Cover Page for Protocol

Sponsor Name	MyoKardia, A Bristol Myers Squibb Company
NCT Number	NCT03470545
Sponsor Trial ID	MYK-461-005
Official Study Title	A Randomized, Double-blind, Placebo-controlled Clinical Study to Evaluate Mavacamten (MYK-461) in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy
Document Date	04 October 2019

CLINICAL STUDY PROTOCOL

Protocol Number:	MYK-461-005 (EXPLORER-HCM)
Protocol Title:	A Randomized, Double-blind, Placebo-controlled Clinical Study to Evaluate Mavacamten (MYK-461) in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy
Indication:	Hypertrophic Cardiomyopathy
Phase:	3
Investigational Medicinal Product:	Mavacamten (MYK-461) or matching placebo
Sponsor:	MyoKardia, Inc. [redacted]
IND Number:	121904
EudraCT Number:	2017-002530-23
US Coordinating Investigator:	Stephen Heitner, MD Oregon Health & Science University Portland, Oregon, USA
EU Coordinating Investigator:	Iacopo Olivotto, MD Careggi University Hospital Florence, Italy
Key Sponsor Contacts:	Hilary Nelson Director, Clinical Operations [redacted] Amy Sehnert, MD Medical Monitor [redacted]
Original Protocol Date:	14 July 2017
Amendment 1:	09 August 2017
Amendment 2:	25 January 2018
Amendment 3:	21 March 2018
Amendment 4:	13 November 2018
Amendment 5:	04 October 2019

PROTOCOL AMENDMENT
SUMMARY OF CHANGES TABLE

Protocol Amendment 5: 04 October 2019

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

Overall Rationale for the Amendment

[redacted]

Section(s)	Summary of Change	Reason(s) for Change
Title Page	[redacted] **Hilary Nelson** [redacted] Director, Clinical Operations [redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Synopsis Secondary Efficacy Endpoints and Section 12.2.2 Secondary Efficacy Endpoints	• Change from baseline to Week 30 in post-exercise LVOT peak gradient • [redacted] **Proportion of participants with at least 1 class improvement in NYHA functional class** from baseline to Week 30 [redacted] • Change from baseline to Week 30 in (pVO_2) as determined by CPET [redacted]	[redacted]

Section(s)	Summary of Change	Reason(s) for Change
	[redacted] • **Change from baseline to Week 30 in participant-reported health-related quality of life as assessed by the KCCQ score** • Change from baseline to Week 30 in patient-reported severity of HCM symptoms as assessed by the HCM Symptom Questionnaire score	[redacted]
[redacted]	[redacted]	[redacted]

Section(s)	Summary of Change	Reason(s) for Change
[redacted]	[redacted]	[redacted]
Synopsis Sample Size and Statistical Analysis and [redacted]	Analyses for echocardiographic indices of cardiac structure as well as systolic and diastolic ventricular function**,** ~~and~~ accelerometer parameters, [redacted] **and HCM risk prediction model** will be specified in the SAP.	[redacted]
Section 4 Description of Other Procedures and Assessments	[redacted]	[redacted]

Section(s)	Summary of Change	Reason(s) for Change
Section 9.1.4.6 HCM Risk Prediction Model	Text was added to describe the HCM Risk Prediction Model that was included as an exploratory endpoint	[redacted]
Section 9.2.4 Hs-Cardiac Troponin-I	Text was added to describe assessment for hs-cardiac troponin-I [redacted]	[redacted]
Section 11.1.1.1 Events Not Meeting the Definition of Adverse Event	Text was added to clarify what does not meet the definition of an adverse event	[redacted]

PROTOCOL SYNOPSIS

Title	A Randomized, Double-blind, Placebo-controlled Clinical Study to Evaluate Mavacamten (MYK-461) in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy
Study Number	MYK-461-005 (EXPLORER-HCM)
Study Phase	3
Number of Centers	~90 sites worldwide
Primary Objective	• To compare the effect of a 30-week course of mavacamten with placebo on clinical response comprising of exercise capacity and clinical symptoms in participants with symptomatic obstructive hypertrophic cardiomyopathy (oHCM)
Secondary Objectives	• To compare the effect of a 30-week course of mavacamten with placebo on symptoms and left ventricular outflow tract (LVOT) obstruction as determined by Doppler echocardiography • To compare the effect of a 30-week course of mavacamten with placebo on exercise capacity, clinical symptoms and Patient Reported Outcomes individually • To assess the safety and tolerability of mavacamten • To assess the pharmacokinetic (PK) characteristics of mavacamten
[redacted]	[redacted]
[redacted]	[redacted]
Study Design	This is a Phase 3, double-blind, randomized, placebo-controlled, multicenter, international, parallel-group study to evaluate the safety, tolerability, and efficacy of mavacamten compared with placebo (1:1) in participants with symptomatic oHCM. Approximately 220 participants will be enrolled. This includes ~80 participants (~40 per treatment group) who consent to participate in a CMR substudy at selected sites. Randomization will be stratified according to New York Heart Association (NYHA) functional classification (II or III), current treatment with β-blocker (yes or no), planned type of ergometer used during the study (treadmill or exercise bicycle), and consent for the CMR substudy (yes or no). The study will comprise 3 periods as follows: **Screening period (Day -35 to Day -1)**: Participants will undergo a variety of general, cardiopulmonary, laboratory, symptom, and PRO assessments over 1 to 2 days in order to assess eligibility (see Table 1

	and Table 2). Key Screening tests include electrocardiogram (ECG); transthoracic echocardiography (TTE) conducted at rest, with Valsalva maneuver, and post-exercise; as well as cardiopulmonary exercise testing (CPET). The following screening assessments may be repeated, as long as within the 35-days screening window: blood tests, ECG, and/or TTE. Repeat assessments are allowed if central core labs require a repeat submission due to quality and in order to better assess inclusion/exclusion values. Participants who screen fail may be considered for rescreening based on the investigator's discretion, taking into consideration the reason(s) for screen fail. One attempt at rescreening will be allowed, and all procedures must be repeated. **Double-blind treatment period (Day 1 [randomization] to Week 30/end of treatment [EOT])**: The double-blind treatment period will include a two-step dose titration scheme designed to achieve safe and effective dosing for each participant based on their own response parameters. Participants who meet all eligibility criteria at Screening will first be randomized via an interactive response system in a 1:1 ratio to receive treatment with mavacamten 5 mg starting dose or matching placebo once daily (QD). Subsequently, assessments including ECG, PK (trough plasma concentrations), and TTE will be performed at each of 7 study visits, beginning at Week 4, and read by core laboratories (see also Safety Monitoring and Study Treatment sections in this synopsis and Table 1). At Week 8 and Week 14, the dose may be increased, decreased, or remain unchanged based upon results of Week 6 and Week 12 assessments, respectively. At Week 8, the dose may be increased to a maximum daily dose of 10 mg (ie, increase from 5 mg QD to 10 mg QD), and at Week 14 to a maximum daily dose of 15 mg (ie, increase from 10 mg QD to 15 mg QD). Dose increases are designed to be step-wise and are not allowed to skip doses (eg, from 5 mg to 15 mg). At Week 30/EOT, participants will complete CPET and post-exercise TTE. For any participants permanently discontinuing treatment prior to Week 30, an early termination (ET) visit should be conducted as soon as possible, including CPET and post-exercise TTE. Participants with ET will also be encouraged to complete all remaining study visits and assessments, including the Week 30 visit. **Posttreatment follow-up period (Week 30/EOT to Week 38/end of study [EOS])**: When double-blind treatment ends at Week 30, participants will be contacted by phone at Week 34 and return to the site at Week 38 for an EOS visit. At the EOS visit, specified assessments will be repeated. This posttreatment follow-up period applies only to participants who are receiving study drug after Week 22.
Safety Monitoring	To maintain safety throughout the double-blind treatment period, a clinic visit will occur every 2 to 4 weeks, beginning at Week 4 for an initial evaluation of clinical tolerability and safety (Table 1). Clinic visits will include but are not limited to clinical evaluation (symptoms, PRO evaluations, adverse event [AE]/serious adverse event [SAE] assessment), ECGs, PK sample, TTEs, and laboratory assessments. Results of TTE performed by study site sonographers at each

	scheduled visit following randomization should be kept blinded to the investigator and other study site personnel. An exception may occur if left ventricular ejection fraction (LVEF) ≤30% is measured at the site, then the investigator will be immediately notified and study drug will be permanently discontinued as described within the protocol. Assessments at Weeks 4, 6, 8, 12, 18, 22, and 26 will be used to guide dose reduction or temporary discontinuation if indicated, based on predefined criteria detailed within the protocol. If at any time during the double-blind treatment period the mavacamten dose is decreased from the previous dose, the participant will continue on the reduced dose to the EOT (Week 30) unless further safety concerns or intolerability arise.
[redacted]	[redacted]
Number of Participants	Approximately 220, with 110 participants in each of 2 treatment groups.
Study Treatment	Participants will receive mavacamten immediate-release capsules 5 mg or matching placebo QD for the first 8 weeks of the dosing period with trough PK samples drawn at Week 4, Week 6, and Week 8. If at Week 4 the trough PK is between 700 ng/mL and 1000 ng/mL, the dose will be decreased to 2.5 mg at Week 6. Otherwise, the dose will be adjusted (increase, decrease, or remain unchanged) at Week 8 based on Week 6 assessments and Week 14 based on Week 12 assessments. The permissible doses after dose adjustment at Week 8 will be 2.5 mg, 5 mg, 10 mg, or placebo. The permissible doses after dose adjustment at Week 14 will be 2.5 mg, 5 mg, 10 mg, 15 mg, or placebo. For added safety, if 700 ng/mL < Week 8 PK < 1000 ng/mL then an unscheduled visit will be arranged 2 weeks later (Week 10) to reduce dose. After Week 14, assessments will continue every 4 weeks to Week 30/EOT for safety monitoring. At any time if PK plasma concentration ≥ 1000 ng/mL, then study drug will be temporarily discontinued.
Study Duration	Each participant will be in the study for up to 43 weeks: for Screening, up to 5 weeks; for study conduct, 38 weeks (±7 days).
Inclusion Criteria	Each participant must meet the following criteria to be included in this study: 1. Able to understand and comply with the study procedures, understand the risks involved in the study, and provide written informed consent according to federal, local, and institutional guidelines before the first study-specific procedure 2. Is at least 18 years old at Screening 3. Body weight is greater than 45 kg at Screening

	4. Has adequate acoustic windows to enable accurate TTEs (refer to Echocardiography Site Instruction Manual) 5. Diagnosed with oHCM consistent with current American College of Cardiology Foundation/American Heart Association and European Society of Cardiology guidelines, ie, satisfy both criteria below (criteria to be documented by the echocardiography core laboratory): A. Has unexplained left ventricular (LV) hypertrophy with nondilated ventricular chambers in the absence of other cardiac (eg, hypertension, aortic stenosis) or systemic disease and with maximal LV wall thickness ≥15 mm (or ≥13 mm with positive family history of hypertrophic cardiomyopathy [HCM]) as determined by core laboratory interpretation, and B. Has LVOT peak gradient ≥50 mmHg during Screening as assessed by echocardiography at rest, after Valsalva maneuver, or post-exercise (confirmed by echocardiography core laboratory interpretation) 6. Has documented LVEF ≥55% by echocardiography core laboratory read of Screening TTE at rest 7. Has LVOT gradient with Valsalva maneuver at Screening TTE of ≥30 mmHg, determined by echocardiography core laboratory 8. Has NYHA Functional Class II or III symptoms at Screening 9. Has documented oxygen saturation at rest ≥90% at Screening 10. Is able to perform an upright CPET and has a respiratory exchange ratio (RER) ≥1.0 at Screening per central reading; if the RER is between 0.91 and 1.0, the participant may be enrolled only if it is determined by the central CPET laboratory that peak exercise has been achieved in the subject (the only permitted reasons for subpeak performance are [1] a decrease in systolic blood pressure or [2] severe angina as described in the CPET Laboratory Manual) 11. Female participants must not be pregnant or lactating and, if sexually active, must use one of the following highly effective birth control methods from the Screening visit through 3 months after the last dose of investigational medicinal product (IMP). • combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation or progestogen-only hormonal contraception associated with inhibition of ovulation by oral, implantable, or injectable route of administration • intrauterine device (IUD) • intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion • Female is surgically sterile for 6 months or postmenopausal for 1 year. Permanent sterilization includes hysterectomy, bilateral oophorectomy, bilateral salpingectomy, and/or documented bilateral tubal occlusion at least 6 months prior to

