Clinical Study Protocol

A Phase III, Randomized, Double-blinded, Placebo-controlled Clinical Study with A Long-term Extension to Evaluate the Efficacy and Safety of Mavacamten in Chinese Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy

Investigational product	Mavacamten Capsules
Protocol No.	LB2001-301
Version and date	3.0/ Dec 25, 2023
Phase of development	III
Registration Category	Chemical Drug Class 1
Proposed Indication	Obstructive Hypertrophic Cardiomyopathy
Sponsor	MyoKardia, Inc.
Sponsor Contact	Victoria Florea, MD Clinical Trial physician Address: 1000 Sierra Point Parkway, Brisbane, CA 94005 USA Phone: +1 786 9993957 Email: victoria.florea@bms.com Sean Little Clinical Scientist Address: 3401 Princeton Pike, Lawrenceville, NJ 08648 USA Phone: +1 330 5694258 Email: sean.little@bms.com
Sponsor Address	1000 Sierra Point Parkway Brisbane, CA 94005, USA
China Operation Affiliate	Bristol-Myers Squibb (China) Investment Co., Ltd.
China Operation Affiliate Adress	1717 West Nanjing Road Shanghai 200040, P.R. China

STATEMENT OF CONFIDENTIALITY

The information contained in this document is owned by MyoKardia, Inc. This document has provided some confidential information to you in accordance with the agreed and signed and Disclosure and Nondisclosure Agreement. Without a prior written permission, this document or its any copy or any information contained in its cannot be disclosed to any third party (except those being participant to the Disclosure and Nondisclosure Agreement and coordinating to carry out the research works in the organization).

Version History

Version Number	Version Date	Content of the Main Revisions and Reason for Revision
3.0	Dec 25, 2023	Sponsor and China Operation Affiliate information updates
2.0	April 18, 2022	1. Exclusion criteria #20: clarified that exclusion criteria for serologic hepatitis B virus test is hepatitis B surface antigen positive. 2. Exclusion criteria #21: updated as excluding participants with current COVID-19 infection or with severe complications, due to the change of clinical manifestations of the new type of COVID-19 virus; 3. Section 4.3.2: clarified that the unscheduled visit in the text of "an unscheduled visit will be arranged 2 weeks later to reduce dose" is drug dispensing visit only. 4. Section 7.4.3: clarified that the "T+4 to 6 weeks" visit is drug dispensing visit only if performing as unscheduled visit. 5. Appendix 4: clarified and updated as: 1) How will TTE be performed in the local hospital; 2) The safety monitoring requirement for maintaining the study drug when the participants are unable to return to the study site; 3) The study drug will be resumed if the study drug is interrupted for < 6 weeks and monitoring can be resumed before Week 20; 4) Washout requirements to re-enter the study; and 5) Patients in LTE phase will not allowed to re-enter the study. 6. Corrigendum: the protocol number in the header is "LB2001-301".
1.0	May 26, 2021	NA

Synopsis

Title	A Phase III, Randomized, Double-blinded, Placebo-controlled Clinical Study with A Long-term Extension to Evaluate the Efficacy and Safety of Mavacamten in Chinese Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy
Short Title	EXPLORER-CN
Protocol No.	LB2001-301
Sponsor	**MyoKardia, Inc.**
China Operation Affiliate	Bristol-Myers Squibb (China) Investment Co., Ltd.
Clinical Phase	III
Investigational Product	· Name: Mavacamten Capsules · Dosage form: Capsules · Strength: 1 mg, 2.5 mg, 5 mg, 10 mg, and 15 mg · Storage condition: 2℃ to 25℃ (36℉ to 77℉)
Study Period	The study will be composed of 4 periods as below: · Screening period: up to 4 weeks · Double-blinded, placebo-controlled treatment period: 30 weeks · Long-term extension (LTE) period: 48 weeks, including a double-blinded LTE phase and an open-label LTE phase · Post treatment follow-up period: 8 weeks (or 20 weeks for poor CYP2C19 metabolizer)

Objectives and Endpoints: The efficacy, safety, and pharmacokinetics (PK) objectives and endpoints of the study are as follows:

Objectives	**Endpoints**
Efficacy	
· **Primary Efficacy**	

To compare the effect of a 30-week course of mavacamten with placebo on Valsalva left ventricular outflow tract (LVOT) peak gradient as determined by Doppler echocardiography	· Change from baseline to Week 30 in Valsalva LVOT peak gradient
• **Secondary Efficacy**	
To compare the effect of a 30-week course of mavacamten with placebo on LVOT obstruction	· Change from baseline to Week 30 in resting LVOT peak gradient · Proportion of participants achieving a Valsalva LVOT peak gradient < 30 mmHg at Week 30 · Proportion of participants achieving a Valsalva LVOT peak gradient < 50 mmHg at Week 30
To compare the effect of a 30-week course of mavacamten with placebo on clinical symptoms	· Proportion of participants with at least 1 class improvement in NYHA functional classification from baseline to Week 30
To compare the effect of a 30-week course of mavacamten with placebo on Participant-Reported health status individually	· Change from baseline to Week 30 in Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score (CSS)
To compare the effect of a 30-week course of mavacamten on cardiac biomarkers	· Change from baseline to Week 30 in N-terminal pro-B-type natriuretic peptide (NT-proBNP) · Change from baseline to Week 30 in cardiac troponin
To compare the effect of a 30-week course of mavacamten with placebo on left ventricular (LV) mass evaluated by cardiac magnetic resonance (CMR) imaging	· Change from baseline to Week 30 in LV mass index
• **Exploratory Efficacy**	
To assess the effect of a 30-week course of mavacamten on cardiac function and structure as evaluated by echocardiography	· Proportion of participants achieving NYHA Class I and LVOT peak gradient < 30 mmHg for resting and Valsalva gradients at Week 30 · Change from baseline to Week 30 in echocardiographic indices of cardiac structure and systolic and diastolic function

To assess the effect of a 30-week course of mavacamten on cardiac function and structure as evaluated by CMR imaging	· Change from baseline to Week 30 in myocardial fibrosis · Change from baseline to Week 30 in cellular hypertrophy, cardiac structure, and function
To assess the effect of a 30-week course of mavacamten on Participant-Reported health status	· Change from baseline to Week 30 in Total Symptom Score and Overall Summary Score from KCCQ
Safety	
To assess the safety of mavacamten during the 30-week double-blinded, placebo-controlled treatment period	· Incidence of left ventricular ejection fraction (LVEF) < 50% determined by transthoracic echocardiography (TTE) · Incidence and severity of treatment-emergent adverse events (TEAEs), and treatment-emergent serious adverse events (SAEs) · Incidence of major adverse cardiac events (MACEs; cardiovascular [CV] death, non-fatal stroke, non-fatal myocardial infarction) · Incidence of hospitalizations (due to CV and non-CV events) · Incidence of heart failure (HF) events including hospitalizations and urgent emergency room/outpatient visits for HF · Incidence of atrial fibrillation/flutter (new from screening, and recurrent) · Incidence of implantable cardioverter-defibrillator (ICD) therapy and resuscitated cardiac arrest · Incidence of ventricular tachyarrhythmias including ventricular tachycardia, ventricular fibrillation, and Torsades de Pointe · Incidence of adverse events of special interest (AESIs; symptomatic overdose, outcomes of pregnancy, LVEF ≤ 30%)
Long-term Extension	

To assess the effects of mavacamten on clinical symptoms, cardiac biomarkers, health status, echocardiographic measures, and CMR measures over time	· Change from baseline in NYHA class, echocardiographic and CMR parameters, cardiac biomarkers, and KCCQ results through End of Study (EOS)
To assess the safety of mavacamten over time	· Incidence of safety events, including: LVEF < 50%; TEAEs and treatment-emergent SAEs; MACEs; hospitalizations; HF events; atrial fibrillation/flutter; ICD therapy and resuscitated cardiac arrest; ventricular tachyarrhythmias, or AESIs
Pharmacokinetics	
To describe the PK characteristics of mavacamten	· Mavacamten plasma concentration over time · PK parameters using a population PK approach
Sample Size	Approximately 81 participants will be randomized in this study with the ratio of 2:1, with 54 participants in mavacamten group and 27 participants in placebo group (2:1 randomization).
Background	There are at least 1 million hypertrophic cardiomyopathy (HCM) patients in China, among whom, the obstructive hypertrophic cardiomyopathy (oHCM) accounts for approximately 70% with poorer prognosis (Zou et al., 2004; Maron et al., 2006). The current guideline-recommended drugs can not alter the natural history of HCM and only have modest effect on LVOT gradient. Although the invasive septal reduction therapy, including surgical septal myectomy and alcohol septal ablation, can effectively improve the outflow obstruction and symptoms of oHCM, these procedures expose patients to the inherent risks and require expertise that is not universally available in China (Heart Failure Committee of Chinese Medical Doctor Association et al., 2017). Mavacamten is a novel, small molecule, selective allosteric inhibitor of cardiac-specific myosin, for the treatment of patients with symptomatic oHCM. The studies including PIONEER-HCM (Phase II) and EXPLORER-HCM (Phase III) have demonstrated the efficacy and safety of mavacamten in the symptomatic oHCM patients (Heitner et al., 2019; Olivotto et al., 2020). This study will assess the efficacy and safety of mavacamten in Chinese adults with symptomatic oHCM.
Study	This is a randomized, double-blinded, placebo-controlled clinical study with a long-term extension to evaluate the efficacy and safety of

Design	mavacamten in Chinese adults with symptomatic oHCM. Approximately 81 eligible participants will be enrolled and randomized in a 2:1 ratio (mavacamten:placebo). Randomization will be stratified according to current treatment with beta-blocker (yes or no). Participants will receive mavacamten or matching placebo for 30 weeks in double-blinded manner. After 30-week double-blinded placebo-controlled treatment, eligible participants will receive mavacamten for additional 48 weeks (placebo group: switch from placebo to mavacamten, mavacamten group: maintain on mavacamten). Treatment allocation and dose will remain blinded until all the participants complete 30-week double-blinded placebo-controlled treatment and 30-week treatment database is locked. Then, the participants will receive treatment in open-label manner.
Inclusion Criteria	Each participant must meet the following criteria to be included in this study: 1） Is at least 18 years old at screening. 2） Body weight is greater than 45 kg at screening. 3） Has adequate acoustic windows to enable accurate TTEs (refer to echocardiography related manual). 4） Diagnosed with oHCM consistent with current American College of Cardiology Foundation/American Heart Association, European Society of Cardiology, and Chinese Society of Cardiology guidelines, i.e., satisfy 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 (e.g., hypertension, aortic stenosis) or systemic disease and with maximal LV wall thickness ≥ 15 mm (or ≥ 13 mm with positive family history of hypertrophic cardiomyopathy), as determined by core laboratory interpretation, and b) Has LVOT peak gradient ≥ 50 mmHg during screening as assessed by echocardiography at rest or after Valsalva maneuver (confirmed by echocardiography core laboratory interpretation). 5） Has documented LVEF ≥ 55% by echocardiography core laboratory read of screening TTE at rest. 6） Has a valid measurement of Valsalva LVOT peak gradient at screening as determined by echocardiography core laboratory. 7） Has NYHA Class II or III symptoms at screening. 8） Has documented oxygen saturation at rest ≥ 90% at screening. 9） Female participants must not be pregnant or lactating and, if sexually active, must be using one of the following acceptable birth control methods from the screening visit through 5 months after the last dose of investigational medicinal product (IMP). a) 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. b) Intrauterine device (IUD). c) Intrauterine hormone-releasing system (IHS). d) Bilateral tubal occlusion. e) Female 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 ≥ 1 year after cessation of all exogenous hormonal treatments, and follicle-stimulating hormone levels are in the postmenopausal range. f) Male partners of female participants must also use a contraceptive (e.g., barrier, condom, or vasectomy) from screening through 5 months after the last dose of study drug. 10） Able to understand and comply with the study procedures, understand the risks involved in the study, and provide written informed consent according to national, local, and institutional guidelines before the first study specific procedure. **LTE inclusion criteria:** 1) Successful completion of 30-week double-blinded, placebo-controlled treatment period (still on the study drug). 2) In the judgment of investigator, participants have no active safety concerns.
Exclusion Criteria	A participant who meets any of the following exclusion criteria will be excluded from this study: 1) 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 (if known), whichever is longer. 2) Known infiltrative or storage disorder causing cardiac hypertrophy that mimics oHCM, such as Fabry disease, amyloidosis, or Noonan syndrome with LV hypertrophy. 3) Has a history of syncope within 6 months prior to screening or sustained ventricular tachyarrhythmia with exercise within 6 months prior to screening. 4) Has a history of resuscitated sudden cardiac arrest (at any time) or known history of appropriate ICD discharge for life-threatening ventricular arrhythmia within 6 months prior to screening.

