

Sung J, Choe E, Elting M, Nag S, Sutton S, Deacon J, Leinwand L, Ruppel K, Spudich J. 2012. 'Single Molecule Studies of Recombinant Human α- and β-Cardiac Myosin to Elucidate Molecular Mechanism of Familial Hypertrophic and Dilated Cardiomyopathies', *Biophys J.*, 102: 613a-14a

Yancy, C. W., M. Jessup, B. Bozkurt, J. Butler, D. E. Casey, Jr., M. H. Drazner, G. C. Fonarow, S. A. Geraci, T. Horwich, J. L. Januzzi, M. R. Johnson, E. K. Kasper, W. C. Levy, F. A. Masoudi, P. E. McBride, J. J. McMurray, J. E. Mitchell, P. N. Peterson, B. Riegel, F. Sam, L. W. Stevenson, W. H. Tang, E. J. Tsai, and B. L. Wilkoff. 2013. '2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines', *Circulation*, 128: 1810-52.

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 • Glucose • Protein • Albumin • eGFR[b]	• Specific gravity • pH • Protein • Glucose • Leukocyte esterase • Blood • Nitrite

ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CPK = creatine phosphokinase; eGRF = estimated glomerular filtration rate; INR = international normalized ratio.
[a] Urine microscopy will be performed if there is a significant abnormality in the dipstick.
[b] eGFR is calculated at screening only.

At screening, follicle stimulating hormone testing will be performed for postmenopausal female subjects to confirm postmenopausal status. Serum and urine (β-hCG) pregnancy tests will be conducted for female subjects of childbearing potential.

In addition, NT-proBNP and cardiac troponin will be measured by the central laboratory and reviewed by the IDMC on a regular basis throughout the study.

The following nonsafety laboratory parameters will also be measured at screening:

- HBV and HCV
- HIV test

APPENDIX 2. PROHIBITED MEDICATIONS

Cardiotoxic Agents

Prior or concomitant treatment with cardiotoxic agents such as doxorubicin or similar is prohibited.

Moderate and Potent CYP2C19 Inhibitors and Potent CYP3A4 Inhibitors

Potent and moderate CYP2C19 inhibitors and potent CYP3A4 inhibitors are prohibited from 14 days prior to screening through the end of the study. Examples are listed below.

- Efavirenz (antiviral)
- Etravirine (antiviral)
- Fluconazole (antifungal)
- Fluvoxamine (selective serotonin reuptake inhibitor [SSRI] / antidepressant)
- Fluoxetine (SSRI / antidepressant)
- Moclobemide (monoamine oxidase [MAO] inhibitor/antidepressant)
- Omeprazole (proton pump inhibitor)
- Esomeprazole (proton pump inhibitor)
- Ticlopidine (platelet inhibitor)
- Voriconazole (antifungal)

St. John's Wort

Use of St. John's Wort is prohibited from 14 days prior to screening through the end of the study.

Biotin Supplements.

Biotin supplements are prohibited from 14 days prior to screening through the end of study visit. Multivitamins which contain biotin should be taken >24 hr prior to clinical visits.

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 (AST/ALT) and total bilirubin (TBL) elevation according to the criteria specified in Section 5.7.2 (3 × upper limit of normal [ULN] for AST/ALT and 2 × ULN for TBL in subjects 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 electronic case report form (eCRF) (eg, Adverse Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities are to be completed and sent to MyoKardia.

Other events of hepatotoxicity and potential DILI are to be reported as SAEs if they meet the criteria for an SAE defined in Section 8.1.3.

Additional Clinical Assessments and Observation

All subjects from whom study drug or protocol-required therapies 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 subject's baseline levels. Assessments to be performed during this period include the following:

- Repeat liver chemistries within 24 to 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 subjects who are far from the study center, it may be difficult to return promptly to the study center. In this case, the subject should be retested locally, but normal laboratory ranges should be recorded, results should be made available to the study investigator immediately, and the data should be included in the eCRF.

Subjects are to be monitored at least twice weekly; testing frequency may decrease to once per week or less if laboratory abnormalities stabilize or the study drug or protocol-required therapies have been discontinued and the subject 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 pharmacokinetics analysis if this has not already been collected.
- Obtain a more detailed history of the following:
  - Prior and/or concurrent diseases or illness

- Exposure to environmental and/or industrial chemical agents
- Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting, and fever
- Prior and/or concurrent use of alcohol, recreational drugs, and special diets
- Concomitant medications (including nonprescription medicines and herbal and dietary supplements).

- Initiate full viral and autoimmune hepatitis evaluation (serologies for hepatitis A, B, C, D, E, Epstein-Barr virus, herpes simplex virus, etc.); evaluate for other potential causes of DILI, including but not limited to: nonalcoholic steatohepatitis (NASH), 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.
- Follow the subject 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 the appropriate eCRFs.

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

Under certain circumstances the site may choose to contract with a community-based facility (with sponsor's approval, by the CRO, or by the sponsor) Service providers must be approved by the sponsor before performing study assessments.

The following provisions may be made to accommodate subjects who are unable to attend on-site study visits for scheduled assessments and dispensation of mavacamten:

Study visits during titration phase and LTE may be performed at a remote location e.g. community physician's office or laboratory facility. .

- Subjects who are unable to be seen at the clinic may be required to temporarily discontinue mavacamten.
- Subjects may be tested for COVID-19 at the discretion of the investigator and/or sponsor.