	Screening. Females are considered postmenopausal if they have had amenorrhea for at least 1 year or more following cessation of all exogenous hormonal treatments and follicle stimulating hormone (FSH) levels are in the postmenopausal range. Male partners must also use a contraceptive (eg, barrier, condom or vasectomy)
Exclusion Criteria	A participant who meets any of the following exclusion criteria may not participate in this study: 1. Previously participated in a clinical study with mavacamten 2. Hypersensitivity to any of the components of the mavacamten formulation 3. Participated in a clinical trial in which the participant received any investigational drug (or is 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. Has any medical condition that precludes upright exercise stress testing 6. Has a history of syncope within 6 months prior to screening or history of sustained ventricular tachyarrhythmia with exercise within 6 months prior to Screening 7. Has a history of resuscitated sudden cardiac arrest (at any time) or known history of appropriate implantable cardioverter-defibrillator (ICD) discharge/shock for life-threatening ventricular arrhythmia within 6 months prior to Screening (Note: history of anti-tachycardia pacing (ATP) within 6 months or ever is allowed) 8. Has paroxysmal, intermittent atrial fibrillation with atrial fibrillation present per the investigator's evaluation of the participant's ECG at the time of Screening 9. Has persistent or permanent atrial fibrillation not on anticoagulation for at least 4 weeks prior to Screening and/or not adequately rate-controlled within 6 months prior to Screening (Note – patients with persistent or permanent atrial fibrillation who are anticoagulated and adequately rate-controlled are allowed) 10. Current treatment (within 14 days prior to Screening) or planned treatment during the study with disopyramide or ranolazine 11. Current treatment (within 14 days prior to Screening) or planned treatment during the study with a combination of β-blockers and verapamil or a combination of β-blockers and diltiazem 12. For individuals on β-blockers, verapamil, or diltiazem, any dose adjustment of that medication <14 days prior to Screening or any

	anticipated change in treatment regimen using these medications during the study 13. Has been successfully treated with invasive septal reduction (surgical myectomy or percutaneous alcohol septal ablation [ASA]) within 6 months prior to Screening or plans to have either of these treatments during the study (note: individuals with myectomy or percutaneous ASA procedure performed >6 months prior to Screening may be enrolled if study eligibility criteria for LVOT gradient criteria are met) 14. ICD placement or pulse generator change within 2 months prior to Screening or planned new ICD placement during the study (pulse generator changes, if needed during the study, are allowed) 15. Has QT interval with Fridericia correction (QTcF) >500 ms at Screening or any other ECG abnormality considered by the investigator to pose a risk to participant safety (eg, second-degree atrioventricular block type II) 16. Has documented obstructive coronary artery disease (>70% stenosis in one or more epicardial coronary arteries) or history of myocardial infarction 17. Has known moderate or severe (as per investigator's judgment) aortic valve stenosis at Screening 18. Has any acute or serious comorbid condition (eg, major infection or hematologic, renal, metabolic, gastrointestinal, or endocrine dysfunction) that, in the judgment of the investigator, could lead to premature termination of study participation or interfere with the measurement or interpretation of the efficacy and safety assessments in the study 19. Has pulmonary disease that limits exercise capacity or systemic arterial oxygen saturation 20. History of malignant disease within 10 years of Screening: • Participants who have been successfully treated for nonmetastatic cutaneous squamous cell or basal cell carcinoma or have been adequately treated for cervical carcinoma in situ or breast ductal carcinoma in situ (DCIS) can be included in the study • Participants with other malignancies who are cancer-free for more than 10 years before Screening can be included in the study 21. Has 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 participant with safety laboratory parameters outside normal limits may be included if he or she meets all of the following criteria:

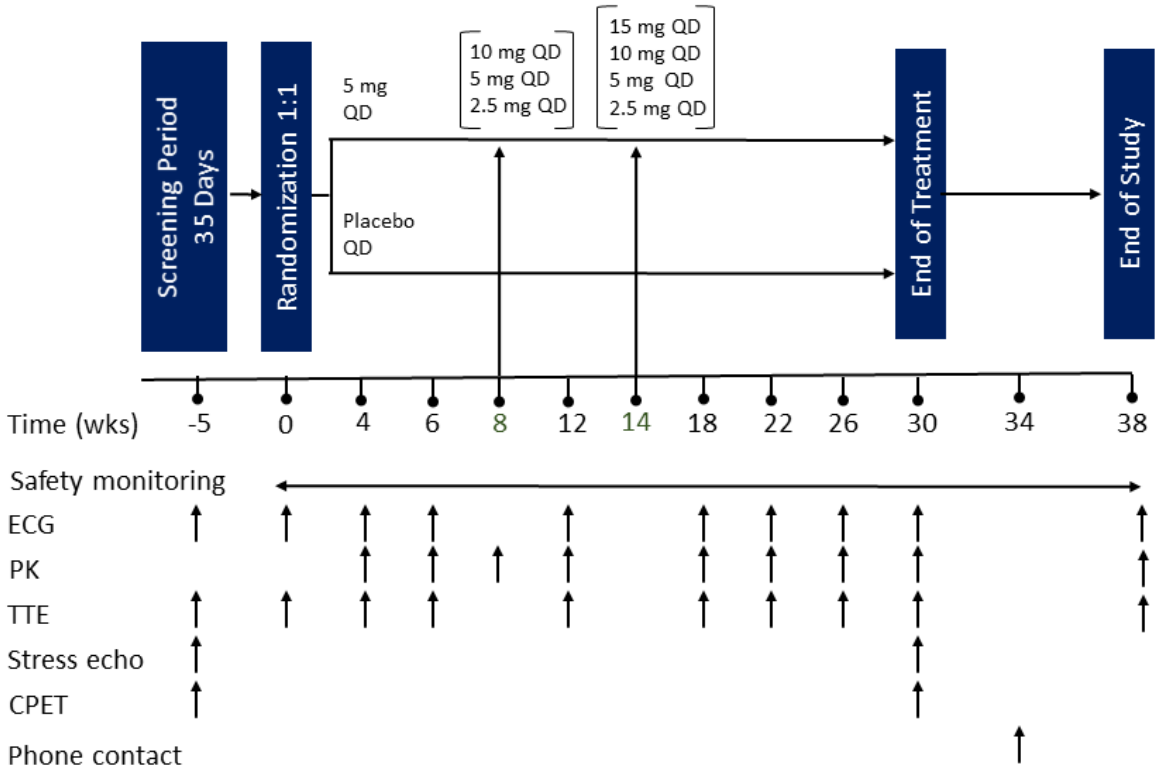
	• The safety laboratory parameter outside normal limits is considered by the investigator to be clinically not significant • If there is an alanine aminotransferase or aspartate aminotransferase result, the value must be <3 × the upper limit of the laboratory reference range • The body size–adjusted estimated glomerular filtration rate is ≥30 mL/min/1.73 m^2 22. Has a positive serologic test at Screening for infection with human immunodeficiency virus, hepatitis C virus, or hepatitis B virus 23. Has a history or evidence of any other clinically significant disorder, condition, or disease that, in the opinion of the investigator, would pose a risk to participant safety or interfere with the study evaluation, procedures, or completion 24. Is currently taking, or has taken within 14 days prior to Screening, a prohibited medication, such as a cytochrome P450 (CYP) 2C19 inhibitor (eg, omeprazole or esomeprazole), a strong CYP 3A4 inhibitor, or St. John's Wort (see Appendix 2 for more details). Alternatives, such as pantoprazole, are allowed and may be discussed with the medical monitor 25. Prior treatment with cardiotoxic agents such as doxorubicin or similar (see Appendix 2) 26. Unable to comply with the study requirements, including the number of required visits to the clinical site 27. Is a first degree relative of personnel directly affiliated with the study at the clinical study site, any study vendor, or the study Sponsor
[redacted]	[redacted]
Primary Efficacy Endpoint	Clinical response defined as achieving: 1) An improvement of at least 1.5 mL/kg/min in peak oxygen consumption (pVO_2) as determined by CPET and a reduction of one or more class in NYHA Functional Classification *or* 2) an improvement of 3.0 mL/kg/min or more in pVO_2 with no worsening in NYHA Functional Class.
Secondary Efficacy Endpoints	• Change from baseline to Week 30 in post-exercise LVOT peak gradient • Proportion of participants with at least 1 class improvement in NYHA functional class from baseline to Week 30

	• Change from baseline to Week 30 in (pVO_2) as determined by CPET • Change from baseline to Week 30 in participant-reported health-related quality of life as assessed by the KCCQ score • Change from baseline to Week 30 in patient-reported severity of HCM symptoms as assessed by the HCM Symptom Questionnaire score
[redacted]	[redacted]
Safety Endpoints	• Incidence of major adverse cardiac events (death, stroke, acute myocardial infarction) • Incidence of hospitalizations (both cardiovascular (CV) and non-CV) • Incidence of heart failure (HF) events, (includes HF hospitalizations and urgent emergency room (ER)/outpatient (OP) visits for HF) • Incidence of atrial fibrillation/flutter (new from screening) • Incidence of ICD therapy and resuscitated cardiac arrest • Incidence of Ventricular tachyarrhythmias (includes ventricular tachycardia (VT), ventricular fibrillation (VF), and Torsades de Pointe) • Incidence of syncope and seizures • Frequency and severity of treatment-emergent adverse events (TEAEs), treatment-emergent SAEs, and laboratory abnormalities (including trends in NT-proBNP)

[redacted]	[redacted]
[redacted]	[redacted]
Sample Size and Statistical Considerations	Approximately 220 participants will be randomized, with 110 participants in each of the 2 groups. Randomization will be stratified for NYHA functional class, current treatment with β-blocker, type of ergometer, and consent for the CMR substudy. The sample size should provide adequate power to determine the superiority of mavacamten in improving pVO_2 and NYHA functional classification relative to placebo. The power calculation is derived assuming a true clinically meaningful difference of 25% between mavacamten and placebo subjects in achieving the clinical response. Based on the MYK-461-004, PIONEER-HCM phase 2 study, 50% of the subjects receiving mavacamten met the clinical responder definition by the end of 12-week treatment period. Assuming the same percentage of subjects in the active treatment arm and 25% in placebo arm will achieve the clinical response at the end of 30-week dosing period in the current study, the proposed sample size of 110 subjects per arm will provide 96% power at two-sided 5% statistical significance level. Subjects who terminate early or cannot be assessed for the clinical response at the end of 30-week dosing period will be considered as non-responders. **Efficacy Analyses** <u>Primary efficacy endpoints analysis</u> The primary efficacy endpoints of clinical response will be analyzed using the Cochran-Mantel-Haenszel test for stratified categorical data. Early dropouts or participants whose response status is unable to be assessed at the end of 30-week dosing period will be classified as non-responders. More detailed statistical analysis strategies will be documented in the Statistical Analysis Plan (SAP). <u>Secondary efficacy endpoints analyses</u> The general analytical approach for the secondary efficacy endpoints are the following: • To minimize false discovery among the secondary endpoints, appropriate methods to control Type 1 errors will be employed; further details will be specified in the SAP. • Categorical endpoints will be analyzed by the Cochran-Mantel-Haenszel test taking into account of stratification factors or Chi-square test without adjusting for stratification factors, whenever appropriate. • Continuous variables will be analyzed by analysis of variance (ANOVA) model comparing between group means.