	5) Has paroxysmal, intermittent atrial fibrillation with atrial fibrillation present per the investigator's evaluation of the participant's ECG at the time of screening. 6) 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: participants with persistent or permanent atrial fibrillation who are anticoagulated and adequately rate-controlled are allowed). 7) Previously participated in a clinical study with mavacamten. 8) Hypersensitivity to any of the components of the mavacamten formulation. 9) Current treatment (within 14 days prior to screening) or planned treatment during the study with disopyramide, cibenzoline, or ranolazine. 10) Current treatment (within 14 days prior to screening) or planned treatment during the double-blinded treatment with a combination of beta-blockers and verapamil or a combination of beta-blockers and diltiazem. 11) For individuals on beta-blockers, verapamil, or diltiazem, any dose adjustment of that medication within 14 days prior to screening or any anticipated change in treatment regimen using these medications during the double-blinded treatment. 12) 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 an unsuccessful myectomy or percutaneous ASA procedure performed > 6 months prior to screening may be enrolled if study eligibility criteria for LVOT gradient criteria are met). 13) ICD placement within 2 months prior to screening or planned ICD placement during the study. 14) Has QT interval with Fridericia correction (QTcF) > 500 msec when QRS interval < 120 msec or QTcF > 520 msec when QRS ≥ 120 msec or any other ECG abnormality considered by the investigator to pose a risk to participant safety (e.g., second-degree atrioventricular block type II). 15) Has documented obstructive coronary artery disease (> 70% stenosis in one or more epicardial coronary arteries) or history of myocardial infarction. 16) Has known moderate or severe (as per investigator's judgment) aortic valve stenosis, constrictive pericarditis, or clinically significant congenital heart disease at screening. 17) Has any acute or serious comorbid condition (e.g., major infection or hematologic, renal, metabolic, gastrointestinal, or endocrine dysfunction) that, in the judgment of the investigator, could lead to premature termination of study participation or interfere with the measurement or interpretation of the efficacy and safety assessments in the study. 18) History of malignant disease within 10 years of screening:

a) 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.

b) Participants with other malignancies who are cancer-free for more than 10 years before screening can be included in the study.

19) Has safety laboratory parameters (chemistry, hematology, coagulation, and urinalysis) outside normal limits (according to the local laboratory reference range) at screening as assessed by the local laboratory; however, a participant with safety laboratory parameters outside normal limits may be included if he or she meets all of the following criteria:

a) The safety laboratory parameter outside normal limits is considered by the investigator to be clinically not significant.

b) If there is an alanine aminotransferase or aspartate aminotransferase result, the value must be < 3 × the upper limit of the laboratory reference range.

c) The body size–adjusted estimated glomerular filtration rate is ≥ 30 mL/min/1.73 m^2.

20) Has a positive serologic test at screening for infection with human immunodeficiency virus, hepatitis C virus, or hepatitis B virus surface antigen.
21) Known uncured COVID-19 (coronavirus disease 2019) infection or with severe complication before screening.
22) 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.
23) Is currently taking, or has taken within 14 days prior to screening, a prohibited medication, such as a cytochrome P450 (CYP) 2C19 inhibitor (e.g., omeprazole or esomeprazole), a strong CYP3A4 inhibitor, or St. John's Wort. Alternatives, such as pantoprazole are allowed and may be discussed with the medical monitor.
24) Prior treatment with cardio toxic agents such as doxorubicin or similar.
25) Unable to comply with the study requirements, including the number of required visits to the clinical site.
26) Is a first degree relative of personnel directly affiliated with the study at the clinical study site, any study vendor, or the study sponsor.
27) Is currently taking, or has taken within 14 days prior to screening, biotin supplements (multivitamins that contain < 1000 mg biotin are allowed during the study but must be stopped 24 hours prior to each study visit).
28) Identified as alcohol addicts.

	CMR exclusion criteria: A participant will be excluded from the CMR assessments if he or she has any of the following: 1) An ICD or pacemaker, or another contraindication or condition not suitable for CMR in the judgment of the investigator. 2) Atrial fibrillation at the time of screening (participants who are in atrial fibrillation at the time of imaging will be asked to return at a later time within the screening period, and if the participant is still in atrial fibrillation, the participant will be disqualified from the CMR assessments). 3) Allergy or contraindication to contrast medium.
Study Procedure	In this study, participants will go through 4 periods as follow: • **Screening period (up to 4 weeks):** Participants who sign the informed consent form (ICF) will undergo a variety of general, cardiac and laboratory examinations to assess eligibility. Screening echocardiogram and electrocardiogram (ECG) results as reported by core laboratories will be used to confirm eligibility for randomization. • **Double-blinded, placebo-controlled treatment period (30 weeks):** Participants who meet all eligibility criteria will be randomized via interactive response system to receive mavacamten or matching placebo. Pharmacodynamics (PD)/PK based dose titration scheme will be designed to achieve safe and effective dosing for each participant. During this period, the assessments including TTE, ECG, Holter, and CMR (if participant is eligible) will be performed at study visits and read by core laboratories. Cardiac biomarkers and PK sample will be collected at study visits and tested by central laboratories. This period will last 30 weeks. The primary endpoint will be evaluated at Week 30 by completing the TTE with Valsalva maneuver. • **LTE period (48 weeks):** Participants who complete the 30-week double-blinded placebo-controlled treatment period and, in the judgment of the investigator, have no active safety concerns will roll directly into the LTE. All participants will receive active mavacamten in double-blinded manner until all the participants complete 30-week placebo-controlled treatment, database of the 30-week treatment is locked. Then the study is unblinded, and participants will receive study treatment in open-label manner. For participants who were in mavacamten group, they will continue on the dose received at the end of Week 30. For participants who were in

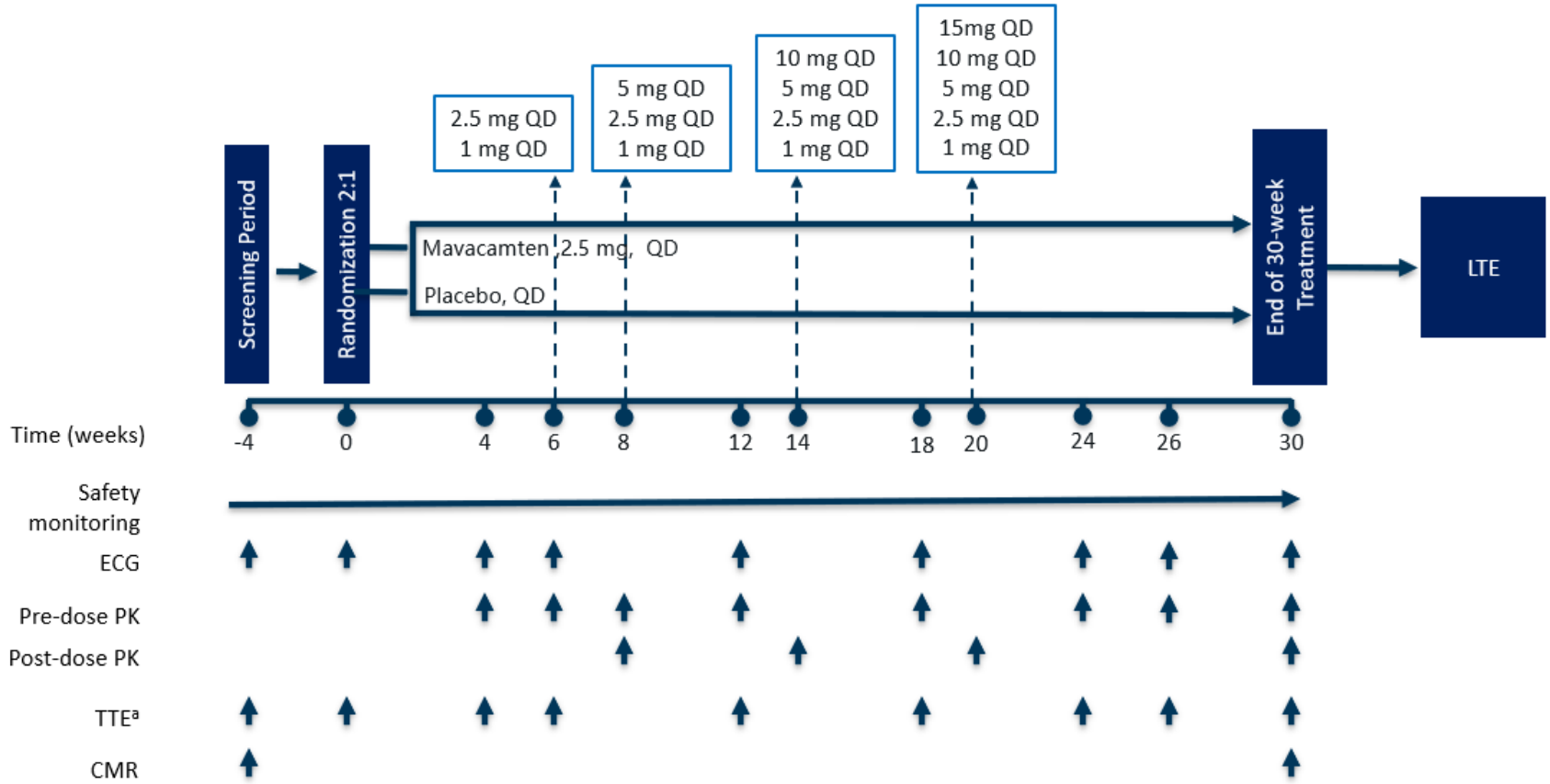
	placebo group, they will receive the 2.5 mg starting dose of mavacamten. The dose will be adjusted via PD-based dose titration scheme. During the double-blinded LTE phase, TTE will be read by core laboratory (data will be blinded to investigator). After study unblinded, TTE will be read by sites (data will be unblinded to investigator) and also be sent to core laboratories for data analysis. Cardiac biomarkers and PK sample will be tested by central laboratories. The LTE period will last 48 weeks. • **Post treatment follow-up period (8 weeks/20 weeks if CYP2C19 poor metabolizer):** Once participants complete the LTE treatment, they will enter the post treatment follow-up period. The participants will receive a phone call visit 4 weeks later and onsite visit 8 weeks later. For CYP2C19 poor metabolizer, an additional onsite visit will perform 20 weeks later. PK sample will be collected at onsite visits and tested by central laboratory.
Dose Regimen and Administration	• **Dose regimen:** **Double-blinded, placebo-controlled treatment period** · Mavacamten group: mavacamten 2.5 mg starting dose once daily (QD). At designated time points, the dose of mavacamten will be adjusted (increase, decrease, or remain unchanged) via a prespecified dose titration scheme based on core laboratory read of echocardiography and pre-dose plasma drug concentration. The permissible doses are 1 mg, 2.5 mg, 5 mg, 10 mg, and 15 mg. · Placebo group: matching placebo QD. **LTE period** · Mavacamten group: remain on dose of mavacamten at the end of Week 30. · Placebo group: mavacamten 2.5 mg starting dose QD. The dose will be adjusted (increase, decrease, or remain unchanged) via a prespecified dose titration scheme based on core laboratory read of echocardiography during double-blinded LTE phase and based on site-read echocardiography during open-label LTE phase. The permissible doses are 1 mg, 2.5 mg, 5 mg, 10 mg, and 15 mg. · The dose may be adjusted after discussion between investigator and Sponsor or Sponsor assigned medical monitor after study is unblinded.
	• **Temporary treatment discontinuation criteria:** **Double-blinded, placebo-controlled treatment period** The treatment should be temporarily discontinued if a participant meets at least one of following criteria: 1) Resting LVEF < 50% (determined by TTE). 2) Pre-dose plasma drug concentration ≥ 1000 ng/mL. Once the participant meets the temporary treatment discontinuation criteria, the 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 be a scheduled or unscheduled visit. At the follow-up visit (T+2 to 4 weeks), plasma drug concentration and TTE assessments will be repeated and another unscheduled visit will be planned for 2 weeks later (T+4 to 6 weeks). If the plasma drug concentration is < 700 ng/mL and resting LVEF is ≥ 50% at T+2 to 4 weeks, participants will restart the treatment at a lower dose at T+4 to 6 weeks. Otherwise, study drug will be switched to placebo. **LTE period** The treatment should be temporarily discontinued when participants meet the following criterion: 1) Resting LVEF < 50% (determined by TTE). Once the participant meets the temporary treatment discontinuation criterion, the investigator will contact the participant 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. At the first follow-up visit (T+2 to 4 weeks), TTE will be repeated to confirm whether resting LVEF is ≥ 50%. If resting LVEF is ≥ 50% at this visit, then study drug will be restarted at a lower dose. If resting LVEF is < 50%, then mavacamten will be discontinued.
	• **Administration:** Participants should be instructed to take mavacamten/placebo at approximately the same time every day (±8 hours). If the dosing window is missed, the participant should not take mavacamten /placebo that day. Participants should never receive 2 doses of study drug within an 8-hour period.
Concomitant Therapy	Background cardiomyopathy therapy (e.g., beta-blockers, verapamil, or diltiazem) is allowed. Participants should be on optimal medical therapy as determined by the primary physician and informed by HCM treatment guidelines. The treatment should be well tolerated for at least 2 weeks prior to screening, and the site investigator should maintain this treatment unchanged (i.e., at a stable dose) during the double-blinded treatment, unless safety or tolerability concerns arise and agreed by both investigator and Sponsor or Sponsor assigned medical monitor. During open-label treatment, investigators should manage background HCM medicines as clinically appropriate. The treatment may be adjusted or stopped as determined by the investigator in conjunction with the Sponsor or Sponsor assigned medical monitor. Any change in HCM medicines must be entered into the electronic case report form (eCRF) with the rationale for the change.