Remote Health Assessment

- Protocol-specified assessments listed below may be conducted at a community based facility or via telemedicine.
  - NHYA may be assessed by the principal investigator via telemedicine
  - Physical examination may be done by a community based professional who is an MD/DO or licensed NP/PA
  - TTE may be acquired at a community echocardiography lab by a sonographer who has been certified by the echocardiography core lab.
  - ECG may be acquired at a community physician's office or ECG laboratory
  - Holter Monitor may be applied and removed at a community physician's office or Holter Lab
  - Phlebotomy may be done at a community phlebotomy facility
  - Under certain circumstances accelerometry may be delivered to subject by courier
  - Under certain circumstances the PRO questionnaires may be delivered to and retrieved from the subject via a messenger service contracted by the study site or sponsor.

Under certain circumstances the site may choose to contract with a community-based facility (with sponsor's approval, by the CRO, or by the sponsor) for the above assessments (e.g. vital signs, ECG, echocardiography upon certification by Core echocardiography lab, application and removal of Holter)

Drug Dispensation

- Mavacamten may be shipped by Direct-to-Subject Study Drug Shipment (see Section 5.2.2)

Temporary Discontinuation of Study Drug

Subjects in Placebo-Controlled Dosing (Day 1 to Week 16)

Under unusual circumstances such as a Pandemic or Natural Disaster, if subjects in the placebo-controlled dosing period of the study, Day 1 to Week 16, cannot be monitored for safety within 1 week of their scheduled study assessment, as they cannot be seen at the site or approved community based physician or laboratory facility, the subject will be contacted by the site at the end of the 1-week period and instructed to stop taking mavacamten.

Subjects who discontinue mavacamten should be contacted by the site every 2-4 weeks from the time of discontinuing mavacamten to assess for AEs and to document concomitant medications until the next study visit.

When the subject can return to the study site, he/she will receive a new subject ID and undergo rescreening to reenter the study. All screening assessments need to be repeated.

- Subjects will restart study drug (mavacamten 5 mg or placebo, consistent with the drug that the subject was randomized to at the beginning of the study, before temporary discontinuation) at Day 1 and resume study visits from Day 1.
- Subjects who do not qualify based on re-screening assessments, on principal investigator consultation with the MyoKardia or CRO Medical Monitor, may be scheduled for repeat screening at a later time. There is no limit to the number of times re-screening can occur when the subject discontinued IP due to a pandemic or natural disaster.

Subjects in Active-Controlled Dosing (Week 16 to Week 32)

Under unusual circumstances such as a Pandemic or Natural Disaster, if subjects in the active-controlled period of the study, Week 16 to Week 32, cannot be monitored for safety within 1 week of their scheduled study assessment, as they cannot be seen at the site, the subject will be contacted by the site at the end of the 1-week period and instructed to stop taking mavacamten.

Subjects who discontinue mavacamten should be contacted by the site every 2-4 weeks from the time of discontinuing mavacamten to assess for AEs and to document concomitant medications until the next study visit.

When the subject can return to the study site, he/she will receive a new subject ID and undergo re-screening to reenter the study. All screening assessments need to be repeated.

- Subjects in the placebo to active cohort will restart mavacamten 5 mg at Week 16 and resume study visits from Week 16.
- Subjects who had been randomized to mavacamten in the placebo-controlled period will resume the dose of mavacamten they were taking at Week 16 and resume study visits from Week 16.
- subjects who do not qualify based on re-screening assessments, on principal investigator consultation with the MyoKardia or CRO Medical Monitor, may be scheduled for repeat screening at a later time. There is no limit to the number of times re-screening can occur when the subject discontinued IP due to a pandemic or natural disaster.

Subjects in LTE Dosing (Week 32 to Week 128)

Under unusual circumstances such as a Pandemic or Natural Disaster, if subjects who are in LTE portion of the study (after Week 32) cannot be monitored for safety within 4 weeks of their scheduled study assessment, as they cannot be seen at the site, the subject will be contacted by the site at the end of the 4-week period and instructed to stop taking mavacamten.

Subjects who discontinue mavacamten should be contacted by the site every 2-4 weeks from the time of discontinuing mavacamten to assess for AEs and to document concomitant medications until the next study visit.

When the subject can return to the study site, he/she will receive a new subject ID and undergo re-entry safety screening to reenter the study. Re-entry safety screening assessments include 12-lead ECG, echocardiography, routine laboratory assessments, and serum pregnancy test or FSH in female subjects.

- Subjects who temporarily discontinue mavacamten after completing their Week 32 visit may resume mavacamten dosing as follows:
- Resume mavacamten at the dose they were taking when they temporarily discontinued, following completion of an unscheduled safety visit.
- Resume study visits at time (T) + x weeks (where T is the study week at discontinuation and x is the number of weeks discontinued).
- Subjects who have discontinued and resumed treatment according to these guidelines may repeat the discontinuation/resumption cycle as often as necessary.

PROTOCOL ACCEPTANCE PAGE

I have read and understood the contents of the clinical protocol, MYK-461-017 (VALOR-HCM) (A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Mavacamten in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy Who Are Eligible for Septal Reduction Therapy), 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 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 Practice (GCP) and all other applicable regulatory requirements to obtain written and dated approval from the ethics committee (ie, central or institutional review board [IRB] or independent ethics committee [IEC]) for the study protocol, written informed consents, consent form updates, subject recruitment procedures, and any other written information to be provided to the subjects before initiating this clinical study
- Not to implement any changes to, or deviations from, the protocol without prior agreement from MyoKardia and documented approval from the IRB/IEC, except to eliminate an immediate hazard to the subjects or when changes involve only logistical or administrative aspects of the clinical study
- To permit direct monitoring and auditing by MyoKardia/designee 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/designee, including, but not limited to, the current Investigator's Brochure
- 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 the conduct of this study are adequately informed about the protocol, IMP/study medication(s), and their clinical study-related duties and functions

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

Printed Name: _____

Protocol Version: _____ Protocol Date: _____