	• Ordinal variables, such as NYHA functional class, will be converted quantitatively as ordinal scores (I-IV classes to 1-4 scores, respectively) and analyzed as continuous variables. [redacted] **Safety Analyses** Safety data will be analyzed using descriptive statistics without formal statistical testing. The safety analysis will focus on the treatment-emergent AE period. This period is defined as the time from the first administration of the IMP to the last administration of the IMP + 56 days.
[redacted]	[redacted]
Study Committees	• Steering Committee • Clinical Event Adjudication Committee • Independent Data Monitoring Committee

Figure 1 Study Schema



Abbreviations: CPET, cardiopulmonary exercise testing; ECG, electrocardiogram; PK, pharmacokinetics; QD, once daily; stress echo, post-exercise stress echocardiography; TTE, transthoracic echocardiogram; wks, weeks.

Table 1 Schedule of Study Procedures

Assessment[a]	Screening[b] Day -35 to Day -1	Day 1	Week 4 (±7 d)	Week 6 (±7 d)	Week 8 (±7 d)	Week 12 (±7 d)	Week 14 (±7 d)	Week 18 (±7 d)	Week 22 (±7 d)	Week 26 (±7 d)	ET[c]	Week 30 (±7 d)/ EOT	Week 34 (±7 d) (call)	Week 38 (±7 d)/ EOS
General Procedures														
Informed consent	X													
Medical history	X													
Randomization		X												
Physical examination[d]	X	X	X	X		X		X	X	X	X	X		X
Body height	X													
Body weight (in clinic)	X										X	X		
Prior/concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs/SAEs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ICD information downloaded[f]	X					X					X	X		
ECG[g]	X	X	X	X		X		X	X	X	X	X		X
Vital signs[h]	X	X	X	X		X		X	X	X	X	X		X
Cardiopulmonary Assessments														
Resting TTE[i]	X	X	X	X		X		X	X	X	X	X		X
Post-exercise stress echocardiography[j]	X										X	X[j]		
CPET[k]	X										X	X		
Cardiac monitoring device[l]	X					X				X				
Accelerometer attached[m]	X									X				
Laboratory Assessments														
Hepatitis panel and HIV test	X													
[redacted]			X	X	X	X		X	X	X	X	X		X
Coagulation panel	X	X		X				X			X	X		
Chemistry	X	X		X				X			X	X		X
Hematology	X										X	X		X
Urinalysis	X										X	X		

Footnotes and abbreviations defined on last page of table.

Table 1 Schedule of Study Procedures (Cont'd)

Assessment[a]	Screening[b] Day -35 to Day -1	Day 1	Week 4 (±7 d)	Week 6 (±7 d)	Week 8 (±7 d)	Week 12 (±7 d)	Week 14 (±7 d)	Week 18 (±7 d)	Week 22 (±7 d)	Week 26 (±7 d)	ET[c]	Week 30 (±7 d)/ EOT	Week 34 (±7 d) (call)	Week 38 (±7 d)/ EOS
Laboratory Assessments (continued)														
hs-cardiac troponin I	X	X		X				X			X	X		X
NT-proBNP[o]		X	X	X	X	X	X	X	X	X	X	X		X
FSH[p]	X													
Serum pregnancy test (women)[q]	X													
Urine pregnancy test (women)[q]		X	X		X	X		X	X	X	X	X	X	X
[redacted]		X												
[redacted]	X													
[redacted]		X									X	X		
Symptom Assessment														
[redacted]	X	X	X	X	X	X	X	X	X	X	X	X		X
Patient-reported outcomes	[redacted]s													
Investigational Medical Product														
IMP QD		←	—	—	—	—	—	—	—	—		→		
IMP administered at site[t]		X	X	X	X	X	X	X	X	X		X		
IMP compliance[u]			X	X	X	X	X	X	X	X	X	X		
Substudy														
[redacted]		X										X		

Abbreviations: AE, adverse event; BP, blood pressure; call, telephone contact; CMR, cardiac magnetic resonance imaging; CPET, cardiopulmonary exercise testing; CYP, cytochrome P450; d, day; DNA, deoxyribonucleic acid; ECG, electrocardiogram; EOS, end of study; EOT, end of treatment, ET, early termination; FSH, follicle-stimulating hormone; HCM, hypertrophic cardiomyopathy; HIV, human immunodeficiency virus; HR, heart rate; hs, high-sensitivity; ICD, implantable cardioverter-defibrillator; ICF, informed consent form; IMP, investigational medicinal product; LVOT, left ventricular outflow tract; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; PK, pharmacokinetic; PRO, patient-reported outcomes; QD, once daily; QTcF, Fridericia correction; SAE, serious adverse event; TTE, transthoracic echocardiography.

[a] Preferred order of assessments is ECG, vital signs, PK, and TTE, all prior to study drug dosing unless otherwise described below.

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

[c] The ET visit will be scheduled as soon as possible after the participant permanently discontinues study drug. The participant will be encouraged to participate in the remaining scheduled study visits, particularly the Week 30 visit and the Week 38/EOS visit. If a participant permanently discontinues treatment at or before Week 22, the final visit will be at Week 30.

[d] At Screening, ET, Week 30/EOT, and Week 38, a complete physical examination will be conducted, including a neurological examination. At all other visits, an abbreviated cardiopulmonary physical examination will be conducted, with other systems assessed as directed by interval history.

[e] Changes in baseline conditions from once the ICF is signed will be recorded as an AE. All changes unless otherwise specified that occur after the administration of study drug will be considered treatment-emergent AEs. This assessment will occur either by phone call or an in-person visit.

[f] For participants who have ICDs, information including rhythm strips and events will be downloaded from the ICDs at baseline, at Week 12, and at Week 30, or as clinically indicated after any ICD discharge interrogation occurring during the double-blind treatment period.

[g] Twelve (12)-lead ECGs will be performed after 10 minutes of rest at Screening and prior to dosing at all onsite study visits (except Weeks 8 and 14). Each time an ECG is completed, a 10-second paper ECG will be obtained and maintained in the study participant's source documentation. QTcF value from Day 1 ECG will not be used for eligibility or for temporary discontinuation. The Day 1 QTcF value will be used as the baseline to determine percent change at future visits when criteria for temporary discontinuation are applied. (Note: If for any reason a D1 QTcF is not determined, then QTcF from screening ECG will be used in percent change calculation.)

[h] At Screening, ET, Week 30/EOT, and Week 38, complete vital signs including temperature, HR, respiratory rate, and BP will be obtained. At all other visits, only HR and BP are required. If PK sampling is conducted at a visit, vital signs should be collected before PK sampling. Vital signs should be taken with the study participant in the same position at all visits. BP should be taken via an automated recorder after resting for at least 5 minutes.

[i] Resting TTE should be performed prior to post-exercise stress echocardiography or CPET. Resting TTE images and views will be acquired at each onsite visit prior to dosing as detailed in the echo site instruction manual. Instantaneous LVOT peak gradient (resting) and provoked LVOT peak gradient (Valsalva maneuver) will be assessed by the core laboratory. Left ventricular ejection fraction (LVEF) will be measured at the clinical site by the certified site sonographer and subsequently by the core laboratory. The LVEF site read will be kept blinded from the investigator and other study site personnel, except in case of locally measured LVEF≤30%.

[j] For post-exercise stress echocardiography, participants will undergo a standard symptom-limited exercise test after a 4-hour fast by standardized treadmill or bicycle ergometer during Screening and Week 30/EOT prior to dosing. Instantaneous LVOT peak gradient will be assessed immediately post-exercise by TTE. Post-exercise stress echocardiography may be performed on a different day than CPET. If the 2 procedures are performed on the same day, participants must exercise only once, and participants will undergo CPET and then post-exercise TTE. Post-exercise stress echocardiography should be acquired the same day or within 72 hours of the Resting TTE and should also be performed as close as possible to ET if it occurs. If post-exercise stress echocardiography and CPET are performed on different days, the same sequence of visits must be performed for both screening and EOT.

[k] CPET by standardized treadmill or bicycle ergometer will be performed during Screening and at Week 30/EOT prior to dosing. CPET is done after a 4-hour fast. Record the fasting status and the date and time of the last dose taken prior to CPET. Any concomitant medication may be administered prior to all exercise testing. CPET should also be performed as close as possible to ET if it occurs.

[l] A cardiac monitoring device will be applied during Screening, Week 12, and at the Week 26 visits and retrieved at the Day 1, Week 14, and Week 30 visits, respectively.

[m] An accelerometer will be fastened to the participant's wrist at Screening (at least 11 days before Day 1) and at the Week 26 visit to collect data on activity. Participants will return the accelerometer at the next study visit for data upload and analysis.

[n] Participants should not take study drug on day of visit prior to blood draw for PK. PK sample will be collected ≤2 hours before dosing. Additionally, on Week 30 (last dose), another PK sample will be collected within 1 to 2 hours postdose.

[o] NT-proBNP should be drawn before exercise testing if exercise testing is being performed that day.

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

[q] Pregnancy testing for all females of childbearing potential: serum pregnancy test at Screening; urine pregnancy test at all other visits shown (every 4-6 weeks), and conduct serum test if any urine test is positive. The Week 34 pregnancy testing will be conducted at home.

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

[s] The pharmacogenetic panel will include CYP 2C19 genotyping and potentially additional DNA sequencing. Pharmacogenetic Screening for CYP 2C19 genotyping will occur at Screening; samples from screen failures must be destroyed.

[t] At all onsite visits, study drug will be administered at the investigational site to facilitate collection of PK samples ≤ 2 hours prior to dosing. Note: There is no PK sample at Day 1 or Week 14. With the exception of Week 30 when a PK sample is also drawn within 1 to 2 hours postdose, Study drug will be administered at the end of the visit when all other assessments have been done, including any drawing of blood.

[u] All participants will return their study drug dosing containers to the site pharmacy for capsule counts. Refer to the Pharmacy Manual for details.

[v] The CMR substudy assessment can be completed up to 5 days before the Day 1 visit and up to 5 days before the EOT visit.

Table 2 Schedule of Patient-reported Outcomes Assessments

PRO Assessment[a]	Screening Day -35 to Day -1	Day 1	Week 4 (±7 d)	Week 6 (±7 d)	Week 10 (±7 d) (home)	Week 12 (±7 d)	Week 14 (±7 d)	Week 18 (±7 d)	Week 22 (±7 d)	Week 26 (±7 d)	Week 30/ EOT (±7 d)	Week 38/ EOS (±7 d)
[redacted]	X[b]	←	—	→	X[c]		X[c]	X[c]	X[c]	X[c]	X[c]	X[c]
[redacted]	X[d]			X	X		X	X	X	X	X	X
[redacted]				X	X		X	X	X	X	X	X
[redacted]		X		X		X		X			X	X
[redacted]		X		X		X		X			X	X
[redacted]		X		X		X		X			X	X

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

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

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

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

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

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

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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
ASA	alcohol septal ablation
AST	aspartate aminotransferase
BP	blood pressure
CEAC	Clinical Event Adjudication Committee
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CMH	Cochran-Mantel-Haenszel
CMR	cardiac magnetic resonance imaging
CPET	cardiopulmonary exercise test or testing
CRF	case report form
CV	cardiovascular
CYP	cytochrome P450
DILI	drug-induced liver injury
EC	ethics committee; refers to an IRB or IEC or equivalent
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ER	emergency room
EM	extensive metabolizers
EQ-5D-5L	EuroQol five dimensions 5-level questionnaire
EOS	end of study
EOT	end of treatment
ESC	European Society of Cardiology
ET	early termination
EV	expired ventilation
FDA	The United States Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HCM	hypertrophic cardiomyopathy
HCMSQ	hypertrophic cardiopathy symptom questionnaire
HF	heart failure
HIV	human immunodeficiency virus
HLGT	high-level group term
HLT	high-level term
HR	heart rate