PK Evaluation	3mL whole blood will be collected at designated time points for mavacamten plasma concentration pre-specified times in enrolled participants.
Safety Evaluation	Safety monitoring will be ongoing during the study. Safety assessments include but are not limited to adverse events (AEs), vital signs, physical examinations, ECG, TTE, clinical laboratory tests (hematology, chemistry, urinalysis and coagulation test), pregnancy test and clinical evaluation, etc. Safety evaluation will be performed from first dose of mavacamten/placebo administration until EOS visits.
Statistical Methods	Approximately 81 participants will be randomized with a ratio of 2:1. The sample size should provide adequate power to determine the superiority of mavacamten in improving Valsalva LVOT gradient relative to placebo. The power calculation assumes a true difference of 30 with a standard deviation of 35 in change from baseline of Valsalva LVOT gradient at 30 weeks between the active treatment arm and the placebo arm. The proposed sample size will provide > 90% power with a 1-sided 2.5% alpha level. Considering the estimated 10% dropout rate, the final sample size is 81 patients (54 mavacamten: 27 placebo). • **Efficacy Analysis:** **Primary Endpoint Analysis** The primary endpoint of Valsalva LVOT peak gradient change from baseline to Week 30 will be summarized using descriptive statistics and compared between treatment groups using Mixed-Effect Model for Repeated Measures (MMRM). The models will include baseline LVOT gradient value and stratification factor as a covariate (current treatment with beta-blocker or not), and treatment, visit and treatment-by-visit interaction as fixed effects, and participants as random effects. More detailed statistical analysis strategies will be documented in the statistical analysis plan (SAP). **Secondary Endpoints Analysis** The general analytical approach for the secondary efficacy endpoints is the following (The p-values generated for secondary endpoints will be considered as descriptive purpose and thus no multiplicity adjustment will be applied): · Continuous variables will be summarized with descriptive statistics, including mean, standard deviation, minimum, median, and maximum, and the comparison of the means between treatment groups will be analyzed by analysis of covariance that adjusts for the baseline value and stratification factor, or MMRM if appropriate. · Categorical variables will be summarized with number and percentage within each category, and the relationship with treatment will be analyzed by Cochran-Mantel-Haenszel test that takes into

	account of the stratification factor. Point estimate and 2-sided 95% CI for proportion difference between the treatment groups will be computed based on the "stratified Miettinen-Nurminen" method. **Exploratory Endpoints Analysis** The exploratory endpoints will be summarized using descriptive statistics. • **Safety Analysis:** Safety data will be analyzed using descriptive statistics without formal statistical testing. The safety analysis will focus on the treatment-emergent adverse event period. All other safety data (vital signs, physical examinations, ECG and clinical laboratory tests, etc.) will be summarized at each protocol scheduled time point. • **Long-term Extension Analysis:** The long-term extension endpoints will be summarized using descriptive statistics. • **Pharmacokinetics Analysis:** Plasma concentration will be summarized using descriptive statistics.
Study Committees	**Clinical Event Adjudication Committee (CEAC)** The 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 MACEs (e.g., CV death, stroke, myocardial infarction). The committee will be composed of experienced cardiovascular specialists and experts who will review all pertinent clinical, and diagnostic source documentation and independently adjudicate any CV events. The processes to identify coded events for submission to the committee members for adjudication will be described in a separate CEAC charter. The CEAC full committee will meet on a pre-defined frequency or as needed to review discordant cases. The CEAC charter 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. **Independent Data Monitoring Committee** An IDMC will meet at regular intervals to safeguard the interest of study participants by assessing unblinded safety data from the ongoing study and to advise the Sponsor on important emerging study conduct issues. The IDMC may provide recommendations regarding the procedures and methodologies by surveying and detecting potential safety signals. Meeting frequency, membership, and conduct will be described in the IDMC charter.

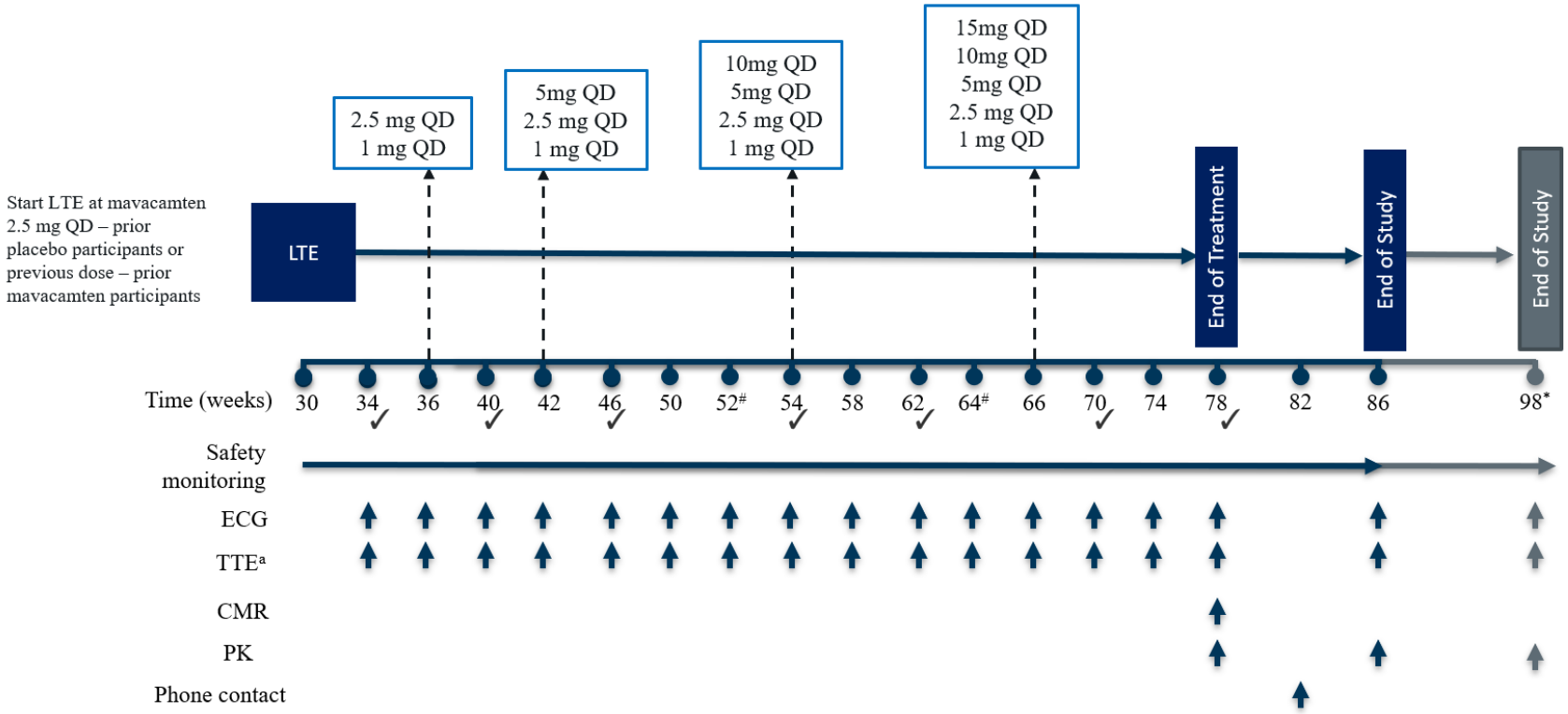
Figure 1 Study Schema<1>: Screening to Week 30



CMR = cardiac magnetic resonance; ECG = electrocardiogram; LTE = long-term extension; PK = pharmacokinetics; QD = once daily; TTE = transthoracic echocardiogram.

[a] Resting and Valsalva TTE.

Figure 2 Study Schema<2>: LTE Period and Post Treatment Follow-up Period



CMR = cardiac magnetic resonance; ECG = electrocardiogram; LTE = long-term extension; PK = pharmacokinetics; QD = once daily; TTE = transthoracic echocardiogram.

Doses listed in the blue boxes refer to possible doses for prior placebo participants. Participants prior on mavacamten can be on any of the 5 doses throughout the LTE period.

[a] Resting and Valsalva TTE.

[#] After the study unblinded (during the open-label LTE phase), Week 52 and Week 64 visits could be removed for prior placebo participants.

√ The required visits for prior mavacamten participants during open-label LTE phase: Week 34, Week 40, Week 46, Week 54, Week 62, Week 70, Week 78.

[*] For CYP2C19 poor metabolizer, an additional onsite visit will perform at Week 98 (20 weeks later after Week 78).

Table 1 Schedule of Study Procedures<1>: Screening to Week 30

	Screening[a]	Double-blinded, Placebo-controlled Treatment Period											ET[b]	Post-treatment Visits[c]		
Visit	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**/**	**4 weeks from ET/W 30**	**8 weeks from ET/W 30**	**20 weeks from ET/W 30**
Day/Week	**Day -28 to Day -1**	**Day 1[d]**	**W 4**	**W 6**	**W 8**	**W 12**	**W 14**	**W 18**	**W 20**	**W24**	**W 26**	**W 30**	**/**	**Phone visit**	**Site visit**	**Site visit**
Window (days)	/	/	±7	±3	±3	±7	±3	±7	±3	±7	±3	±7	/	±7	±7	±15
***Assessment*:**																
General procedures																
Informed consent	X															
Medical history	X															
Demographics	X															
Inclusion/exclusion criteria	X	X														
Roll into LTE												X				
Randomization		X														
Physical examination[1]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Body height, weight	X											X	X			
Prior/concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ICD download[2]	X					X						X	X			
Vital signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Cardiac Assessments																
12-lead ECG[4]	X	X	X	X		X		X		X	X	X	X		X	X
Holter	X					X					X					

	Screening[a]	Double-blinded, Placebo-controlled Treatment Period											ET[b]	Post-treatment Visits[c]		
Visit	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**/**	**4 weeks from ET/W 30**	**8 weeks from ET/W 30**	**20 weeks from ET/W 30**
Day/Week	**Day -28 to Day -1**	**Day 1[d]**	**W 4**	**W 6**	**W 8**	**W 12**	**W 14**	**W 18**	**W 20**	**W24**	**W 26**	**W 30**	**/**	**Phone visit**	**Site visit**	**Site visit**
Window (days)	/	/	**±7**	**±3**	**±3**	**±7**	**±3**	**±7**	**±3**	**±7**	**±3**	**±7**	/	**±7**	**±7**	**±15**
Resting and Valsalva TTE[5]	X	X	X	X		X		X		X	X	X	X		X	X
CMR[6]	X											X	X			
Laboratory Assessments																
Hepatitis panel and HIV test	X															
PK sampling (pre-dose)[7]			X	X	X	X		X		X	X	X	X		X	X
PK sampling (post-dose)[8]					X		X		X			X				
Coagulation test[9]	X	X		X		X		X				X	X		X	X
Chemistry[10]	X	X		X		X		X				X	X		X	X
Hematology[11]	X	X										X	X		X	X
Urinalysis[12]	X	X										X	X		X	X
Cardiac troponin	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
NT-proBNP	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
FSH[13]	X															
Pregnancy test (β-hCG)[14]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Pharmacogenetics[15]		X														
Symptom Assessments																
NYHA functional classification	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X

	Screening[a]	Double-blinded, Placebo-controlled Treatment Period											ET[b]	Post-treatment Visits[c]		
Visit	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**/**	**4 weeks from ET/W 30**	**8 weeks from ET/W 30**	**20 weeks from ET/W 30**
Day/Week	**Day -28 to Day -1**	**Day 1[d]**	**W 4**	**W 6**	**W 8**	**W 12**	**W 14**	**W 18**	**W 20**	**W24**	**W 26**	**W 30**	**/**	**Phone visit**	**Site visit**	**Site visit**
Window (days)	/	/	**±7**	**±3**	**±3**	**±7**	**±3**	**±7**	**±3**	**±7**	**±3**	**±7**	/	**±7**	**±7**	**±15**
KCCQ		X		X		X		X				X	X		X	X
Investigational Medical Product																
IMP QD		←										→				
IMP administered at site[16]		X	X	X	X	X	X	X	X	X	X	X				
IMP compliance[17]			X	X	X	X	X	X	X	X	X	X	X			

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BP = blood pressure; CK = creatine kinase; CMR = cardiac magnetic resonance; CYP = cytochrome P450; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ET = early termination; FIB = fibrinogen; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; HR = heart rate; ICD = implantable cardioverter-defibrillator; IMP = investigational medicinal product; INR = international normalized ratio; KCCQ = Kansas City Cardiomyopathy Questionnaire; LTE = long term extension; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; PK = pharmacokinetic; PT = prothrombin time; QD = once daily; RBC = red blood cell; SAE = serious AE; TT = thrombin time; TTE = transthoracic echocardiography; WBC = white blood cell; β-hCG = beta human chorionic gonadotropin.

