	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

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

- 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

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.

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]
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[redacted]ative site staff.

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[redacted]

9.3 Safety Assessments

Safety will be assessed throughout the study. Safety assessments include medical history, physical examinations, ECGs, vital signs, observed and participant-reported AEs, 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.

- 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.

[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

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.

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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.

[redacted]

- 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.

	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

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

(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:

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

[redacted]

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

[redacted]

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.

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.

- 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.

[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.

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

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

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: _____