IB	Investigator's Brochure
ICD	implantable cardioverter-defibrillator
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
ITT	intention-to-treat
IUD	intrauterine device
IUS	intrauterine system
IXRS	interactive response system
KCCQ-23	23-item Kansas City Cardiomyopathy Questionnaire
LV	left ventricular
LVEF	left ventricular ejection fraction
LVOT	left ventricular outflow tract
MAD	multiple ascending-dose
MedDRA	Medical Dictionary for Regulatory Activities
MR	mitral regurgitation
NASH	nonalcoholic steatohepatitis
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
oHCM	obstructive hypertrophic cardiomyopathy
OP	outpatient
PD	pharmacodynamics(s)
PGIC	Patient Global Impression of Change questionnaire
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PRO	patient-reported outcomes
PT	preferred term
pVO_2	peak oxygen consumption
QD	once daily
QTc	corrected QT interval
QTcF	QT interval with Fridericia correction
RER	respiratory exchange ratio
RNA	ribonucleic acid
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	Steering Committee
SCD	sudden cardiac death
SD	standard deviation

SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
T	time (variable)
$t_{1/2}$	terminal half-life
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TTE	transthoracic echocardiography, transthoracic echocardiogram
ULN	upper limit of normal
US	United States
VAS	visual analog scale
VCO_2	carbon dioxide production
VE	expired ventilation
VF	ventricular fibrillation
VT	ventricular tachycardia
VO_2	oxygen uptake
WPAI-SHP	Work Productivity and Activity Impairment questionnaire

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is:

- To compare the effect of a 30-week course of mavacamten with placebo on clinical response comprising of exercise capacity and clinical symptoms in participants with symptomatic oHCM

3.2 Secondary Objectives

The secondary efficacy objectives of this study are:

- To compare the effect of a 30-week course of mavacamten with placebo on symptoms and LVOT obstruction as determined by Doppler echocardiography
- To compare the effect of a 30-week course of mavacamten with placebo on exercise capacity, clinical symptoms and Patient Reported Outcomes individually

- To assess the safety and tolerability of mavacamten
- To assess the PK characteristics of mavacamten

[redacted]

4 OVERALL STUDY DESIGN AND PLAN

This is a Phase 3, double-blind, randomized, placebo-controlled, multicenter, international, parallel-group study to evaluate the safety, tolerability, and efficacy of mavacamten compared with placebo (1:1) in participants with symptomatic oHCM. Approximately 220 participants will be enrolled. [redacted] Randomization will be stratified according to NYHA functional classification (II or III), current treatment with β-blocker (yes or no), planned type of ergometer used during the study (treadmill or exercise bicycle), and consent for the CMR substudy (yes or no).

The study will comprise 3 periods (Figure 1).

Screening period (Day -35 to Day -1): Participants will undergo a variety of general, cardiopulmonary, laboratory, symptom, and PRO assessments over 1 to 2 days (Table 1 and Table 2) in order to assess eligibility criteria, including presence of HCM and presence of obstruction (at rest or provoked). The investigator should also confirm that participants can adequately perform a Valsalva maneuver. Key Screening tests include ECG; TTE conducted at rest, with Valsalva maneuver, and post-exercise; and CPET. The following screening assessments may be repeated, as long as they fall within the 35-days screening window: blood tests, ECG, and/or TTE. Repeat assessments are allowed if central core labs require a repeat submission due to quality and in order to better assess inclusion/exclusion values. Screening test results as reported by core laboratories (electrocardiogram core laboratory, echocardiography core laboratory, and CPET core laboratory) will be used to confirm eligibility for randomization.

- CPET and post-exercise TTE may be conducted on the same day or separate days during the Screening period. If CPET and post-exercise TTE are conducted on the same day, participants must be exercised only once for both procedures, and participants will undergo CPET followed by post-exercise TTE. If the participants undergo CPET and post-exercise TTE on different days, then participants will first undergo resting, Valsalva, and post-exercise TTE (and send the echocardiogram to the core laboratory to determine LVOT gradients for each) and undergo CPET on a later day. If CPET and post-exercise TTE are performed on different days, the same sequence of visits must be used for both screening and EOT.
- Participants who are receiving treatment for their oHCM condition should be on optimal medical therapy for their condition as determined by the investigator and informed by HCM treatment guidelines (eg, β-blocker, verapamil, or diltiazem). This treatment should be stable and well-tolerated for at least 2 weeks prior to Screening. Concomitant medications at Screening should be maintained at a stable dose throughout the study, unless safety or tolerability concerns arise.
- A participant may also be considered for enrollment if the investigator has determined that receiving no treatment for their underlying oHCM condition is a valid option (eg, in case of prior intolerance or contra-indication to β-blockers). In such cases, there should be no plan to initiate treatment (with β-blocker, verapamil, or diltiazem) after randomization in the study.

Participants who screen fail may be considered for rescreening based on the investigator's discretion, taking into consideration the reason(s) for screen fail. One attempt at rescreening will be allowed, and all procedures must be repeated.

Double-blind treatment period (Day 1 [randomization] to Week 30/EOT): Participants who meet all eligibility criteria will first be randomized via an interactive response system (IXRS) in a 1:1 ratio to receive treatment with mavacamten 5 mg starting dose or matching placebo QD.

Overall, the 30-week, double-blind treatment period includes a total of 10 scheduled clinic visits, allowing the maintenance of participant contact every 2 to 4 weeks (Table 1 and Table 2). All clinic visits will include but are not limited to: clinical evaluation (symptoms, PRO assessments, adverse event (AE)/SAE assessments, concomitant medications). At all visits except the Week 8 and Week 14 visits, ECGs, TTEs, and laboratory assessments will also be conducted. Blood for PK (trough plasma concentrations) will be drawn at all visits except Day 1 and Week 14. Results of TTEs performed at each scheduled visit following randomization should be kept blinded to the investigator and study site personnel. An exception may occur if LVEF ≤30% is measured at the site, then the investigator will be notified and study drug will be permanently discontinued (see Section 7.3.3).

After randomization, participants will first be seen at Week 4 for an initial evaluation of clinical tolerability and safety. PK sample collection and blinded TTE will be performed at this visit. In the unlikely event that the results from Week 4 exceed PK/PD criteria

(700 ng/mL < trough PK < 1000 ng/mL), the dose will be decreased at Week 6 to 2.5 mg via the IXRS (see Table 3).

Participants will subsequently be seen at Week 6 and Week 12 for repeat evaluation. Blinded assessments including trough PK, and TTE measures of LVEF and LVOT gradient with Valsalva will be performed to guide dose adjustment via the IXRS. At Week 8 and Week 14, the dose will be adjusted (dose increase, dose decrease, dose remain unchanged) based upon results of Week 6 and Week 12 assessments, respectively, as specified in Section 7.3.1.

For added safety, a Week 8 blood sample will be drawn to determine trough plasma PK. If PK is greater than 700 and less than 1000 ng/mL, then an unscheduled visit will be arranged 2 weeks later to reduce dose as specified in Section 7.3.3. At any time if PK plasma concentration ≥ 1000 ng/mL, then study drug will be temporarily discontinued.

After Week 14, there are no additional scheduled dose titrations. Blinded assessments at Weeks 18, 22, and 26 can inform dose reduction or temporary discontinuation of study drug based on predefined criteria detailed in Section 7.3.2. Whenever a mavacamten dose is decreased, the participant will continue on the reduced dose to the EOT (Week 30) unless further safety concerns or intolerability arise.

At Week 30/EOT, participants will complete post-exercise TTE (between Week 26 and Week 30) and CPET (at Week 30). For any participants permanently discontinuing treatment prior to Week 30, an early termination (ET) visit should be conducted as soon as possible, including CPET and post-exercise TTE. Participants with ET will also be encouraged to complete all remaining study visits and assessments, including Week 30 (see Section 10.1.4).

Post-treatment follow-up period (Week 30/EOT to Week 38/end of study [EOS]): After the end of the double-blind treatment period (Week 30), participants will be contacted by phone at Week 34 and return at Week 38 for an EOS visit. At the EOS visit, baseline resting assessments will be repeated. This posttreatment follow-up period applies only to participants who are receiving study drug after Week 22.

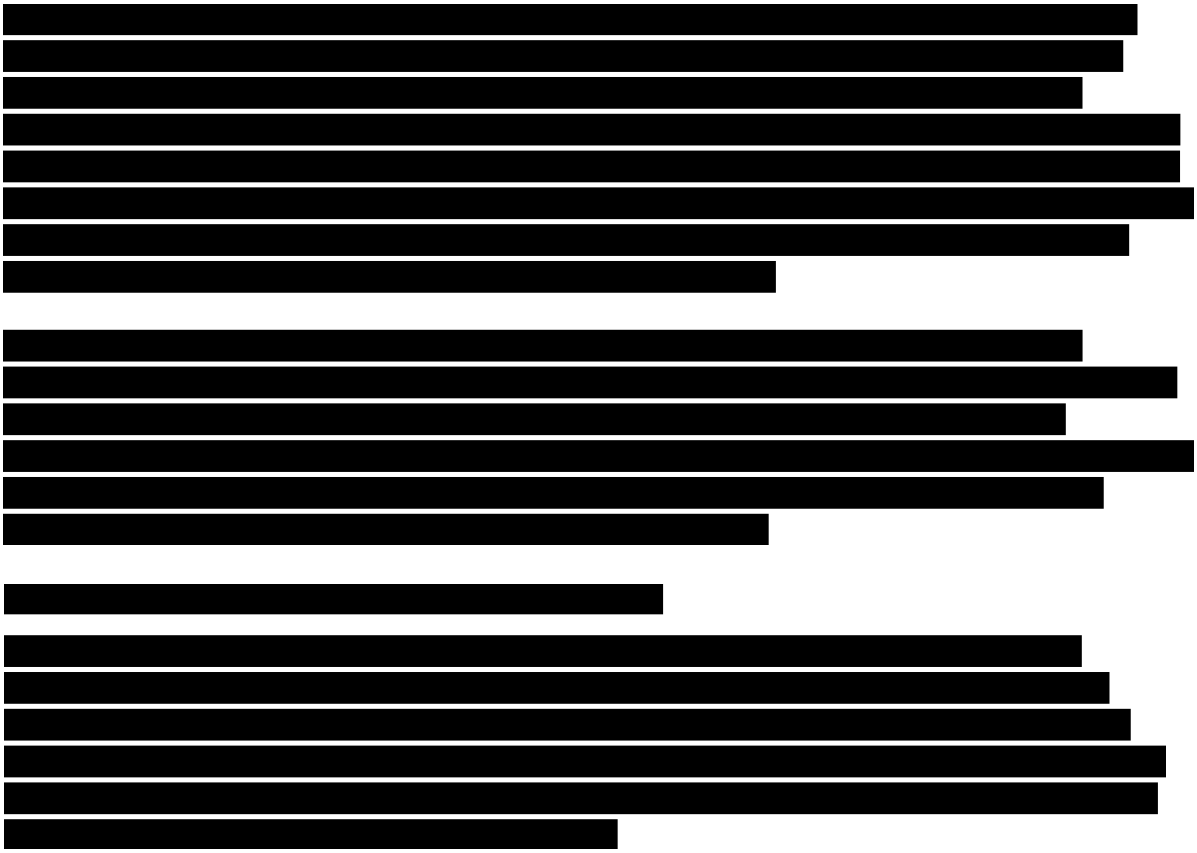
Description of Patient-reported Outcomes

PRO assessments will be completed on an electronic device provided to each participant during the Screening period (see Sections 9.1.3 and 9.1.4). Data from these PRO assessments will not be made available to the investigators and other site personnel throughout the study. Participants will first be informed of this when they fill out the consent form that is required in order to participate in the trial. The form will include information explaining that the PRO information gathered via the device is not shared with their healthcare provider and they should therefore report any concerning symptoms directly to their physician. Participants will then be reminded of this each time they go to complete the assessment on their handheld device. When the participant logs onto their handheld device to complete the assessments, a message screen will be shown advising the participant to consult their healthcare provider if they have any concerning symptoms. The participant will not be able to continue with the PRO assessments until they have acknowledged that they have read this message. The exact message text states:

Please note: If you are having any symptoms, health issues, or other concerns, please be sure to discuss these with your doctor or nurse. The answers you provide to the questions are for research purposes only and are not being routinely shared with the members of your healthcare team. Please note, however, that you are always free to share any and all information with your doctor including information about the answers you will provide in this questionnaire that may help address your concerns.