Note: Preferred order of assessments is ECG, vital signs, pre-dose PK, and TTE (TTE might be prior to pre-dose PK) if these assessments are to be conducted at the same visit, all prior to study drug dosing unless otherwise described below.

a Screening: Participants who sign the ICF could receive examinations in screening. Screening may require more than 1 visit to accommodate all of the study procedures.

b ET: Participants who prematurely discontinue the study drug will attend an ET visit as soon as possible. After ET visit, participant will participate the post-treatment visits and Week 30 visit. Week 30 visit could be earlier (if ET occurs after Week 22) or later (if ET occurs before Week 22) than 8-week post-treatment onsite visit. If the interval between Week 30 visit and 8-week post-treatment onsite visit within 2 weeks, only 1 visit is needed. Attempt will be made to obtain assessments at Week 30, if possible.

c Post-treatment visits: If a participant does not proceed to the LTE period or ET occurs, the participants will be contacted by phone 4 weeks later and return to the site 8 weeks later for an onsite visit after ET or Week 30 visit. For CYP2C19 poor metabolizer, an additional onsite visit will perform 20 weeks after ET or Week 30 visit.

d Day 1: If the latest laboratory tests (hematology, chemistry, urinalysis, coagulation test) is more than 14 days, these examinations need to be repeated on Day 1. Otherwise, these tests don't need to be repeated on Day 1. Pregnancy test is required to be repeated on Day 1 if applicable.

1 Physical examination: At screening, ET and Week 30, a complete physical examination will be conducted, including neurological examinations. At all other visits, an abbreviated cardiopulmonary physical examination will be conducted.

2 ICD download: For participants who have ICDs, information including rhythm strips and events will be downloaded from the ICDs at screening, Week 12, ET and Week 30, or as clinically indicated after any ICD discharge interrogation occurring during the placebo-controlled treatment period.

3 Vital signs: At screening, ET and Week 30, 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.

4 12-lead ECG: 12-lead ECGs will be performed after 10 minutes of rest at screening and prior to examination of vital signs and PK sample collection at onsite study visits.

5 Resting and Valsalva TTE: Resting TTE images and views will be acquired at each onsite visit prior to dosing as detailed in the echocardiogram related manual. Instantaneous LVOT peak gradient (resting) and provoked LVOT peak gradient (Valsalva maneuver) will be assessed by the core laboratory. 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 blinded study site personnel, except in case of locally measured LVEF $\leq$ 30%.

6 CMR: The CMR assessments can be completed up to 5 days before the Week 30 visit. CMR should also be performed as close as possible to ET if it occurs. If CMR is performed at ET visit, CMR is not required for Week 30 visit.

7 Pre-dose PK sampling: Participants should not take study drug on day of visit prior to blood draw for pre-dose PK. PK sample will be collected within 2 hours before dosing.

8 Post-dose PK sampling: post-dose PK sample will be collected within 0.5 to 3 hours post dose.

9 Coagulation test: PT, INR, APTT, FIB, TT.

10 Chemistry: ALP, ALT, AST, creatinine, eGFR, potassium, sodium, chloride, magnesium, calcium, direct bilirubin, total bilirubin, total protein, albumin, CK, uric acid, glucose.

11 Hematology: hematocrit, hemoglobin, RBC counts, WBC counts including differentials, platelets.

12 Urinalysis: glucose, ketones, pH, protein, specific gravity, RBC, WBC.

13 FSH: FSH test will be performed at screening for postmenopausal women to confirm postmenopausal status. If the FSH test result shows the participant is not in postmenopausal status, serum pregnancy test needs to be done during screening to ensure the participant has no pregnancy.

14 Pregnancy test (β-hCG): For all females of childbearing potential, serum pregnancy test will be performed at screening, and urine pregnancy tests will be performed at all other onsite visits shown and serum test will be performed if any urine test is positive.

15 Pharmacogenetics: Pharmacogenetic screening for CYP2C19 genotyping preferably will occur on Day 1.

16 IMP administered at site: At all onsite visits, study drug will be administered at the investigational site to facilitate collection of PK samples within 2 hours prior to dosing. Note: There is no pre-dose PK sample at Day 1, Week 14 and Week 20. Study drug will be administered at the end of the visit when other assessments have been done, including drawing of blood for safety laboratory tests and cardiac biomarkers (except post-dose PK sampling, drawing of blood for post-dose PK will be done after study drug administration).

17 IMP compliance: All participants will return their study drug dosing containers to the site pharmacy for capsule counts. Refer to the related Pharmacy manual for details.

Table 2 Schedule of Study Procedures<2>: LTE and Post Treatment Follow-up Period

	LTE Period															ET[a]	Post-treatment Visits[b]		
Week	**34[d]**	**36**	**40[d]**	**42**	**46[d]**	**50**	**52[c]**	**54[d]**	**58**	**62[d]**	**64[c]**	**66**	**70[d]**	**74**	**78[d]**	**/**	**4 weeks from ET/W 78 Phone visit**	**8 weeks from ET/W 78 Site visit**	**20 weeks from ET/W 78 Site visit**
Window (days)[e]	**±7**	**±3**	**±7**	**±3**	**±7**	**±7**	**±3**	**±3**	**±7**	**±7**	**±3**	**±3**	**±7**	**±7**	**±7**	**/**	**±7**	**±7**	**±15**
Assessment																			
General Procedures																			
Physical examination[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Body height, weight															X	X			
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ICD download[2]															X	X			
Vital signs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Cardiac Assessments																			
12-lead ECG[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Holter													X						
Resting and Valsalva TTE[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
CMR[6]															X	X			
Laboratory Assessments																			
PK sampling[7]															X	X		X	X
Hematology[8]															X	X		X	X
Coagulation test[9]	X		X		X			X		X			X		X	X		X	X
Chemistry[10]	X		X		X			X		X			X		X	X		X	X
Urinalysis[11]															X	X		X	X
Pregnancy test (β-hCG)[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
NT-proBNP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Cardiac troponin	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X

	LTE Period															ET[a]	Post-treatment Visits[b]		
Week	**34[d]**	**36**	**40[d]**	**42**	**46[d]**	**50**	**52[c]**	**54[d]**	**58**	**62[d]**	**64[c]**	**66**	**70[d]**	**74**	**78[d]**	**/**	**4 weeks from ET/W 78 Phone visit**	**8 weeks from ET/W 78 Site visit**	**20 weeks from ET/W 78 Site visit**
Window (days)[e]	**±7**	**±3**	**±7**	**±3**	**±7**	**±7**	**±3**	**±3**	**±7**	**±7**	**±3**	**±3**	**±7**	**±7**	**±7**	**/**	**±7**	**±7**	**±15**
Symptom Assessment																			
NYHA functional classification	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
KCCQ	X		X		X			X		X			X		X	X		X	X
Investigational Medical Product																			
Dose titration[13]		X		X				X				X							
IMP QD		←	―	―	―	―	―	―	―	―	―	―	―	―	→				
IMP administered at site[14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
IMP compliance[15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BP = blood pressure; CK = creatine kinase; CMR = cardiac magnetic resonance; CYP = cytochrome P450; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ET = early termination; FIB = fibrinogen; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; HR = heart rate; ICD = implantable cardioverter-defibrillator; IMP = investigational medicinal product; INR = international normalized ratio; KCCQ = Kansas City Cardiomyopathy Questionnaire; LTE = long term extension; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; PK = pharmacokinetic; PT = prothrombin time; QD = once daily; RBC = red blood cell; SAE = serious AE; TT = thrombin time; TTE = transthoracic echocardiography; WBC = white blood cell; β hCG = beta human chorionic gonadotropin.

Note: LTE period include a double-blinded phase and an open-label phase. Preferred order of assessments is ECG, vital signs, pre-dose PK, and TTE if these assessments are to be conducted at the same visit (TTE might be prior to pre-dose PK), all prior to study drug dosing unless otherwise described below.

a ET: Participants who prematurely discontinue the study will attend an early termination visit as soon as possible.

b Post-treatment visits: If participants are prematurely discontinue the study, or complete the Week 78 visit, the participants will be contacted by phone 4 weeks later and onsite visit 8 weeks later. For CYP2C19 poor metabolizer, an additional onsite visit will perform 20 weeks later.

c Week 52 and Week 64: Week 52 and Week 64 visits could be removed for prior placebo participants during the open-label LTE phase.

d Week 34, 40, 46, 54, 62, 70, 78: During open-label LTE phase, only these visits are required for prior mavacamten participants.

e Window: Window for Week 54 and Week 66 visits could be **±7** if Week 52 and Week 64 visits are removed during the open-label LTE phase.

1 Physical examination: At Week 78/ET, a complete physical examination will be conducted, including neurological examinations. At all other visits, an abbreviated cardiopulmonary physical examination will be conducted, with other systems assessed as directed by interval history.

2 ICD download: For participants who have ICDs, information including rhythm strips and events will be downloaded from the ICDs at Week 78/ET, or as clinically indicated after any ICD discharge interrogation occurring.

3 Vital signs: At Week 78/ET, 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 sample 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.

4 12-lead ECG: 12-lead ECGs will be performed after 10 minutes of rest and prior to examination of vital signs at onsite study visits.

5 Resting and Valsalva TTE: Resting TTE images and views will be acquired at each onsite visit prior to dosing as detailed in the echocardiogram related manual. During double-blinded LTE phase, the TTE results will be kept blinded from the investigator and other blinded study site personnel, except in case of locally measured LVEF ≤ 30%. During the open-label phase, TTE results will be read by site and not blinded to investigators.

6 CMR: The CMR assessments can be completed up to 5 days before the Week 78 visit. CMR should also be performed as close as possible to ET if it occurs.

7 PK sampling: pre-dose PK sampling will be collected at Week 78/ET. Participants should not take study drug on day of visit prior to blood draw for pre-dose PK. Pre-dose PK sample will be collected within 2 hours before dosing. Post-dose PK sample will be collected within 0.5 to 3 hours post dose at Week 78 (last dose). PK samples will be collected at post-treatment onsite visits.

8 Hematology: hematocrit, hemoglobin, RBC counts, WBC counts, including differentials, platelets.

9 Coagulation test: PT, INR, APTT, FIB, TT.

10 Chemistry: ALP, ALT, AST, creatinine, eGFR, chloride, potassium, sodium, calcium, magnesium, direct bilirubin, total bilirubin, total protein, albumin, CK, uric acid, glucose.

11 Urinalysis: glucose, ketones, pH, protein, specific gravity, RBC, WBC.

12 Pregnancy test (β-hCG): For all females of childbearing potential, urine pregnancy tests will be performed at all onsite visits shown and serum test will be performed if any urine test is positive.

13 Dose titration: For prior placebo participants. During open-label LTE period, dose titration at Week 36, Week 42, Week 54 and Week 66 is based on site-read TTE on the day of visit. No scheduled dose titration for prior mavacamten participants.

14 IMP administered at site: At all onsite visits, study drug will be administered at the investigational site. Study drug will be administered at the end of the visit when other assessments have been done (except post-dose PK sampling).

15 IMP compliance: All participants will return their study drug dosing containers to the site pharmacy for capsule counts. Refer to the Pharmacy Manual for details.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

Abbreviations	Definitions
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
AESI	Adverse Event of Special Interest
AF	Atrial Fibrillation
AHA	American Heart Association
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
ASA	Alcohol Septal Ablation
AST	Aspartate Aminotransferase
APTT	Activated Partial Thromboplastin Time
AUC	Area under the Curve
BIL	Bilirubin
BP	Blood Pressure
β-hCG	beta Human Chorionic Gonadotropin
CEAC	Clinical Event Adjudication Committee
CHF	Congestive Heart Failure
cGMP	Current Good Manufacturing Practices
C_{max}	maximum concentration
CMR	Cardiac Magnetic Resonance
CPET	Cardiopulmonary exercise test
CK	Creatine Kinase
CRF	Case report form
COVID-19	Coronavirus Disease 2019
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CSS	Clinical Summary Score
CV	Cardiovascular
CYP	Cytochrome P450
DCIS	Ductal Carcinoma in Situ
DDI	Drug-drug Interaction
DILI	Drug-induced Liver Injury
EC	Ethics Committee; refers to an IRB or IEC or equivalent
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECVF	Extracellular Volume Fraction
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EMs	Extensive Metabolizers
EOS	End of Study
EOT	End of Treatment
ESC	European Society of Cardiology
ET	Early Termination

Abbreviations	Definitions
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIB	Fibrinogen
FPI	First Patient in
FSH	Follicle-stimulating Hormone
GCP	Good Clinical Practice
HB	Hemoglobin
HBV	Hepatitis B Virus
HCM	Hypertrophic Cardiomyopathy
HCV	Hepatitis C Virus
hERG	Human Ether-à-go-go-Related Gene
HF	Heart Failure
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IB	Investigator's Brochure
ICD	Implantable Cardioverter-Defibrillator
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHS	Intrauterine Hormone-releasing System
IME	Important Medical Events
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-releasing System
IV	Intravenous
IxRS	Interactive Response System
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAVI	Left Atrial Volume Index
LFT	Liver Function Test
LGE	Late Gadolinium Enhancement
LLN	Low Limit of Normal
LTE	Long-term Extension
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
LVH	Left Ventricular Hypertrophy
LVOT	Left Ventricular Outflow Tract
LVOTO	Left Ventricular Outflow Track Obstruction
MACE	Major Adverse Cardiac Events
MAD	Multiple Ascending-dose
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviations	Definitions
MET	Metabolic Equivalents
MMRM	Mixed-Effect Model for Repeated Measures
MR	Mitral Regurgitation
NASH	Nonalcoholic Steatohepatitis
nHCM	Non-hypertrophic Cardiomyopathy
NIMP	Non-investigational Medicinal Product
NT-proBNP	N-terminal pro B-type Natriuretic Peptide
NYHA	New York Heart Association
oHCM	obstructive Hypertrophic Cardiomyopathy
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	Pharmacokinetics Set
PLT	Platelet
PMs	Poor Metabolizers
PT	Preferred Term
PT	Prothrombin Time
PPS	Per-Protocol Set
pVO_2	Peak O_2 Consumption
QD	Once Daily
QTc	Corrected QT interval
QTcF	QT Interval Corrected by Heart Rate using Fridericia's Formula
RBC	Red Blood Cell
SAD	Single-ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SBP	Systolic Blood Pressure
SCD	Sudden Cardiac Death
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedures
SRT	Septal Reduction Therapy
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Half-life
TBL	Total Bilirubin
TEAE	Treatment-emergent Adverse Events
t_{max}	Time to Reach Maximum Concentration
TT	Thrombin Time
TTE	Transthoracic Echocardiography
ULN	Upper Limit of Normal
WBC	White Blood Cell
WOCBP	Women of Child Bearing Potential

1. Introduction

1.1 Background

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder defined by left ventricular (LV) hypertrophy that cannot be explained by another cardiac or systemic disease. HCM is a chronic, progressive disease of the cardiomyocyte, and largely of the cardiac sarcomere, with a diverse clinical presentation and course. Over time, HCM results in tissue remodeling characterized histologically by myocyte hypertrophy and disarray, microvascular remodeling, and fibrosis (Frey et al., 2011). Approximately 40% of affected individuals overall and 60% of those with a family history of clinical disease have a mutation in one or more sarcomeric structural genes (Hershberger et al., 2009; Gersh et al., 2011; Maron et al., 2012; Alfares et al., 2015). Mutations in cardiac myosin and other sarcomeric proteins appear to increase net power generation by the sarcomere (Chuan et al., 2012; Sommese et al., 2013; Sung J. 2012), which is consistent with the generally hypercontractile state and impaired compliance of the myocardium observed clinically in HCM. Recent estimates of the prevalence of HCM using information from large administrative databases indicate that the prevalence of clinically diagnosed HCM ranges from 3 to 7 per 10,000 (Maron et al., 2016; Husser et al., 2018; Pujades-Rodriguez et al., 2018; Moon et al., 2020). In China, it is estimated that there are more than 1 million adults affected by HCM (Zou et al., 2004).

Two HCM phenotypes are recognized based on the presence or absence of obstruction of the LV outflow tract (LVOT), obstructive HCM (oHCM, also known as HOCM) and non-obstructive HCM (nHCM), where obstruction is defined as a peak LVOT gradient ≥ 30 mmHg at rest or with provocation (Gersh et al., 2011). Approximately 70% of individuals diagnosed with HCM have oHCM (Maron et al., 2006). Based on this, the prevalence rate of oHCM is likely between 2 and 5 per 10,000, based on the recent estimates of HCM. The combination of the abnormal ventricular geometry caused by septal hypertrophy, reduced ventricular cavity size, and the pathologic elongation of the mitral valve are considered contributing factors (Sherrid et al., 2000), but the precise mechanism of LVOT obstruction is unknown. Ventricular obstruction produces increased LV systolic pressure and an array of subsequent abnormalities, including prolongation of ventricular relaxation, elevation of LV diastolic pressure, mitral regurgitation (MR), atrial fibrillation (AF), myocardial ischemia, and decreased forward cardiac output (Maron et al., 2003). The presence of LVOT obstruction is an important prognostic factor in HCM, and is associated with an increased risk of disease progression, congestive heart failure (CHF), stroke, and death (Elliott et al., 2006;

Autore et al., 2005). The risk of sudden cardiac death (SCD), which is one of the most common nontraumatic causes of death in young adults and sometimes the first manifestation of HCM, is also increased in the presence of LVOT obstruction (Ho et al., 2002; Gersh et al., 2011; Ho et al., 2018).

Current guidelines for the pharmacologic management of HCM rely on empirical use of established cardiovascular (CV) medications (including beta-blockers, verapamil, diltiazem, and disopyramide) (Ommen SR et al., 2020; Elliott et al., 2014; Heart Failure Committee of Chinese Medical Doctor Association et al., 2017) that cannot alter the natural history of HCM and only have modest effect on LVOT gradient. In oHCM, septal reduction therapy (SRT) may reduce obstruction and improve LV outflow, and an implantable cardioverter-defibrillator (ICD) may prevent SCD, but both involve invasive procedures, require specialized operators and clinic settings, and may not be available to all patients (Kim et al., 2016). Cardiac transplant is the only option when treatment fail to adequately manage oHCM. None of these treatment options address the underlying etiology of HCM.

Mavacamten is a small-molecule allosteric inhibitor of cardiac myosin that reversibly inhibits its binding to actin, thereby relieving systolic hypercontractility and improving ventricular compliance. Sponsor is developing mavacamten for the treatment of adults with symptomatic oHCM in China.

1.2 Clinical experience with mavacamten

To date, 18 clinical studies have been initiated to investigate the safety and tolerability of mavacamten. 15 studies have been completed as follows:

- Study MYK-461-001, a single-ascending dose (SAD) study in 15 participants with HCM.
- Study MYK-461-002, a SAD study in 48 healthy participants.
- Study MYK-461-003, a multiple ascending-dose (MAD) study in 60 healthy participants.
- Study MYK-461-004 (PIONEER-HCM), a Phase II study in 21 participants with oHCM.
- Study MYK-461-005 (EXPLORER-HCM), a Phase III, multinational, randomized, double-blind, placebo-controlled study in 251 participants with symptomatic oHCM.
- Study MYK-461-006 (MAVERICK-HCM), a Phase II randomized, double-blind, placebo-controlled, concentration-guided exploratory study in 59 participants with symptomatic nHCM.
- Study MYK-461-009, a drug-interaction study with verapamil in 25 healthy participants.

- Study MYK-461-010, a drug-interaction study with an oral contraceptive in 13 healthy women.
- Study MYK-461-011, an ethnobridging pharmacokinetic (PK) study in 20 Japanese and 8 Caucasian participants.
- Study MYK-461-012, an intrinsic factor PK study in 16 healthy participants who are CYP2C19 poor metabolizers (PMs) (8 participants) or CYP2C19 normal metabolizers (8 participants).
- Study MYK-461-013, a single-dose, mass-balance study in 6 healthy participants.
- Study MYK-461-014, a 3-period cross-over study in 24 healthy participants to assess the relative bioavailability of the initial capsule formulation and the final commercial formulation of mavacamten, and the effect of food on the final commercial formulation.
- Study MYK-461-015, an intrinsic factor study in 27 participants to assess the effect of mild and moderate hepatic impairment on the PK of mavacamten.
- MYK-461-016, a drug-interaction study with midazolam in 13 healthy participants with CYP2C19 genotype *1/*1, *1/*17, or *17/*17.
- MYK-461-018, a drug-interaction study with omeprazole in 29 healthy participants with CYP2C19 genotype *1/*1 or *1/*17.

Ongoing studies includes:

- Study MYK-461-007 (MAVA-LTE), an ongoing, open-label extension study in 267 participants with HCM who were previously enrolled in Studies MYK-461-006 (MAVERICK-HCM) or MYK-461-005 (EXPLORER-HCM) studies
- Study MYK-461-008 (PIONEER-OLE), an ongoing, open-label extension study in 13 participants with symptomatic oHCM who were previously enrolled in Study MYK-461-004 PIONEER-HCM study
- Study MYK-461-017 (VALOR-HCM), an ongoing, randomized, double-blind, placebo-controlled study to evaluate mavacamten in adults with symptomatic oHCM who are eligible for septal reduction therapy.

In total, 647 participants with HCM or healthy participants have been enrolled across the completed studies, 590 of whom were exposed to at least 1 dose of mavacamten (date of data cut: 30-Oct-2020). Key points regarding dosing, preliminary efficacy, preliminary safety, PK profile, and drug interactions are summarized below.

In the MYK-461-001 and MYK-461-003 studies, oral doses of mavacamten up to 96 mg (single doses administered in 8 even aliquots every 15 minutes) and 18.5 mg once daily (QD) (28-day course) were well tolerated, respectively. The predefined stopping criterion for dose escalation (reduction in left ventricular ejection fraction [LVEF] by ≥ 20%) was satisfied in both of these studies, at 144 mg in the single-dose study (MYK-

461-001) and at 25 mg daily up to 25 days in the 28-day multidose study (MYK-461-003).

Preliminary efficacy was demonstrated in a 21-participant study, in which participants with symptomatic oHCM received open-label mavacamten at doses ranging from 2 to 20 mg for 12 weeks (Study MYK-461-004; PIONEER-HCM). This 2-part study demonstrated a marked reduction in LVOT gradient to levels considered clinically insignificant at plasma mavacamten concentrations ≥ 350 ng/mL with LVEF remaining essentially within normal range at concentrations of up to 1000 ng/mL. The gradient reduction was accompanied by the resolution of systolic anterior motion of the mitral valve (SAM) in all but 2 participants (9 of 11 [82%]) in the high-dose portion of the study. The study also demonstrated an improvement in New York Heart Association (NYHA) class and dyspnea score, a decrease in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and a trend toward improved exercise tolerance as measured by peak oxygen consumption (pVO_2) on cardiopulmonary exercise testing (CPET). Lastly, there were improvements in diastolic function as measured by echocardiographic criteria. Overall, mavacamten was well tolerated; there was 1 serious adverse event (SAE) of AF in a participant with a history of AF.

In the EXPLORER-HCM (MYK-461-005) Phase III, randomized, double-blinded, placebo-controlled study, patients with oHCM were assigned (1:1) to receive mavacamten (starting at 5 mg) or placebo for 30 weeks (Ho et al., 2020). Treatment with mavacamten was superior to placebo across the primary endpoint and all secondary endpoints in a study population with 92% of participants on either beta-blocker or non-dihydropyridine calcium channel blocker therapy. Participants treated with mavacamten demonstrated twice the response rate of those in the placebo group on the composite functional primary endpoint (36.6% vs 17.2%), with a highly statistically significant between-group difference (19.4% [95% CI: 8.67, 30.13], p = 0.0005). Additionally, 20.3% of participants treated with mavacamten met the criteria of ≥ 3.0 mL/kg/min increase in pVO_2 and ≥ 1 NYHA class improvement compared with 7.8% of participants on placebo. Mavacamten treatment was also effective in reducing LVOT gradients and improving symptoms, exercise performance, and health status, as shown by significant improvement in all secondary endpoints (Olivotto et al., 2020).

MAVERICK-HCM (MYK-461-006) was the first therapeutic study to demonstrate a substantial reduction of NT-proBNP in nHCM patients. Although this dose-ranging, exploratory study was underpowered to detect clinical benefit as reflected by pVO_2 or NYHA class, the rapid and sustained dose-dependent reduction in NT-proBNP with mavacamten treatment suggests physiological benefit (Ho et al., 2020).

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

Treatment with mavacamten was well tolerated in the EXPLORER-HCM (MYK-461-005) study through 30 weeks of treatment. Overall, treatment-emergent adverse events

(TEAEs) were higher in the mavacamten group compared with the placebo group during the on-treatment (Day 1 to Week 30) period (87.8% vs 78.9%) and treatment-emergent (Day 1 to Week 38) period (87.8% and 81.3%). It is notable that the TEAE rate did not increase in the mavacamten group with 8 weeks of additional observation during study drug washout. The proportion of participants in the mavacamten group with treatment discontinuations due to TEAEs was 1.6% (2 of 123 participants). No participants in the placebo group discontinued treatment due to TEAEs. SAEs were balanced between treatment groups; on-treatment rates of SAEs were 8.1% in the mavacamten group versus 8.6% in the placebo group, and rates of treatment-emergent SAEs were 11.4% and 9.4%, respectively (Olivotto et al., 2020).

Treatment with mavacamten was well tolerated in the MAVERICK-HCM (MYK-461-006) study (Ho et al., 2020). The majority of TEAEs were mild or moderate in severity, with few severe TEAEs and no fatal adverse events (AEs). The types of TEAEs reported were similar for the mavacamten and placebo groups and were representative of the underlying disease. The incidence of SAEs was low, and the only SAE reported for > 1 participant was AF. No life-threatening or fatal TEAEs were reported. Five participants (2 participants in the 200 ng/mL group and 3 participants in the 500 ng/mL group) discontinued treatment due to meeting the protocol-specified stopping criteria of LVEF ≤ 45% and/or heart failure (HF) with systolic dysfunction. In all cases, LVEF increased and mavacamten concentrations decreased upon discontinuation of study drug.

The PK profile of mavacamten is characterized by a biphasic profile with a rapid absorption (time to reach maximum concentration [t_{max}] generally between 1 and 2 h) and a long terminal half-life ($t_{1/2}$) with a mean of 6 to 9 days in CYP2C19 extensive metabolizers (EMs). In CYP2C19 PMs, $t_{1/2}$ is approximately 24 days and the area under the curve (AUC) is increased up to approximately 3-fold and maximum concentration (C_{max}) by 50% compared to EM (i.e., *1/*1 genotype). The exposure is slightly greater than dose proportional starting at doses of 12.5 mg. At steady state, the peak-to-trough plasma concentration ratio with QD dosing is very low (1.5 to 1). Clearance and volume of distribution have not been determined in humans as they require intravenous (IV) administration; however, data are consistent with a low clearance and high volume of distribution, as shown in nonclinical studies. Four metabolites have been detected in human plasma from the MAD clinical trial (MYK-461-003). The exposure of the most abundant metabolite in human plasma was less than 5% of the exposure of mavacamten, and the other metabolites had exposure less than 1% of the exposure of mavacamten. This was confirmed in a human ^{14}C absorption, distribution, metabolism, and excretion (ADME) study where all plasma metabolites were < 10% of the parent. The available data thus far indicate that approximately 75% of the metabolism occurs through CYP2C19, 16% through 3A4/5 and the rest through CYP2C19. Approximately 2% of the administered drug is found unchanged in the urine. Pilot data indicate a food effect of less than 15% reduction in exposure when mavacamten was administered after a high fat meal vs the fasted state. In most cases, the between-participant variability (coefficient of variation) for exposure is moderate (in the 30 to 50% range).