Description of Other Procedures and Assessments

Participants with implantable cardioverter-defibrillators (ICDs) will have their data downloaded at baseline, at Week 12, and at Week 30, or as clinically indicated whenever device discharge is interrogated and/or prior to any device reset.



4.1 Study Duration

The expected study duration is approximately 43 weeks: up to 5 weeks for Screening, a 30-week treatment period, and an 8-week posttreatment follow-up period (±7 days).

4.2 Study Committees

4.2.1 Steering Committee

The Steering Committee (SC) 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-461-005 EXPLORER-HCM study. The SC will be composed of members who are experts in cardiovascular disease, including HCM, with relevant clinical and methodological expertise. The SC will include 2 co-chairs, approximately 5 members, and Sponsor representatives. All SC members will remain blinded to treatment assignments (unless unblinding is required for participant safety) until the conclusion of the study. Specific responsibilities will be further described in the SC Charter.

4.2.2 Clinical Event Adjudication Committee

The Clinical Event Adjudication Committee (CEAC) will be assembled to ensure quality and timely event reporting. The role of the CEAC will be to adjudicate a pre-specified set of safety endpoints, including major adverse cardiac events (eg, death, stroke, acute myocardial infarction) as listed in Section 9.3. The committee will be composed of experienced cardiovascular specialists and experts who will review all pertinent blinded, clinical, and diagnostic source documentation and independently adjudicate any cardiovascular (CV) events. The processes to identify coded events for submission to the committee members for adjudication and their completion of electronic case report forms (eCRFs) will be described in a separate CEAC Charter. The CEAC full committee will meet quarterly or as needed to review discordant cases and conduct their responsibilities as outlined in the CEAC Charter. The CEAC Charter and associated data management plan will also describe how the communication of information to and from the CEAC will be handled to ensure timely delivery of adjudicated data for Independent Data Monitoring Committee (IDMC) meetings.

4.2.3 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 with respect to safeguarding the interest of study participants, assessing interim unblinded safety data, and advising the Sponsor on important emerging study conduct issues. The IDMC may formulate recommendations in relation to the evaluation procedures and methodologies being employed to survey and detect potential safety signals. Meeting frequency, membership, and conduct will be described in the IDMC Charter.

5 SELECTION OF STUDY POPULATION

5.1 General Study Population and Clinical Sites

Approximately 220 participants with symptomatic oHCM are expected to enroll in this study at up to ~90 clinical sites worldwide.

5.2 Inclusion Criteria

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

1. Able to understand and comply with the study procedures, understand the risks involved in the study, and provide written informed consent according to federal, local, and institutional guidelines before the first study-specific procedure

2. Is at least 18 years old at Screening
3. Body weight is greater than 45 kg at Screening
4. Has adequate acoustic windows to enable accurate TTEs (refer to Echocardiography Site Instruction Manual)
5. Diagnosed with oHCM consistent with current AACF/AMA and ESC guidelines, ie, satisfy both criteria below (criteria to be documented by the echocardiography core laboratory):
    a. Has unexplained LV hypertrophy with nondilated ventricular chambers in the absence of other cardiac (eg, hypertension, aortic stenosis) or systemic disease and with maximal LV wall thickness ≥15 mm (or ≥13 mm with positive family history of HCM) as determined by core laboratory interpretation, and
    b. Has LVOT peak gradient ≥50 mmHg during Screening as assessed by echocardiography at rest, after Valsalva maneuver, or post-exercise (confirmed by echocardiography core laboratory interpretation)
6. Has documented LVEF ≥55% by echocardiography core laboratory read of Screening TTE at rest
7. Has LVOT gradient with Valsalva maneuver at Screening TTE of ≥30 mmHg, determined by echocardiography core laboratory
8. Has NYHA Functional Class II or III symptoms at Screening
9. Has documented oxygen saturation at rest ≥90% at Screening
10. Is able to perform an upright CPET and has a respiratory exchange ratio (RER) ≥1.0 at Screening per central reading; if the RER is between 0.91 and 1.0, the participant may be enrolled only if it is determined by the central CPET laboratory that peak exercise has been achieved in the subject (the only permitted reasons for subpeak performance are [1] a decrease in systolic blood pressure (SBP) or [2] severe angina as described in the CPET Laboratory Manual)
11. Female participants must not be pregnant or lactating and, if sexually active, must use one of the following highly effective birth control methods from the Screening visit through 3 months after the last dose of investigational medicinal product (IMP).
    - combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation or progestogen-only hormonal contraception associated with inhibition of ovulation by oral, implantable, or injectable route of administration
    - intrauterine device (IUD)
    - intrauterine hormone-releasing system (IUS)
    - bilateral tubal occlusion
    - Female is surgically sterile for 6 months or postmenopausal for 1 year. Permanent sterilization includes hysterectomy, bilateral oophorectomy, bilateral salpingectomy, and/or documented bilateral tubal occlusion at least 6 months prior to Screening.

Females are considered postmenopausal if they have had amenorrhea for at least 1 year or more following cessation of all exogenous hormonal treatments and follicle stimulating hormone levels (FSH) are in the postmenopausal range.

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

5.3 Exclusion Criteria

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

1. Previously participated in a clinical study with mavacamten
2. Hypersensitivity to any of the components of the mavacamten formulation
3. Participated in a clinical trial in which the participant received any investigational drug (or is 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. Has any medical condition that precludes upright exercise stress testing
6. Has a history of syncope within 6 months prior to screening or history of sustained ventricular tachyarrhythmia with exercise within 6 months prior to Screening
7. Has a history of resuscitated sudden cardiac arrest (at any time) or known history of appropriate ICD discharge/shock for life-threatening ventricular arrhythmia within 6 months prior to Screening (Note: history of anti-tachycardia pacing (ATP) within 6 months or ever is allowed)
8. Has paroxysmal, intermittent atrial fibrillation with atrial fibrillation present per the investigator's evaluation of the participant's ECG at the time of Screening
9. Has persistent or permanent atrial fibrillation not on anticoagulation for at least 4 weeks prior to Screening and/or not adequately rate controlled within 6 months of Screening (Note – patients with persistent or permanent atrial fibrillation who are anticoagulated and adequately rate-controlled are allowed)
10. Current treatment (within 14 days prior to Screening) or planned treatment during the study with disopyramide or ranolazine
11. Current treatment (within 14 days prior to Screening) or planned treatment during the study with a combination of β-blockers and verapamil or a combination of β-blockers and diltiazem
12. For individuals on β-blockers, verapamil, or diltiazem, any dose adjustment of that medication <14 days prior to Screening or an anticipated change in treatment regimen using these medications during the study
13. Has been successfully treated with invasive septal reduction (surgical myectomy or percutaneous ASA) within 6 months prior to Screening or plans to have either of these treatments during the study (note: individuals with myectomy or percutaneous ASA

performed >6 months prior to Screening may be enrolled if study eligibility criteria for LVOT gradient criteria are met)

14. ICD placement or pulse generator change within 2 months prior to Screening or planned new ICD placement during the study (pulse generator changes, if needed during the study, are allowed)
15. Has QT interval with Fridericia correction (QTcF) >500 ms at Screening or any other ECG abnormality considered by the investigator to pose a risk to participant safety (eg, second-degree atrioventricular block type II)
16. Has documented obstructive coronary artery disease (>70% stenosis in one or more epicardial coronary arteries) or history of myocardial infarction
17. Has known moderate or severe (as per investigator's judgment) aortic valve stenosis at Screening
18. Has any acute or serious comorbid condition (eg, major infection or hematologic, renal, metabolic, gastrointestinal, or endocrine dysfunction) that, in the judgment of the investigator, could lead to premature termination of study participation or interfere with the measurement or interpretation of the efficacy and safety assessments in the study
19. Has pulmonary disease that limits exercise capacity or systemic arterial oxygen saturation
20. History of malignant disease within 10 years of Screening:
    - Participants who have been successfully treated for nonmetastatic cutaneous squamous cell or basal cell carcinoma or have been adequately treated for cervical carcinoma in situ or breast ductal carcinoma in situ (DCIS) can be included in the study
    - Participants with other malignancies who are cancer-free for more than 10 years before Screening can be included in the study
21. Has 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 participant with safety laboratory parameters outside normal limits may be included if he or she meets all of the following criteria:
    - The safety laboratory parameter outside normal limits is considered by the investigator to be clinically not significant
    - If there is an alanine aminotransferase or aspartate aminotransferase result, the value must be <3 × the upper limit of the laboratory reference range
    - The body size–adjusted estimated glomerular filtration rate is ≥30 mL/min/1.73 m^2
22. Has a positive serologic test at Screening for infection with human immunodeficiency virus, hepatitis C virus, or hepatitis B virus
23. Has a history or evidence of any other clinically significant disorder, condition, or disease that, in the opinion of the investigator, would pose a risk to participant safety or interfere with the study evaluation, procedures, or completion

24. Is currently taking, or has taken within 14 days prior to Screening, a prohibited medication, such as a cytochrome P450 (CYP) 2C19 inhibitor (eg, omeprazole or esomeprazole), a strong CYP 3A4 inhibitor, or St. John's Wort (see Appendix 2 for more details). Alternatives, such as pantoprazole are allowed and may be discussed with the medical monitor
25. Prior treatment with cardiotoxic agents such as doxorubicin or similar (see Appendix 2)
26. Unable to comply with the study requirements, including the number of required visits to the clinical site
27. Is a first degree relative of personnel directly affiliated with the study at the clinical study site, any study vendor, or the study Sponsor

[redacted]

5.5 Screening and Enrollment

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

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

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

6 RANDOMIZATION AND BLINDING PROCEDURES

6.1 Randomization

Participants who meet the inclusion/exclusion criteria will be randomized via an IXRS in a 1:1 ratio to receive double-blind treatment with either mavacamten 5 mg or matching placebo QD. Randomization will be stratified according to NYHA functional classification (II or III), current treatment with β-blocker (yes or no), type of ergometer (treadmill or exercise bicycle), and consent for the CMR substudy (yes or no).

6.2 Study Blinding

Participants will be randomized to receive mavacamten or matching placebo in a double-blind manner such that the principal investigator, site staff including the pharmacist, and the participant will not know which study drug is being administered. In addition, the Sponsor, the central and core laboratories, and clinical site monitors will be blinded to assigned treatment. Mavacamten and matching placebo will be identical in appearance in order to preserve the blind. Study drug (mavacamten or matching placebo) will be labeled with a unique identifying number that will be assigned to a participant through the IXRS.

Blinded results (ie, echocardiography results, and PK data) will be transferred to the IXRS by the respective core laboratories in order to perform dose adjustments and dose discontinuations in a blinded manner. In addition, sham dose discontinuation and unscheduled visits, if necessary, will be performed in the placebo arm in order to keep the blind. However, site personnel who perform specific tasks such as reviewing echocardiograms for safety may be unblinded (see Study Reference Manual). In the case of LVEF ≤30% the investigator will be notified as described in Section 7.3.3. The pharmacovigilance team will be unblinded for suspected unexpected serious adverse reaction (SUSAR) reporting. The IDMC may also be unblinded to treatment allocation and all safety and efficacy data.

6.3 Methods for Unblinding

All efforts should be made to keep participants blinded to treatment assignment. However, participants 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 participant. Unblinding by the investigator independently of the Sponsor also may occur if an AE or toxicity necessitates identification of the medication for the welfare of the participant. Please refer to the Suvoda Interactive Web Response System Manual for the unblinding process and contact information.

7 STUDY TREATMENT

Study drug is defined as mavacamten (MYK-461) or placebo.

All randomized study participants will receive either mavacamten or placebo in a double-blinded manner.