A drug-interaction study with the moderate CYP3A4 inhibitor, verapamil, which is frequently used in oHCM, revealed no changes in AUC and a 50% increase in C_{max} after a single dose of mavacamten. These changes are not considered clinically significant, especially when using a dosing strategy of starting every participant on a low dose of mavacamten and increasing the dose as needed. An ethnobridging study indicated no important PK differences between Japanese and Caucasian CYP2C19 EMs.

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

A drug-drug interaction study with omeprazole (MYK-461-018), assessed the effect of omeprazole, a moderate CYP2C19 inhibitor, on the PK of mavacamten 15 mg administered as a single dose to healthy participants. When coadministered with a 31-day course of omeprazole 20 mg daily, a single 15 mg dose of mavacamten resulted in a 58% higher $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}last}$ than the same mavacamten dose administered alone. Other PK parameters including C_{max}, t_{max}, and $t_{1/2}$ were not affected appreciably. In this study, omeprazole and esomeprazole are prohibited.

1.3 Known and potential benefits and risks

The potential clinical benefit of mavacamten in this study is to provide therapeutic effect in participants with symptomatic oHCM.

Based on nonclinical data and the available clinical data, four important risks have been described in the latest Development Safety Update Report with data lock point of 30-Oct-2020: heart failure due to systolic dysfunction defined as symptomatic LVEF < 50%, teratogenicity, QT prolongation, and increased risk of heart failure due to interaction with CYP2C19 and potent CYP3A4 inhibitors.

- **Heart failure due to systolic dysfunction （defined as symptomatic LVEF < 50%**

In the mavacamten program, systolic dysfunction associated with mavacamten was observed as episodes of reversible LVEF reduction below the normal range. This systolic dysfunction ranged from drops in LVEF (either symptomatic or asymptomatic), and contrasted with LVEF reductions in the setting of clinical events of cardiac failure observed in complex clinical scenarios with other acute conditions such as stress cardiomyopathy, AF, anaphylactic shock, or other intercurrent acute conditions that confounded the causality assessment for mavacamten. Systolic dysfunction with mavacamten has been reversible and has not resulted in a picture of progressive cardiac failure (recurrent hospitalizations and progressive LVEF reduction) as described in the literature associated with progression of underlying HCM. However, the serious risk of cardiac failure due to systolic dysfunction (defined as symptomatic

LVEF < 50%) is an important identified risk, and cardiac failure and systolic dysfunction are considered as adverse drug reactions for mavacamten.

- **Teratogenicity**

Oral administration of mavacamten in reproductive toxicity studies in 2 species (rats, rabbits) resulted in developmental toxicity in preclinical studies (post-implantation loss, decrease in fetal body weight, and skeletal malformations in rats; visceral and skeletal malformations in rabbits), suggestive of a teratogenic potential of the compound. There are no clinical data on the safety of mavacamten during pregnancy, and highly effective contraception is required in the ongoing clinical studies.

- **QT Prolongation**

In healthy hearts, modest dose-dependent and concentration-dependent QTc prolongation has been observed. However, nonclinical data demonstrated that QTc prolongation in healthy hearts is not torsadogenic and did not result from an off-target direct effect of mavacamten; instead, the findings are attributed to an adaptive response to myosin inhibition in hearts with normal LV contractility. No torsadogenic clinical events (e.g., malignant ventricular arrhythmias, seizures, or sudden death) have been observed to date in the mavacamten clinical program other than 1 event of sudden death (study MYK-005) observed on placebo treatment. In participants p with oHCM, centrally read ECG results were consistent with a regression analysis demonstrating a negative correlation between mavacamten plasma concentrations and changes in QTcF.

Based on the findings in healthy hearts, and due to abnormalities of QTcF in HCM patients in clinical practice (e.g., interventricular conduction delay, bundle branch block, or repolarization changes due to underlying disease, use of implantable cardioverter-defibrillators/pacemakers, or concomitant use of proarrhythmic drugs), as well as the limited experience of concomitant use of mavacamten with known QT-prolonging drugs commonly used in the HCM population, QTc interval change remains an important potential risk for mavacamten.

- **Increased risk of heart failure due to interaction with CYP2C19 and potent CYP3A4 inhibitors**

Mavacamten is primarily metabolized by CYP2C19 and CYP3A4. Starting or increasing the dose of any CYP2C19 or potent CYP3A4 inhibitors may increase the risk of systolic dysfunction. Stopping or decreasing dose of a CYP2C19 or potent CYP3A4 inhibitor may lead to a loss of therapeutic response to mavacamten. The potential for drug interactions with a CYP2C19 inhibitor, including over-the-counter medications (such as omeprazole or esomeprazole), must be considered prior to and during mavacamten therapy. A list of prohibited medications for participants in mavacamten clinical trials are utilized for screening and monitoring of participants in the program.

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

definition and management of overdose, see Section 7.6.

Notably, clinical studies for mavacamten are ongoing. New safety information could emerge from ongoing clinical studies, which would be reflected in the Investigator's Brochure and Developmental Safety Update Report.

2. Rationale for the Study and Dosing

2.1 Rationale for the study

Mavacamten is a novel, small molecule, allosteric inhibitor of cardiac-specific myosin, for the treatment of patients with symptomatic oHCM, a condition with significant unmet medical need, with the goals of eliminating LVOT gradient, improving exercise capacity, functional capacity, and symptoms including fatigue and dyspnea. This Phase III study is designed to evaluate the safety and efficacy of a 30-week course of mavacamten compared with placebo and the long-term effects of mavacamten in Chinese participants with symptomatic oHCM.

In preclinical and early clinical studies, treatment with mavacamten successfully relieved LVOT gradients and improved parameters of left ventricular filling. In the Phase II, open-label PIONEER-HCM study, mavacamten was well tolerated and significantly reduced LVOT gradients in oHCM. The EXPLORER-HCM study demonstrated a mean change in Valsalva LVOT gradient of -49 (standard deviation [SD] 34.4) mmHg at Week 30 in the mavacamten group vs -12 (SD 31.0) mmHg in the placebo group (Olivotto et al., 2020).

The proposed primary endpoint in this study is the change from baseline to Week 30 in Valsalva LVOT peak gradient. The sample size of 81 (2:1 ratio) would provide approximately > 90% power to detect a treatment difference of 30 with a SD of 35 in change from baseline of LVOT gradient at 30 weeks between the active treatment arm and the placebo arm with a 1-sided 2.5% alpha level and assuming dropout rate at 10%.

NYHA functional class, other resting and Valsalva transthoracic echocardiography (TTE) parameters, Kansas City Cardiomyopathy Questionnaire (KCCQ), and safety of mavacamten will be assessed to determine 30 week's outcomes of participants receiving mavacamten.

Cardiac magnetic resonance (CMR) imaging is an important tool for the diagnosis and management of HCM and has an added value over other imaging modalities. CMR can provide three-dimensional tomographic cardiac imaging and help diagnosis by characterizing the HCM phenotype (Quarta et al., 2018). CMR is considered a standard of reference for the assessment of ventricular volumes and function. Additionally, the evaluation of fibrosis by late gadolinium enhancement (LGE) has been extensively investigated and associated with clinical outcomes (Maron et al., 2012; Moravsky et al., 2012). The results of the EXPLORER-HCM CMR sub-study primary endpoint showed a decrease in LV mass index after 30 weeks of mavacamten treatment compared with placebo, with a between-group difference in the change from baseline of -16 g/m^2 (95% CI: -22.6, -9.0046). Importantly, left atrial volume, a predictor of adverse cardiac events and AF in HCM decreased from baseline to Week 30 in the mavacamten group (between-group differences at Week 30 were -10 mL/m^2 [95% CI: -16.0, -4.6] for maximum left atrial volume index [LAVI] and -8.8 mL/m^2 [95% CI: -15.1, -2.5] for minimum LAVI compared with no changes in the placebo group. Finally,

there were no notable between-group differences on measures of fibrosis by LGE or extracellular volume fraction (ECVF; a reflection of the total interstitial space) (Olivotto et al., 2020). This study will evaluate the effect of mavacamten on cardiac function and structure, and fibrosis assessed by CMR.

After 30 weeks of placebo-controlled treatment period, participants will be rolled into the long-term extension (LTE) period if eligible. The participants from placebo group will have the opportunity to receive mavacamten for additional 48 weeks during the LTE period. During this LTE period, efficacy and safety of mavacamten will be assessed to determine long-term outcomes of participants receiving mavacamten.

2.2 Rationale for dosing

The rationale for dosing in this study is to ensure safety by titrating to the lowest effective dose in each individual participant based on their own PK/ pharmacodynamic (PD) response parameters and avoiding excessive pharmacologic effects. In the Phase II PIONEER-HCM study, significant reductions in LVOT gradient to levels below 30 mmHg were achieved while maintaining normal LVEF (50% to 70%) at plasma concentrations of mavacamten between 350 ng/mL and 700 ng/mL. Improvements in exercise capacity and symptoms were also seen in this range.

Clinical, nonclinical, PK modeling studies, and Exposure-Response Modeling study using Chinese participants' body weight and CYP2C19 genotype parameters have shown that mavacamten 2.5 mg QD is expected to be a safe starting dose, even in participants with reduced clearance due to CYP2C19 PMs or other factors.

During double-blinded, placebo-controlled treatment period, the dose will be adjusted with an up-titration scheme to a maximum of 15 mg QD, designed to achieve safe and effective dosing for each participant based on their own PK/PD response parameters. PD response parameters evaluated by TTE are read by core laboratories.

During the LTE period, dose titration is designed be step-wise based on PD response parameters (evaluated by TTE) and are not allowed to skip dose levels.

3. Objectives and Endpoints

The efficacy, safety, and PK objectives and endpoints of the study are as follows:

Table 3 Objectives and Endpoints

Objectives	Endpoints
Efficacy	
• **Primary Efficacy**	
To compare the effect of a 30-week course of mavacamten with placebo on Valsalva LVOT gradient peak as determined by Doppler echocardiography	· Change from baseline to Week 30 in Valsalva LVOT peak gradient
• **Secondary Efficacy**	
To compare the effect of a 30-week course of mavacamten with placebo on LVOT obstruction	· Change from baseline to Week 30 in resting LVOT peak gradient · Proportion of participants achieving a Valsalva LVOT peak gradient < 30 mmHg at Week 30 · Proportion of participants achieving a Valsalva LVOT peak gradient < 50 mmHg at Week 30
To compare the effect of a 30-week course of mavacamten with placebo on clinical symptoms	· Proportion of participants with at least 1 class improvement in NYHA functional classification from baseline to Week 30
To compare the effect of a 30-week course of mavacamten with placebo on Participant-Reported health status individually	· Change from baseline to Week 30 in KCCQ Clinical Summary Score (CSS)
To compare the effect of a 30-week course of mavacamten on cardiac biomarkers	· Change from baseline to Week 30 in NT-proBNP · Change from baseline to Week 30 in cardiac troponin
To compare the effect of a 30-week course of mavacamten with placebo on LV mass evaluated by CMR imaging	· Change from baseline to Week 30 in LV mass index
• **Exploratory Efficacy**	

To assess the effect of a 30-week course of mavacamten on cardiac function and structure as evaluated by echocardiography	· Proportion of participants achieving NYHA Class I and resting and Valsalva LVOT peak gradient < 30 mmHg at Week 30 · Change from baseline to Week 30 in echocardiographic indices of cardiac structure and systolic and diastolic function
To assess the effect of a 30-week course of mavacamten on Cardiac function and structure as evaluated by CMR imaging	· Change from baseline to Week 30 in myocardial fibrosis · Change from baseline to Week 30 in cellular hypertrophy, cardiac structure, and function
To assess the effect of a 30-week course of mavacamten on Participant-Reported health status	· Change from baseline to Week 30 in Total Symptom Score and Overall Summary Score from KCCQ
Safety	
To assess the safety of mavacamten during the 30-week double-blinded, placebo-controlled treatment period	· Incidence of LVEF < 50% determined by TTE · Incidence and severity of TEAEs, and treatment-emergent SAEs · Incidence of major adverse cardiac events (MACEs; CV death, non-fatal stroke, non-fatal myocardial infarction) · Incidence of hospitalizations (due to CV and non-CV events) · Incidence of HF events, including hospitalizations and urgent emergency room/outpatient visits for HF · Incidence of atrial fibrillation/flutter (new from screening, and recurrent) · Incidence of ICD therapy and resuscitated cardiac arrest · Incidence of ventricular tachyarrhythmias including ventricular tachycardia, ventricular fibrillation, and Torsades de Pointe · Incidence of adverse events of special interest (AESIs; symptomatic overdose, outcomes of pregnancy, LVEF ≤ 30%)
Long-term Extension	
To assess the effects of mavacamten on Clinical symptoms, cardiac	· Change from baseline in NYHA, echocardiographic and CMR parameters,

biomarkers, health status, echocardiographic measures, and CMR measures over time	cardiac biomarkers, and KCCQ results through end of study (EOS)
To assess the safety of mavacamten over time	· Incidence of safety events, including: LVEF < 50%, TEAEs and treatment-emergent SAEs, MACEs, hospitalizations, HF events, atrial fibrillation/flutter, ICD therapy and resuscitated cardiac arrest, ventricular tachyarrhythmias, or AESIs
Pharmacokinetics	
To describe the PK characteristics of mavacamten	· Mavacamten plasma concentration over time · PK parameters using a population PK approach

4. Overall Study Design

4.1 Study design

This is a Phase III, randomized, double-blinded, placebo-controlled, multicenter, parallel-group clinical study with a long-term extension to evaluate the efficacy, safety, and PK of mavacamten in Chinese adults with symptomatic oHCM. Approximately 81 eligible participants will be enrolled and randomized (2:1). Randomization will be stratified according to current treatment with beta-blocker (yes or no).

4.2 Study period

The study will be composed of 4 periods as below:

- Screening period: up to 4 weeks
- Double-blinded, placebo-controlled treatment period: 30 weeks
- LTE period: 48 weeks, including a double-blinded LTE phase and an open-label LTE phase
- Post treatment follow-up period: 8 weeks (or 20 weeks for poor CYP2C19 metabolizer)

4.3 Study procedure

4.3.1 Screening period (Day – 28 to Day -1)

Participants who sign the informed consent form (ICF) will undergo a variety of general, cardiac and laboratory assessments to assess eligibility (**see Table 1**). A goal of at least 25% of the participants will be NYHA functional class III. Key screening tests include electrocardiogram (ECG) and TTE conducted at rest, with Valsalva maneuver. Screening ECG and TTE test results as reported by core laboratories will be used to confirm eligibility for randomization. In other assessments, CMR (if participant is eligible) will be read by core laboratory; Cardiac biomarkers will be tested by central laboratory; Safety laboratory tests will be tested by local laboratories.

The screening assessments may be repeated, as long as they are within the 28-day screening window. Repeat assessments are allowed if central/core laboratories require a repeat submission due to quality, or investigator considers to be necessary.

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

4.3.2 Double-blinded, placebo-controlled treatment period (Day 1 to Week 30)

Participants who meet all eligibility criteria will first be randomized via an interactive response system (IxRS) in a 2:1 ratio (mavacamten: placebo) to receive mavacamten 2.5 mg starting dose or matching placebo QD. Dose titration scheme was designed to achieve safe and effective dosing for each participant (please **see Table 5-6** for more

details). The permissible doses during the study are 1 mg, 2.5 mg, 5 mg, 10 mg, and 15 mg.

All clinic visits will include but are not limited to clinical evaluation (symptoms, KCCQ results), AE/SAE assessments, concomitant medications, laboratory tests. PK (plasma concentrations), cardiac biomarkers, TTE, CMR (if participant is eligible), Holter, and ECG will be collected/performed at study visits and read by core/central laboratories (**see Table 1**). Results of TTEs performed at each scheduled visit following randomization should be kept blinded to the participants, investigator and other blinded study site personnel. An exception may occur if LVEF ⩽ 30% is measured at the site, then the investigator will be notified at the first moment by site TTE reporter and study drug will be permanently discontinued (**see Section 8.1**).

After randomization, participants will first be seen at Week 4 for an initial evaluation of clinical tolerability and safety. Pre-dose PK sample collection will be performed at this visit. In the event that the results from Week 4 meet pre-dose PK criteria for down-titration (700 ng/mL < pre-dose plasma concentration < 1000 ng/mL), the dose will be decreased at Week 6 to 1 mg via the IxRS (**see Table 5**).

Participants will subsequently be seen at Week 6, Week 12, and Week 18 for repeat evaluation. Blinded assessments including pre-dose PK, and TTE measures of LVEF and LVOT gradient with Valsalva will be performed to guide dose adjustment via the IxRS. At Week 8, Week 14, and Week 20, the dose will be adjusted (increase, decrease, remain unchanged) based upon results of Week 6, Week 12 and Week 18 assessments, respectively, as specified in **Table 6 and Section 7.4.1**. For added safety, blinded assessments at Week 8 can inform dose reduction or temporary discontinuation of study drug based on predefined criteria detailed in **Section 7.4.1** and **Section 7.4.3**. If criteria met, an unscheduled visit (a drug dispensing visit only) will be arranged 2 weeks later to reduce dose as specified in **Section 7.4.1** and **Section 7.4.3**.

After Week 20, there are no additional scheduled dose titrations. Blinded assessments at Weeks 24, and 26 can inform dose reduction or temporary discontinuation of study drug based on predefined criteria detailed in **Section 7.4.1** and **Section 7.4.3.**

At any time if pre-dose plasma concentration ≥ 1000 ng/mL or LVEF < 50%, then the study will be temporarily discontinued (**see Section 7.4.3**).

The primary endpoint will be evaluated at Week 30. Participants will complete at rest, with Valsalva maneuver TTE, and CMR (if participant is eligible) for endpoints evaluation. Attempt will be made to obtain these assessments at Week 30, if possible.

For any participant permanently discontinuing treatment prior to Week 30, an early termination (ET) visit should be conducted as soon as possible, including resting and Valsalva TTE, and CMR (if participant is eligible) assessments. After ET visit, the participant will participate post-treatment visits (as outlined in **Table 1**) and Week 30 visit. Week 30 visit could be earlier (if ET occurs after Week 22) or later (If ET occurs before Week 22) than 8-week onsite post-treatment visit. If the interval between Week 30 and 8-week onsite post-treatment visit within 2 weeks, only 1 visit is needed. Attempt will be made to obtain assessments at Week 30, if possible.

4.3.3 LTE period (48 weeks)

Participants who complete the 30-week double-blinded, placebo-controlled treatment period and, in the judgment of the investigator, have no active safety concerns will roll directly into the LTE period. All participants will receive active mavacamten in blinded manner (double-blinded LTE phase, prior treatment allocation and study drug dosage remain blinded) until all the participants complete 30-week placebo-controlled treatment, database of the 30-week treatment is locked. Once the study is unblinded, participants will receive study treatment in open-label manner (Open-label LTE phase). All participants will receive active study drug (mavacamten) QD for a duration of 48 weeks during the LTE period (an exception will occur if participants who were randomized to mavacamten group but already switched to placebo, they will continue on placebo during the double-blinded LTE period).

During LTE period, clinic visits will include but are not limited to clinical evaluation (symptoms, KCCQ results), AE/SAE assessments, concomitant medications, laboratory tests (**see Table 2**). During the double-blinded phase, TTE will be read by core laboratory. Results of TTEs performed at each scheduled visit during double-blinded LTE period should remain to be blinded to the participants and investigator. An exception may occur if LVEF ≤ 30% is measured at the site. During the open-label LTE phase, TEE will be read by site. Results of TTE will be unblinded to participants and investigator. TTE will also be sent to core laboratories for data analysis. PK (plasma concentrations), cardiac biomarkers, CMR (if participant is eligible), Holter, and ECG will be collected/performed at study visits and read by core/central laboratories (**see Table 2**).

Participants who were previously in mavacamten group will continue to receive dose received at Week 30, unless any of dose discontinuation criteria is met (detailed in **Section 7.4.3**). After study is unblinded, visits are required at Week 34, 40, 46, 54, 62, 70 and 78. During the open-label LTE phase, increases in dosage are permitted after discussion between investigator and Sponsor or Sponsor assigned medical monitor (maximum dose 15 mg QD, **see Section 7.4.2**). For participants who were randomized to mavacamten group but already switched to placebo, a retrial of mavacamten 1 mg might be considered after discussion between investigator and Sponsor or Sponsor assigned medical monitor. If LVEF again falls to <50%, mavacamten will be permanently discontinued.

Participants who were previously in placebo group will receive mavacamten (2.5 mg, QD). During the double-blinded phase, the dose will be adjusted at Week 36, Week 42, Week 54, and Week 66 based on TTE measures of LVEF and LVOT gradient with Valsalva at Week 34, Week 40, Week 52, and Week 64 (read by core laboratory) via the IxRS (**see Table 7**, **see Section 7.4.2**). After study unblinded, the dose will be adjusted at Week 36, Week 42, Week 54, and Week 66 based on TTE assessment on the day of visit (read by site). Week 52 and Week 64 visit could be removed during the open-label phase. After Week 66, there are no additional scheduled dose titrations. The

dose may be reduced or discontinued at any time based on the predefined criteria (**see Section 7.4.3**) during the LTE period.

At Week 78 (end of treatment, EOT), participants will complete at rest, with Valsalva maneuver TTE, and CMR (if participant is eligible).

For any participant who is not rolled into LTE period, post-treatment visits (phone call-visit and onsite visits) will be conducted (**see Table 1**). For any participant permanently discontinuing treatment prior to Week 78, an ET visit should be conducted as soon as possible, including resting and Valsalva TTE, and CMR (if participant is eligible) assessments. Participants who prematurely discontinue the study will attend an ET visit, post-treatment visits (phone call-visit and onsite visits) as outlined in **Table 2**.

4.3.4 Post treatment follow-up period (8 weeks/ CYP2C19 poor metabolizer, 20 weeks)

Once a participant has completed the treatment at Week 78, the participant will be contacted by phone 4 weeks (Week 82) later and return to the site 8 weeks (Week 86) later for an onsite visit. For CYP2C19 poor metabolizer, an additional onsite visit will perform 20 weeks later (Week 98).

Telephone assessments will include AEs, and concomitant medications. Onsite visit will include but not be limited to symptoms, AE/SAE assessments, ECG, TTE, KCCQ results, laboratory tests, PK, NT-proBNP and cardiac troponin.

In the context of COVID-19 or other pandemics, natural disasters, or major disruptions, provisions may be made to accommodate participants who are unable to attend onsite study visits for scheduled assessments and dispensation of mavacamten. Guidance on participants management in these situations is outlined in **Appendix 4**.

4.3.5 Description of other procedures and assessments

Participant with ICDs will have their data downloaded at screening, Week 12, ET and Week 30 in the placebo-controlled treatment period, and at Week 78/ET in the LTE period, or as clinically indicated whenever device discharge is interrogated and/or prior to any device reset (**see Table 1-2**).

Eligible participants will undergo CMR during screening, ET and Week 30 (If ET occurs and CMR is performed at ET visit, CMR is not required at Week 30 visit) in the placebo-controlled treatment period, Week 78/ET in the LTE period to evaluate changes in LV mass, myocardial fibrosis, cellular hypertrophy, and cardiac structure and function **(see Table 1-2**).

The KCCQ assessment will be completed at the visits of D1, Week 6, Week 12, Week 18, ET and Week 30 in the placebo-controlled treatment period; Week 34, Week 40, Week 46, Week 54, Week 62, Week 70, Week 78/ET in the LTE period and post-treatment onsite visits (**see Table 1-2**).

Blood samples will be collected for analysis of CYP2C19 polymorphism.

4.4 Study committees

4.4.1 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 (e.g., CV death, stroke, myocardial infarction). 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 CV events. The processes to identify coded events for submission to the committee members for adjudication will be described in a related CEAC charter. The CEAC full committee will meet on a pre-defined frequency or as needed to review discordant cases and conduct their responsibilities as outlined in the related CEAC charter. The related 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.

4.4.2 Independent data monitoring committee

An IDMC will meet at regular intervals to safeguard the interest of study participants by assessing unblinded safety data from the ongoing study and to advise the Sponsor on important emerging study conduct issues. The IDMC may provide recommendations regarding the procedures and methodologies by surveying and detecting potential safety signals. Meeting frequency, membership, and conduct will be described in the related IDMC charter.

5. Study Population

Approximately 81 participants with symptomatic oHCM are expected to enroll in this study from approximately 15 clinical sites in China.

5.1 Inclusion criteria

Each participant must meet the following criteria to be included in this study:

1) Is at least 18 years old at screening.
2) Body weight is greater than 45 kg at screening.
3) Has adequate acoustic windows to enable accurate TTEs (refer to echocardiography related manual).
4) Diagnosed with oHCM consistent with current American College of Cardiology Foundation/American Heart Association, European Society of Cardiology, and Chinese Society of Cardiology guidelines, i.e., satisfy 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 (e.g., hypertension, aortic stenosis) or systemic disease and with maximal LV wall thickness ≥ 15 mm (or ≥ 13 mm with positive family history of hypertrophic cardiomyopathy), as determined by core laboratory interpretation, and

   B. Has LVOT peak gradient ≥ 50 mmHg during screening as assessed by echocardiography at rest or after Valsalva maneuver (confirmed by echocardiography core laboratory interpretation).