7.1 Mavacamten and Matching Placebo, Administration, and Schedule

Mavacamten capsules and matching placebo have the same appearance. The study drug presentation is size 2, blue opaque capsules printed with a yellow band on the body and black band on the cap. Each capsule contains white to off-white powder. The active capsules are supplied in 4 strengths: 2.5 mg, 5 mg, 10 mg, and 15 mg.

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

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

Study drug will be supplied to participants in 30-count high-density polyethylene bottles that are appropriately labeled. Refer to Table 1 for the complete schedule of study drug administration. Participants will take study drug as directed by the study investigator. The participants will be instructed to store the study drug capsules and bottles in a cool, dry place. Study drug should be taken with approximately 8 ounces (48 tablespoons or ~235 mL) of water.

7.2 Treatment Compliance

Compliance with study drug will be monitored by capsule count at all study visits. Refer to the Pharmacy Manual for details.

Participants should be instructed to take the study drug at approximately the same time every day (±8 hours). If the dosing window is missed, the participant should not take study drug that day. Participants should never receive 2 doses of study drug within an 8-hour period.

On study visit days, participants should wait to take study drug until after they reach the clinic and have a PK blood sample taken as indicated in the schedule of study procedures (Table 1). Any concomitant medication may to be administered prior to all exercise testing.

7.3 Dose Adjustments

7.3.1 Blinded Dose Adjustments During Double-blind Treatment Period

7.3.1.1 Dose Titration Period (Day 1 to Week 14)

The double-blind treatment period will include a two-step dose titration scheme at Week 8 and Week 14 designed to achieve safe and effective dosing for each participant based on their own PK/PD response parameters (Figure 1 and Table 3).

In this study, the starting dose of study drug is mavacamten 5 mg or matching placebo QD, and each participant will receive this dose of study drug from Day 1 through Week 8 unless a

PK/PD criterion is met at Week 4, in which case the dose will be reduced at Week 6 (Table 3).

At Weeks 8 and 14, participants will undergo dose adjustment (dose increase, dose decrease, or dose unchanged) based on their results from PK/PD assessments at Week 6 and Week 12, respectively (Table 3). Note that Table 3 is provided for IXRS programming. Sites and investigators will not be actively adjusting doses. All dose adjustments will occur in a double-blind manner via IXRS, and all participants, whether receiving mavacamten or matching placebo, will undergo assessments that could lead to a blinded dose adjustment. However, note that participants who are on placebo will remain on placebo (in blinded fashion) unless the participant has a temporary discontinuation as described in Section 7.3.2 or a permanent treatment discontinuation as described in Section 7.3.3 and Section 10.1.3.

For added safety, a Week 8 blood sample will be drawn to determine trough plasma PK. If PK is greater than 700 and less than 1000 ng/mL, then an unscheduled visit will be arranged 2 weeks later to reduce dose (see Table 3). Dose reduction will occur via IXRS. To avoid potential bias the IXRS will randomly select a participant from the placebo arm to undergo an unscheduled follow-up visit (see also Section 6.2).

If the mavacamten dose is decreased at any time during the study, then the participant will continue on the reduced dose to the EOT (Week 30) unless safety concerns or intolerability arise requiring further dose reduction or dose discontinuation.

Based on PK modeling informed by prior mavacamten clinical studies, and depending on the demographics of enrolled patients, it is estimated that the following percentages of participants will reach the target steady-state concentrations for the following doses: 2.5 mg (< 1%), 5 mg (5–20%), 10 mg (40–50%), and 15 mg (30–55%).

If the PK/PD criteria for down-titration are met, then dose reduction will be implemented as follows:

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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

7.3.1.2 Dosing Period (Week 14 to Week 30)

After the second dose titration at Week 14, there are no further up-titrations; the intent is for dose to remain unchanged unless for safety or other reasons for premature discontinuation (see Section 7.3.2 and Section 10.1). After Week 14, participants will return to the clinical site for monitoring at scheduled 4-week intervals (Weeks 18, 22, 26, and 30 [±7 days]). At each visit, AEs, concomitant medications, and symptoms will be assessed, and ECG, plasma PK, and TTE will be performed for ongoing safety monitoring. Compliance with study drug will also be monitored by capsule count at each visit. If PK/PD criteria are met, then an unscheduled visit 2 weeks later will be required to reduce dose as shown in Table 4.

[redacted]

7.3.2 Blinded Dose Adjustment Leading to Temporary Discontinuation

In addition to the blinded dose adjustments described above (which are not preceded by dose discontinuation), at any time (T) during the treatment period, dosing may be temporarily discontinued in the case of exaggerated pharmacologic effect (systolic dysfunction), higher than expected plasma concentration, or excessive QTcF prolongation as described below.

If participant has a resting LVEF <50%, plasma drug concentration ≥1000 ng/mL, or QTcF stopping criteria described below, as determined by the echocardiography central laboratory, PK analysis laboratory, or ECG core laboratory, respectively, it will be communicated to the investigator and Sponsor that a criterion for temporary discontinuation has been met. Upon receipt of this information, the study site/investigator will contact the participant by telephone and instruct the participant to discontinue study drug and to return for an onsite visit within 2 to 4 weeks (T+2 to 4 weeks). This could correspond to a scheduled or unscheduled visit. Note that to avoid potential bias the IXRS will randomly select participant(s) from the placebo arm to undergo an unscheduled follow-up visit (see also Section 6.2).

Criteria for temporary discontinuation due to QTcF prolongation are as follows and depend on QRS width as determined by the ECG core laboratory:

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

At the follow-up visit (T+2 to 4 weeks), ECG, plasma PK, and TTE will be repeated and another unscheduled visit will be planned for 2 weeks later (T+4 to 6 weeks). If LVEF ≥50% AND plasma drug concentration <1000 ng/mL AND QTcF duration is below programmed discontinuation rules, then the study drug will be restarted at a lower dose (at T+6 weeks) for remainder of the study as follows (previous dose → restart dose):

- Placebo → placebo
- 2.5 mg → placebo
- 5 mg → 2.5 mg
- 10 mg → 5 mg
- 15 mg → 10 mg

If LVEF, plasma drug concentration and/or QTcF persist out of range at the follow-up visit, then study drug will be switched permanently to placebo.

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

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

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

7.3.4 Management of Double-blind Treatment in the Case of New or Worsening Heart Failure

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

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

7.4 Hepatotoxicity Stopping and Rechallenge Rules

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

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

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

- TBL >2 × upper limit of normal (ULN) or international normalized ratio >1.5
- AND increased AST or ALT, if the baseline value was <ULN and AST or ALT elevation is >3 × ULN
- AND no other cause for the combination of laboratory abnormalities is immediately apparent. Important potential causes for abnormal AST/ALT or TBL values include, but are not limited to, the following:
  - Obstructive 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 developed than what is noted above, the investigator will determine whether study drug and other protocol-required therapies should be permanently or temporarily discontinued based on participant population and/or severity of the hepatotoxicity or event, as deemed appropriate for the safety of the participant.

7.4.2 Criteria for Conditional Withholding of Study Drug Due to Potential Hepatotoxicity

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

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

OR: ALP >8× ULN at any time

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

7.4.3 Criteria for Rechallenge of Study Drug After Potential Hepatotoxicity

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

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

7.5 Overdose

An overdose is defined as taking more capsules of study drug than directed. An overdose may be suspected by the investigator or spontaneously reported by the participant. An overdose may be symptomatic or asymptomatic.

In the event of suspected overdose, the investigator should contact the medical monitor. No further double-blind treatment should be administered. The participant should be closely monitored clinically for AEs/SAEs, with supportive measures undertaken as clinically indicated. If necessary, corrective measures such as initiation of inotropic support with adrenergic agents, levosimendan, and/or PDE III inhibitors and other supportive measures as described in the 2013 ACCF/AHA Guideline for the Management of Heart Failure [redacted] and in the 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure [redacted] [Table 12.5]) should be implemented.

7.5.1 Reporting and Follow-up of Overdose

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

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8 RISKS AND PRECAUTIONS

8.1 General

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

Safety testing in other mammalian species has demonstrated that dose-limiting toxicity is related to exaggerated pharmacologic effect and not to off-target adverse effects. For overdose, see Section 7.5.

8.2 Pregnancy

8.2.1 Avoidance of Pregnancy

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

8.2.2 Acceptable Forms of Contraception

Highly effective methods of birth control are defined as those that result in a low failure rate (<1% per year) when used consistently and correctly. From the time of Screening through 3 months after the last dose of study drug, female participants should practice true abstinence or use effective means of contraception as follows:

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

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

8.2.3 Reporting and Follow-up of Pregnancies

All pregnancies in female participants and female partners of male participants receiving at least 1 dose of study drug must be reported if they occur anytime from first dose to 3 months after the last dose of study drug. The investigator is responsible for informing MyoKardia within 24 hours of knowledge of the pregnancy even if no AE has occurred. The participant will be asked to provide information on the outcome of the pregnancy, including premature termination. Spontaneous miscarriage and congenital abnormalities will be reported as SAEs.

9 STUDY ASSESSMENTS AND PROCEDURES

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

The following describes the study procedures to be performed during the study. Additional details are provided in Table 1 and Table 2 of this document. When several assessments are to be conducted at the same time point, the preferred order of assessments is ECG, vital signs, PK, and then TTE all prior to study drug dosing. The order of assessments may vary slightly at specific time points (eg, additional 1-hour postdose PK sampling on Day 1 and Week 30/EOT) to facilitate the most contemporaneous performance of the required assessments. Unscheduled or additional safety assessments may be performed if necessary, in the opinion of the investigator. Whenever possible discussion with the medical monitor is encouraged.

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

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9.3 Safety Assessments

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

The following safety endpoints will be adjudicated by the CEAC: Death, stroke, acute myocardial infarction, all hospitalizations (CV and non-CV), heart failure (HF) events (includes HF hospitalizations and urgent emergency room (ER)/outpatient (OP) visits for HF), atrial fibrillation/flutter (new from screening), ICD therapy, resuscitated cardiac arrest, ventricular tachyarrhythmias (includes ventricular tachycardia (VT) and ventricular fibrillation (VF); also any Torsades de Pointe identified during CEAC review).

9.3.1 Medical History

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

9.3.2 Physical Examination

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

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

Body weight will be captured in clinic at Screening and Week 30.

9.3.3 12-lead ECG

12-lead ECG evaluations will be performed after 10 minutes of rest at Screening and at all onsite study visits except for the Day 1, Week 8 and 14 visits. On visits during the treatment

period ECGs will be taken prior to dosing. All ECG data will be sent to a central cardiac laboratory and transmitted to IXRS.

The investigator may perform 12-lead ECG safety assessments if he/she considers it is required for any other safety reason. These assessments should be recorded as an unscheduled assessment.

9.3.4 Cardiac Monitoring Device

At 3 time points during the study, participants will wear a small device to collect continuous HR and rhythm data for approximately 48 hours (Table 1). The monitoring device uses surface electrodes, internal electronics to capture a continuous ECG waveform, removable memory card to store data over 48 hours, and a battery to power the device (see manual). Following a period of data collection, the memory card will be transported to a core laboratory where the continuous ECG waveforms will be uploaded for analysis. The analysis will provide full disclosure capabilities for HR and heart rhythm over the period during which the device was properly applied and functioning. The device will be used to explore the pattern of HR and heart rhythm before and during treatment with study drug.

9.3.5 Vital Signs

Vital signs are to be assessed at each onsite study visit except the Week 8 and 14 visits. At Screening, ET, Week 30/EOT, and Week 38, complete vital signs including temperature, HR, respiratory rate, and blood pressure (BP) will be obtained. At all other visits, only HR and BP are required.

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

At all visits, vital signs will be taken prior to dosing. Alert values will be flagged. Refer to the Study Laboratory Manual for additional details.

9.3.6 Other Safety Assessments

Refer to Section 11 for information on AE assessment and Section 7.6.3 for concomitant therapy assessments.

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

Serum pregnancy testing will be performed at Screening for all females of childbearing potential. In addition, urine pregnancy testing either in clinic or at home will be conducted every 4–6 weeks throughout the study. Confirmatory serum testing will be performed if any urine test is positive.

9.4 Cardiac Magnetic Resonance Imaging Substudy

For qualified participating sites, participants will have the option to participate in the CMR substudy. Approximately 80 participants will be enrolled (~40 per treatment group). Participants will undergo CMR up to 5 days prior to Day 1 and up to 5 days prior to Week 30. Refer to the CMR Substudy Reference Manual for additional details.

9.5 Participant Restrictions During this Study

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

- Starting 72 hours prior to the first dose until the final follow-up visit, participants should not engage in unaccustomed intensive exercise except during protocol-specified exercise tests
- Starting at Screening, participants will be required to abstain from blood or plasma donation until 3 months after the final study visit
- Starting on Day 1 until the final follow-up visit, participants will be asked to abstain from grapefruit or grapefruit juice, Seville oranges, and quinine (eg, tonic water)

Contraception requirements are discussed in Section 8.2.

9.6 Study Procedures by Visit

Study procedures are presented by visit in Table 1 and Table 2. Every effort should be made to avoid protocol deviations.

At the investigator's discretion, unscheduled visits may be conducted for the assessment of AEs, new or worsening symptoms, physical examinations, vital signs, laboratory tests, ECGs, and/or TTEs. The investigator should make best effort to contact the medical monitor before conducting an unblinded TTE if possible. Refer also to Section 7.3.2. All information collected from unscheduled visits will be recorded on the eCRF and included in the clinical database.

9.7 Visit Scheduling

All visits should occur within the visit window (±7 days). If an evaluation is missed, reschedule and perform it as close as possible to the original date.

10 TREATMENT DISCONTINUATION AND WITHDRAWAL FROM STUDY

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

10.1 Treatment Discontinuation

10.1.1 Temporary Treatment Discontinuation

Temporary treatment discontinuation

- Will be implemented when a predefined safety threshold has been met (see Section 7.3.2)
- May be considered by the investigator in the case of an AE/SAE or for another reason

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

If a temporary treatment discontinuation was caused by a safety threshold being met, blinded treatment will be resumed approximately 4 to 6 weeks later, either at a lower dose or with permanent switch to placebo, transmitted via IXRS (see Section 7.3.2).

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

All temporary treatment interruptions should be recorded in the eCRF.

10.1.2 Permanent Treatment Discontinuation

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

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

Any permanent treatment discontinuation should be recorded in the eCRF.

10.1.3 Criteria for Permanent Treatment Discontinuation

The following reasons will lead to permanent treatment discontinuation:

- Pregnancy
- LVEF ≤30% as determined by local site
- New or worsening heart failure associated with systolic dysfunction
- Any breaking of the study blind requested by the investigator
- Continued administration of study drug is considered by the investigator to be detrimental to the participant's safety or well-being
- If all the criteria are met for possible DILI (see Section 7.4.1)
- The participant requests to discontinue study drug
- The Sponsor requests that the participant permanently discontinues study drug

10.1.4 Management of Participants After Permanent Treatment Discontinuation

If a participant permanently discontinues treatment prior to Week 30/EOT, the participant will be asked to undergo an ET visit as soon as possible after stopping study drug, using the procedure normally planned for the EOT visit, including post-exercise echocardiogram and CPET. Subsequently, every effort will be made to have the participant return to the site at the times corresponding to his or her remaining scheduled visits (ie, until the end of the study and including final CPET study at Week 30), or through the recovery or stabilization of any AE to be followed as specified in this protocol, whichever comes last.

Under circumstances of permanent treatment discontinuation, study participants can:

- Withdraw from treatment (permanent treatment discontinuation) and agree to participate in ET, EOT, and EOS visits. Participants are eligible to complete ET, EOT, and EOS visits only if they have received 22 weeks or more of study drug. If they have received less than 22 weeks of study drug, they are eligible to participate in the ET visit and visits up to EOT (week 30) but not beyond week 30.
- Withdraw from treatment (permanent treatment discontinuation) and agree to participate in the ET and EOT visit. This is the preferred follow-up for participants who have received less than 22 weeks of study drug.
- Withdraw from treatment (permanent treatment discontinuation) and agree to participate in the ET visit. This is the preferred follow-up for participants who have received study drug, regardless of treatment duration and who do not wish to be followed beyond ET visit.

- Withdraw from treatment (permanent treatment discontinuation) and all follow-up (see Section 10.2)

In case of difficulties to comply and return for all study visits until Week 30, every effort should be made to have the participant return for as many study visits as possible, especially the Week 30 visit with final CPET.

For participants who do not withdraw consent for ongoing study participation but fail to return to the site, the investigator should make every effort to contact the participant (eg, contacting participant's family or private physician, reviewing available registries or health care databases), and to determine his/her health status, particularly vital status. Attempts to contact such participants must be documented in the participant's records (eg, number of attempts and dates of attempted telephone contact and receipt for sending a registered letter). Then participants will receive a phone call from the investigator at Week 38 for vital status assessment.

10.2 Withdrawal from Study

10.2.1 Withdrawal of Consent for Ongoing Study Participation

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

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

All study withdrawals should be recorded by the investigator in the appropriate eCRF and in the participant's medical records when considered as confirmed. The date of the withdrawal and the reason should be documented.

The Statistical Analysis Plan (SAP) will specify how these participants lost to follow-up will be considered for their primary endpoints.

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

10.2.2 Replacement of Participants Who Withdraw from the Study

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

11 EVALUATION, RECORDING, AND REPORTING OF ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Event

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

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

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

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

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

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

- Any test result that meets the definition of an SAE
- Any clinically important test abnormality that suggests a disease and/or organ toxicity is worsening or is new (eg, >3× deviation from the upper or lower limit of the analyzing laboratory reference range, or as otherwise specified in the protocol)

- Any test abnormality that requires the participant to have study medication discontinued or interrupted or in the clinical judgment of the investigator
- Any test abnormality that requires the participant to receive specific corrective therapy, close observation, more frequent follow-up assessment, or further diagnostic investigation

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

11.1.1.1 Events Not Meeting the Definition of Adverse Event

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

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease under study, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that led to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
    - The subject has not experienced an AE.
    - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery or procedure became necessary because of the expected normal progression of the disease.

11.1.2 Serious Adverse Event

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

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

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

11.2 Adverse Event Reporting and Descriptions

11.2.1 Reporting Period and Follow-up

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

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

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

11.2.2 Adverse Event Attributes

The following attributes will be recorded for each AE. Additional attributes may be collected as required by MyoKardia.

11.2.2.1 Description

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

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

Death is an outcome and not the name of the event. In this situation, the event that led to the death is the name of the event. If the cause of death is unknown, "found dead" is an acceptable description.

11.2.2.2 Start Date/Time and Stop Date/Time

The date (and time during the period of residency) that the AE 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.

11.2.2.3 Relationship to Study Treatment (Suspected Adverse Reactions)

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

11.2.2.4 Intensity

Record the intensity or severity of the event using the following guide:

- 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)

11.2.2.5 Seriousness

Record SAE criteria described in Section 11.1.2 or indicate that the AE is not serious.

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

Severity is a measure of intensity (Section 11.2.2.4), whereas seriousness is defined by the criteria in Section 11.1.2.

An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

11.2.2.6 Outcome

Record the outcome of the event based on the options provided on the eCRF.

11.3 Reporting and Evaluation of Serious Adverse Events

All SAEs occurring during the treatment-emergent period (defined as the period from the first administration of study drug to 56 days [5 half-lives] after the last administration of study drug [corresponding to Week 30]) 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 medication or study procedure must also be reported. SAE reporting instructions are provided in the Study Reference Manual.

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

11.4 Reporting Adverse Events of Special Interest

Overdose, pregnancy, and LVEF ≤30% as determined by local site read echocardiogram are considered Adverse Events of Special Interest (AESI). If AESI occurs, this must be reported within 24 hours to MyoKardia.

12 STATISTICAL METHODS

12.1 Determination of Sample Size

Approximately 220 participants will be randomized, with 110 participants in each of the 2 groups. Randomization will be stratified for NYHA functional classification (II or III), current treatment with β-blocker (yes/no), type of ergometer (treadmill or exercise bicycle), and consent for the CMR substudy (yes or no). The sample size should provide adequate power to determine the superiority of mavacamten in improving pVO_2 and NYHA functional class relative to placebo (see Section 12.2.1). The power calculation is derived assuming a true clinically meaningful difference of 25% between mavacamten and placebo participants in achieving the clinical response. Based on the MYK-461-004 PIONEER-HCM phase 2 study, 50% of the participants receiving mavacamten met the clinical responder definition by the end of 12-week treatment period. Assuming the same percentage of participants in the active treatment arm and 25% in placebo arm will achieve the clinical response at the end of 30-week dosing period in the current study, the proposed sample size of 110 participants per arm will provide 96% power at two-sided 5% statistical significance level. Participants who terminate early or cannot be assessed for the clinical response at the end of 30-week dosing period will be considered as non-responders.

12.2 Study Endpoints

The study design is a randomized two-arm double-blinded trial, and the conceptual analytical approach is to compare the mavacamten treatment arm with the placebo arm.

12.2.1 Primary Efficacy Endpoints

- Clinical response defined as achieving: 1) An improvement of at least 1.5 mL/kg/min in peak oxygen consumption (pVO_2) as determined by CPET and a reduction of one or more class in NYHA Functional Classification *or* 2) an improvement of 3.0 mL/kg/min or more in pVO_2 with no worsening in NYHA Functional Class.

12.2.2 Secondary Efficacy Endpoints

- Change from baseline to Week 30 in post-exercise LVOT peak gradient
- Proportion of participants with at least 1 class improvement in NYHA functional class from baseline to Week 30
- Change from baseline to Week 30 in pVO_2 as determined by CPET
- Change from baseline to Week 30 in participant-reported health-related quality of life as assessed by the KCCQ score
- Change from baseline to Week 30 in patient-reported severity of HCM symptoms as assessed by the HCMSQ score

[redacted]

12.2.5 Safety Endpoints

- Incidence of major adverse cardiac events (death, stroke, acute myocardial infarction)
- Incidence of hospitalizations (both cardiovascular (CV) and non-CV))
- Incidence of heart failure (HF) events, (includes HF hospitalizations and urgent emergency room (ER)/outpatient (OP) visits for HF)
- Incidence of atrial fibrillation/flutter (new from screening)
- Incidence of ICD therapy and resuscitated cardiac arrest
- Incidence of Ventricular tachyarrhythmias (includes VT, VF, and Torsades de Pointe)
- Incidence of syncope and seizures
- Frequency and severity of treatment-emergent adverse events (TEAE), treatment-emergent SAEs, and laboratory abnormalities (including trends in NT-proBNP)

[redacted]

12.4 Statistical Analysis

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

12.4.1 Analysis Populations

Six analysis populations are defined in this study:

- Intention-to-treat (ITT) Population: all randomized participants regardless of whether they receive study drug, with analyses conducted according to the randomized treatment assignment
- Per Protocol Population: all randomized participants who reached Week 30 visit and completed all efficacy assessments, with analyses conducted by actual treatment received
- Safety Analysis Population: all randomized participants who receive at least 1 dose of study drug, with analyses conducted by actual treatment received
- PK Analysis Population: all randomized participants who receive at least 1 dose of study drug [redacted]

[redacted]

12.4.2 General Considerations

Descriptive summary statistics for continuous variables will include the number of participants, mean, standard deviation (SD) or standard error, median, minimum, and maximum. Nominal categorical variables will be summarized using counts and percentages. Ordinal variables may be analyzed as continuous variables as if they were continuously scaled.

12.4.3 Participant Disposition

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

12.4.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively.

12.4.5 Extent of Study Treatment Exposure and Compliance

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

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

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

Treatment compliance, above-planned and under-planned dosing percentages will be summarized descriptively (number [n], mean, SD, median, minimum, and maximum). The participants with compliance <80% will be fully described and summarized. In addition, number and percentage of participants with at least 1 dosing administration will be given, as well as the number and percentage of participants with 0, (0, 20%), and >20% under-planned dosing administrations.

12.4.6 Efficacy Analyses

All efficacy analyses will be performed on the ITT population, with sensitivity analysis also performed on the Per Protocol Population.

12.4.6.1 Primary Efficacy Endpoint Analyses

The primary efficacy endpoints of clinical response will be analyzed using the Cochran-Mantel-Haenszel (CMH) test for stratified categorical data. Early dropouts or participants whose response status is unable to be assessed at the end of 30-week dosing period will be classified as non-responders. More detailed statistical analysis strategies will be documented in the SAP.

12.4.6.2 Secondary Efficacy Endpoints Analyses

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

- To minimize false discovery among the secondary endpoints appropriate methods will be employed to control the familywise Type 1 error. Further 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 with adjusting for stratification factors, or Chi-square tests without adjusting for stratification factors, whenever appropriate.
- Continuous variables will be analyzed by analysis of variance (ANOVA) evaluating the treatment group differences against the null of zero difference.
- Ordinal variables, such as NYHA functional class, will be converted quantitatively as ordinal scores (I-IV classes to 1-4 scores, respectively) and analyzed as continuous variables.

Specific details will be provided in the SAP.

[redacted]

[redacted]

[redacted]

12.4.8 Safety Analyses

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

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

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

12.4.8.1 Adverse Events

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

Adverse event incidence tables will present the number and percentage of participants experiencing at least one TEAE by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high-level term (HLT) and PT in alphabetical order for each treatment group. Multiple occurrences of the same event in the same

participant will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

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

Potential Drug-induced Liver Injury

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

Deaths

The following deaths summaries will be generated:

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

Pregnancy

The following pregnancy summaries will be generated:

- Number of participants or partners of participants who became pregnant summarized by treatment received
- Outcomes of the pregnancies and analysis of the outcomes
- TEAE experienced during the pregnancy by primary SOC, HGLT, HLT, and PT showing the number and percent of participants sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT

Overdose

The following summaries for reports of overdose will be generated:

- Number of participants who experienced overdose summarized by treatment received
- Analysis of the cause and occurrence of the overdose

- TEAE experienced during the overdose by primary SOC, HGLT, HLT, and PT showing the number and percent of participants sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT

12.4.8.2 12-lead Electrocardiogram

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

Correction for Heart Rate

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

Fridericia's Correction:

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

ECG Numeric Variables

HR, PR, QRS, and QTcF will be summarized using descriptive statistics. QRS duration, manually over-read, will be used to determine which threshold criterion rules to apply for temporary discontinuation based on QTcF (eg, QRS duration <120 msec or QRS duration ≥120 msec). See Section 7.3.2. The change from baseline of these ECG parameters at each time point will be listed for each participant. For each time point of measurement, the changes from baseline will be summarized using descriptive statistics.

Categorical Analysis

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

Morphology Findings

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

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

Concentration-QTc Analyses

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

12.4.8.3 Laboratory Data

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

Listings of participants with laboratory values that are out of the reference range will be produced.

Potential Drug-induced Liver Injury

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

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

The normalization (to ≤1 × ULN or return to baseline if baseline >ULN) of elevated liver function tests will be summarized by categories of elevation (3 × ULN, 5 × ULN, 10 × ULN, 20 × ULN for ALT and AST, 1.5 × ULN for ALP, and 1.5 × ULN and 2 × ULN for TBL), with the following categories of normalization: never normalized, normalized after permanent discontinuation of study drug. Note that a participant will be counted only under the maximum elevation category (1-3 × ULN, 3-5 × ULN, 5-10 × ULN, 10-20 × ULN, >20 × ULN).

12.4.8.4 Vital Signs Data

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

Listings of participants with vital signs values that are out of the reference range will be produced.

12.4.8.5 Other Safety Analyses

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

[redacted]

12.4.10 Interim Analysis

No interim analysis is planned.

[redacted]

13 STUDY COMPLIANCE AND ETHICAL CONSIDERATIONS

13.1 Compliance Statement

This study will be conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines; US Title 21 Code of Federal Regulations (CFR) Parts 11, 50, 54, 56, and 312; European Union (EU) GCP; cGMP; the principles enunciated in the Declaration of Helsinki; and all human clinical research regulations in the countries where the study is to be conducted.

13.2 Informed Consent

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

Prior to participation in any study-related procedures, participants must sign and date an EC-approved written ICF in a language the participant can understand. The informed consent

process must be conducted, documented in the source document (including the date), and the form must be signed before the participant undergoes any study-specific procedures.

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

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

13.3 Ethics Committee

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

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

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

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

- All SUSARs (as described in Section 11.3)
- Any new information that may affect adversely the safety of the participants or the conduct of the trial
- Protocol deviations
- A synopsis of the study report upon study completion

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

14 ADMINISTRATIVE PROCEDURES

14.1 Sponsor's Responsibilities

MyoKardia reserves the right to terminate the study at any time. MyoKardia and the investigators will assure that adequate consideration is given to the protection of the participants' interests. MyoKardia retains the right to terminate the study and remove all study materials from a clinical site at any time. Specific circumstances that may precipitate such termination are:

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

14.1.1 Participant Confidentiality

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

MyoKardia ensures that the personal data are:

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

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

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

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

[redacted]

14.1.3 Investigator Training

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

14.1.4 Ongoing Communication of Safety Information During the Study

MyoKardia will provide the investigator(s) with documentation of SAEs from this study and other studies that are related to mavacamten study drug and are unexpected (refer to Section 11.3), as appropriate. The investigator(s) must forward this documentation to the EC as described in Section 11.3.

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

14.1.5 Study Monitoring

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

14.1.6 Study Auditing and Inspecting

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

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

14.2 Investigator's Responsibilities

14.2.1 Screening Log

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

14.2.2 Mavacamten Accountability

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

14.2.3 Reporting and Recording of Study Data

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

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

An eCRF must be completed for each participant who receives at least 1 dose of IMP. All entries into the eCRF are ultimately the responsibility of the investigator before approving them via an electronic signature. The investigator is responsible for ensuring accurate, authentic, and complete records for each participant.

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

14.2.4 Source Data and Source Documents

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

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

- Participant identification and contact information (name, date of birth, sex, address, phone)
- Documentation verifying participant eligibility (ie, medical history, physical examination)
- Informed consent process documentation and ICF
- Record of all visits and other contacts
- Record of all AEs and other safety parameters and all event attributes
- Record of all concomitant therapy (including start/stop dates, indication for use, dose)
- Date of study completion and reason for early discontinuation, if applicable

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

14.2.5 Participant Identification Information

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

14.2.6 Records Retention

MyoKardia will inform the investigator in writing when it is acceptable to dispose of any study records. To enable evaluation and/or audits from regulatory authorities or MyoKardia, the investigator agrees to keep records, including the identity of all participants (eg, participant identification code list and all source documents), all original signed ICFs, copies of all eCRFs, original laboratory reports, detailed records of study medication disposition, and all essential documents for the conduct of a clinical study. To comply with international regulations, the records should be retained by the investigator for at 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.

14.2.7 Protocol Deviations

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

14.2.8 Blood Sample Collection/Storage

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

After the study, samples may be used for additional investigation to help identify factors that may influence response to therapy. Such samples will be used in compliance with guidelines defined by US FDA Guidance on Informed Consent for In Vitro Dialogistic Device Studies Using Leftover Human Specimens That are Not Individually Identifiable (issued 25 Apr 2006) and European Medicines Agency's Reflection Paper on Pharmacogenomic Samples, Testing and Data Handling

14.3 Clinical Trial Insurance

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

14.4 Protocol Amendments and Study Administrative Letters

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

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

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

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

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

15 DATA QUALITY ASSURANCE

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

16 ADMINISTRATIVE CONSIDERATIONS

16.1 Use of Computerized Systems

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

- EDC system to capture protocol-required participant data: clinical sites will enter data from source documents onto eCRFs for each study visit using a web-based interface. Study monitors and data management personnel will use this system to review data and generate queries and reports as needed
- Cardiac clinical data management systems will be used to analyze ECG, CPET, echocardiographic, and CMR data from digital equipment used by clinical site personnel to collect participant data
- IXRS to dispense IMP and transfer data in double-blind manner
- Electronic clinical outcomes assessment equipment to allow participants to complete the HCMSQ and other PRO questionnaires

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

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

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

16.2 Study Records

The investigator and affiliated institution shall maintain the study documents and records as specified in “Essential Documents for the Conduct of a Clinical Trial” (ICH E6 Section 8), and as required by the applicable regulatory requirement(s). This includes, but is not limited to, the protocol, eCRFs, AE reports, participant source data (original records or certified

copies), correspondence with health authorities and EC, consent forms, investigator's curriculum vitae, monitor visit logs, laboratory reference ranges and laboratory certification or quality control procedures, and laboratory director curriculum vitae.

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

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

17 PUBLICATION

The data and results of the study will be owned solely by MyoKardia and shall be confidential information of MyoKardia, participant to the investigator's publication rights, all as outlined in the agreement between the investigator/institution and MyoKardia regarding the conduct of the clinical study (the "Clinical Study Agreement"). It is understood by the investigator that MyoKardia may use the information developed in this study in connection with the development of MyoKardia's proprietary IMP and, therefore, may disclose such information as necessary or useful to other clinical investigators or regulatory agencies. To allow for the use of the information derived from the study, the investigator understands that he/she has an obligation to provide and disclose all study results and all data developed during this study to MyoKardia.

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

[redacted]

[redacted]

[redacted]

APPENDIX 1 LABORATORY ASSESSMENTS

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

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

ALT, alanine aminotransferase; ALP, alkaline phosphatase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood count; CPK, creatine phosphokinase; INR, international normalized ratio.

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

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

In addition, NT-proBNP and hs-troponin I 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 be measured at Screening:

- Hepatitis panel (HVB and HVC)
- HIV test
- FSH

[redacted]

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

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

- The event is to be reported to MyoKardia as an SAE within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)

The appropriate case report form (CRF) (eg, Adverse Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities are to be completed and sent to MyoKardia.

Other events of hepatotoxicity and potential DILI are to be reported as SAEs if they meet the criteria for an SAE defined in Section 11.1.2.

Additional Clinical Assessments and Observation

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

- Repeat liver chemistries within 24-48 hours (ALT, AST, alkaline phosphatase [ALP], TBL); in cases of TBL > 2 × ULN or AST/ALT much greater than 3 × ULN, retesting is to be performed within 24 hours
    - For participants that are far away from the trial site, it may be difficult for the participants to return to the trial site promptly. In this case, the participants should be retested locally, but normal laboratory ranges should be recorded, results should be made available to trial investigators immediately, and the data should be included in the case reports

Participants are to be monitored at least twice weekly; testing frequency may decrease to once per week or less if laboratory abnormalities stabilize or the investigational product(s) or protocol-required therapies have been discontinued AND the participant is asymptomatic.

- Obtain prothrombin time/international normalized ratio, fractionated bilirubin, and any other potentially relevant laboratory evaluations of liver function or disease
- Obtain complete blood count with differential to assess for eosinophilia

- Obtain appropriate blood sampling for pharmacokinetic (PK) analysis if 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 as specified in Section 7.4
- Follow the participant until all laboratory abnormalities return to baseline or normal. The "close observation period" is to continue for a minimum of 4 weeks after investigational product(s) or protocol-required therapies discontinuation

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

APPENDIX 4 INVESTIGATOR'S SIGNATURE AMENDMENT 5

I have read and understood the contents of the clinical protocol, MYK-461-005, A Randomized, Double-blind, Placebo-controlled Clinical Study to Evaluate Mavacamten (MYK-461) in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy (EXPLORER-HCM), and I agree to the following:

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

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

Printed Name: _____