5) Has documented LVEF ≥ 55% by echocardiography core laboratory read of screening TTE at rest.
6) Has a valid measurement of Valsalva LVOT peak gradient at screening as determined by echocardiography core laboratory.
7) Has NYHA Class II or III symptoms at screening.
8) Has documented oxygen saturation at rest ≥ 90% at screening.
9) Female participants must not be pregnant or lactating and, if sexually active, must be using one of the following acceptable birth control methods from the screening visit through 5 months after the last dose of investigational medicinal product (IMP).

   a) 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.

   b) Intrauterine device (IUD).

   c) Intrauterine hormone-releasing system (IHS).

   d) Bilateral tubal occlusion.

e) Female 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 ≥1 year after cessation of all exogenous hormonal treatments, and follicle-stimulating hormone levels are in the postmenopausal range.

f) Male partners of female participants must also use a contraceptive (e.g., barrier, condom, or vasectomy) from screening through 5 months after the last dose of study drug.

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

LTE inclusion criteria:

1) Successful completion of 30-week double-blinded, placebo-controlled treatment period (still on the study drug).
2) In the judgment of the investigator, participants have no active safety concerns.

5.2 Exclusion criteria

A participant who meets any of the following exclusion criteria will be excluded from this study:

1) 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 (if known), whichever is longer.
2) Known infiltrative or storage disorder causing cardiac hypertrophy that mimics oHCM, such as Fabry disease, amyloidosis, or Noonan syndrome with LV hypertrophy.
3) Has a history of syncope within 6 months prior to screening or sustained ventricular tachyarrhythmia with exercise within 6 months prior to screening.
4) Has a history of resuscitated sudden cardiac arrest (at any time) or known history of appropriate ICD discharge for life-threatening ventricular arrhythmia within 6 months prior to screening.
5) Has paroxysmal, intermittent atrial fibrillation with atrial fibrillation present per the investigator's evaluation of the participant's ECG at the time of screening.
6) 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: participants with persistent or permanent atrial fibrillation who are anticoagulated and adequately rate-controlled are allowed).
7) Previously participated in a clinical study with mavacamten.
8) Hypersensitivity to any of the components of the mavacamten formulation.
9) Current treatment (within 14 days prior to screening) or planned treatment during the study with disopyramide, cibenzoline, or ranolazine.

10) Current treatment (within 14 days prior to screening) or planned treatment during the double-blinded treatment with a combination of beta-blockers and verapamil or a combination of beta blockers and diltiazem.
11) For individuals on beta-blockers, verapamil, or diltiazem, any dose adjustment of that medication within14 days prior to screening or any anticipated change in treatment regimen using these medications during the double-blinded treatment.
12) 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 an unsuccessful myectomy or percutaneous ASA procedure performed > 6 months prior to screening may be enrolled if study eligibility criteria for LVOT gradient criteria are met).
13) ICD placement within 2 months prior to screening or planned ICD placement during the study.
14) Has QTcF > 500 msec when QRS interval < 120 msec or QTcF > 520 msec when QRS ≥ 120 msec or any other ECG abnormality considered by the investigator to pose a risk to participant safety (e.g., second-degree atrioventricular block type II).
15) Has documented obstructive coronary artery disease (> 70% stenosis in one or more epicardial coronary arteries) or history of myocardial infarction.
16) Has known moderate or severe (as per investigator's judgment) aortic valve stenosis, constrictive pericarditis, or clinically significant congenital heart disease at screening.
17) Has any acute or serious comorbid condition (e.g., major infection or hematologic, renal, metabolic, gastrointestinal, or endocrine dysfunction) that, in the judgment of the investigator, could lead to premature termination of study participation or interfere with the measurement or interpretation of the efficacy and safety assessments in the study.
18) History of malignant disease within 10 years of screening:

    a) 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.

    b) Participants with other malignancies who are cancer free for more than 10 years before screening can be included in the study.

19) Has safety laboratory parameters (chemistry, hematology, coagulation, and urinalysis) outside normal limits (according to the local laboratory reference range) at screening as assessed by the local laboratory; however, a participant with safety laboratory parameters outside normal limits may be included if he or she meets all of the following criteria:

    a) The safety laboratory parameter outside normal limits is considered by the investigator to be clinically not significant.

    b) If there is an alanine aminotransferase or aspartate aminotransferase result, the

value must be < 3 × the upper limit of the laboratory reference range.

c) The body size–adjusted estimated glomerular filtration rate is ≥30 mL/min/1.73 m^2.

20) Has a positive serologic test at screening for infection with human immunodeficiency virus, hepatitis C virus, or hepatitis B virus surface antigen.
21) Known uncured COVID-19 (coronavirus disease 2019) infection or with severe complication before screening.
22) 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.
23) Is currently taking, or has taken within 14 days prior to screening, a prohibited medication, such as a cytochrome CYP2C19 inhibitor (e.g., omeprazole or esomeprazole), a strong CYP3A4 inhibitor, or St. John's Wort. Alternatives, such as pantoprazole are allowed and may be discussed with the medical monitor.
24) Prior treatment with cardio toxic agents such as doxorubicin or similar.
25) Unable to comply with the study requirements, including the number of required visits to the clinical site.
26) Is a first degree relative of personnel directly affiliated with the study at the clinical study site, any study vendor, or the study sponsor.
27) Is currently taking, or has taken within 14 days prior to screening, biotin supplements (multivitamins that contain < 1000 mg biotin are allowed during the study but must be stopped 24 hours prior to each study visit).
28) Identified as alcohol addicts.

CMR exclusion criteria:

A participant will be excluded from the CMR assessments if he or she has any of the following:

1) An ICD or pacemaker, or another contraindication for CMR or conditions not suitable for CMR in the judgment of the investigator.
2) Atrial fibrillation at the time of screening (participants who are in atrial fibrillation at the time of imaging will be asked to return at a later time within the screening period, and if the participant is still in atrial fibrillation, the participant will be disqualified from the CMR assessments).
3) Allergy or contraindication to contrast medium.

5.3 Screening and enrollment

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

If possible, each participant should keep his or her unique identification number that was assigned upon entry into the study. Numbers do not include identifiable information. The identification number will be used to identify the participant throughout the study.

Once a participant signs the ICF, the screening window opens, and participants shall finish all screening tests and evaluations within 28 days.

Participants who fail to meet all enrollment criteria may be re-screened. Sponsor or Sponsor assigned medical monitor should be contacted to discuss the specific situation.

6. Randomization and Blinding Procedures

6.1 Randomization

A stratified block randomization scheme will be used in this study. Randomization will be stratified according to current treatment with beta-blocker or not. A computer-generated stratified block randomization schedule will be prepared by an unblinded statistician prior to the start of the study.

After signing the ICF, each participant will be given a screening number according to the screening order. Following the screening, participants who meet the inclusion criteria and none of the exclusion criteria are to be randomly assigned to receive either mavacamten or placebo (2: 1), in accordance with the randomization schedule. At the time of randomization, the participant will be assigned a unique randomization number, which will be allocated sequentially based on the predetermined stratified block randomization schedule and according to the chronological order of enrollment in the study. The allocation of participants to treatment will be performed via an IxRS. Confirmation of the treatment number allocated will be documented in the drug accountability records and recorded in the eCRF.

6.2 Study blinding

During double-blinded, placebo-controlled treatment period and double-blinded LTE phase, the investigator, site staff, Sponsor, the central/core laboratories, relevant contract research organization (CRO) staff, and participants are all blinded to treatment assignment. No individual-participant information that can potentially unblind the investigator or participants will be reported until the 30-week treatment database is locked and the unblinding is informed by the Sponsor. 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 and assigned to participants through the IxRS.

During double-blinded, placebo-controlled treatment period and double-blinded LTE phase, results of titration required parameters (i.e., echocardiography results and plasma drug concentration data) will be transferred to the IxRS by the respective core/central 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 (unblinded site personnel, e.g., sonographer or unblinded clinician/cardiologist) may be unblinded to these parameters, but still blinded to the treatment allocation. In the case of LVEF ≤ 30%, the investigator will be notified as described in **Section 7.4.4.** During blinded treatment, the pharmacovigilance (PV) operation team or designee will be unblinded for suspected unexpected serious adverse reaction (SUSAR) for health authority reporting purpose. The IDMC may also be unblinded to treatment allocation and all

safety and efficacy data. During open-label LTE period, results of TTE assessments are not blinded to the participants and investigators.

6.3 Methods for unblinding

All efforts should be made to keep participants blinded to treatment assignment before study unblinded. However, participants may be unblinded to treatment assignment upon request from the investigator and agreement by the Sponsor by following reasons:

1) A serious, unexpected, treatment-related events for reasons of participant safety,
2) An urgent safety measure taken by the investigator or Sponsor to protect participants against immediate hazard to health,
3) A potential life-threatening drug interaction,
4) Ethical consideration such as medical emergency where understanding the treatment assignment will impact future treatments or clinical care of the participants.

Unblinding by the investigator independently of the Sponsor also may occur if an SAE or other medical emergency where identification of the medication for the welfare of the participants.

The unblinding for emergency purposes will be performed via the IxRS. The date and reason for unblinding must be clearly documented.

The final unblinding will be performed after the database of 30-week treatment is locked and the unblinding is informed by the Sponsor.

7. Study Treatment

7.1 Study treatment administered

The study treatments administered in this study are mavacamten and matching placebo. Mavacamten is supplied as 1 mg, 2.5 mg, 5 mg, 10 mg, and 15 mg capsules. Mavacamten capsules of all strengths are identical in appearance. Matching placebo is supplied as a single capsule to match all mavacamten strengths and is identical in appearance to mavacamten capsules.

Participants will receive mavacamten (1 mg, 2.5 mg, 5 mg, 10 mg, or 15 mg) or matching placebo QD for 30 weeks (Day 1 to Week 30) in a double-blind manner. Beginning LTE period, all participants (i.e., mavacamten group and placebo-to-active group) will receive mavacamten QD through Week 78. During the study, there are opportunities for mavacamten dose titration as described in Section 7.4

Study drug will be supplied to participants via the IxRS in 30 count high-density polyethylene bottles that are appropriately labeled. Refer to **Table 1-2** for the complete schedule of study drug administration. The participants will be instructed to store the study drug capsules and bottles in a cool, dry place.

Participants will take study drug as directed by the study investigator. Participants should be instructed to take the study drug at approximately the same time every day (± 8 hours). Study drug should be taken with approximately 8 ounces (~240 mL) of water. If the dosing window is missed, the participant should not take study drug that day. In the event of vomiting, dose should not be repeated, but taken again the next day. Participants should never take 2 doses of study drug within an 8-hour period.

Table 4 provides an overview of the study treatments during double-blinded, placebo-controlled period.

Table 4 Study Treatments

	Treatment Group	
	Mavacamten	**Placebo**
Name of Study Treatment	Mavacamten	Placebo
Type	Study drug	Placebo
Dose Formulation	Capsules	Capsules
Unit Dose Strength	1 mg, 2.5 mg, 5 mg, 10 mg, and 15 mg	Placebo capsule matching all mavacamten strengths
Dosage Level	1 mg, 2.5 mg, 5 mg, 10 mg, or 15 mg QD	Placebo QD
Route of Administration	Oral	
Sourcing	Sponsor	
Packaging and Labeling	see Section 7.2	
Current/Former Name	Mavacamten/MYK-461	Not applicable

Abbreviations: QD = once daily.

7.2 Study drug preparation, handling, storage, and accountability

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

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

The investigator/designee is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). Further guidance and information for the final disposition of unused study drug are provided in the related pharmacy manual.

7.2.1 Formulation, packaging, and labeling of study drug

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

Mavacamten capsules are supplied in 1 mg, 2.5 mg, 5 mg, 10 mg, and 15 mg strengths. Mavacamten capsules of all strengths are identical in appearance. Matching placebo capsules are identical in appearance to mavacamten capsules.

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

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

7.3 Study drug administration and schedule

7.3.1 Treatment compliance

Compliance with study drug will be monitored by capsule count at all study visits. Refer to the related pharmacy manual for details.

On study visit days, participants should wait to do examinations before taking study drug as indicated in the schedule of study procedures.

7.4 Dose adjustments

Dose adjustments will be made by the investigator using the IxRS which will dispense IMP in a double-blind manner during 30-week double-blinded treatment period and double-blinded LTE phase. During open-label LTE phase, the dose adjustments will be made by investigator using the IxRS in an open-label manner. The **Tables 5-7** outline how the dose may be adjusted and the IxRS will be programmed accordingly, but the

investigator and the participant will not know the dose during the double-blinded treatment.

7.4.1 Blinded dose adjustments during double-blinded placebo-controlled treatment period

The double-blinded placebo-controlled treatment period will include a three-step dose titration scheme at Weeks 8, 14 and Week 20 designed to achieve safe and effective dosing for each participant based on their own PK/PD response parameters (**see Table 5-6**).

In this study, the starting dose of study drug is mavacamten 2.5 mg or matching placebo QD and each participant will receive this dose of study drug from Day 1 through Week 8 unless the PK/PD criteria for down-titration is met at Week 4, in which case the dose will be reduced at Week 6 (**see Table 5**).

At Weeks 8, 14 and 20, participants will undergo dose titration (increase or remain unchanged) based on their results of pre-dose plasma concentration, resting LVEF and Valsalva gradient determined by TTE at Week 6, 12 and 18, respectively (**see Table 6**). After the dose titration at Week 20, there are no further dose up-titrations. The intent is for dose to remain unchanged unless for safety or other reasons for premature discontinuation.

If the PK/PD criteria for down-titration is met at Week 6, Week 8, Week 12, Week 18, Week 24, or Week 26, then a scheduled or unscheduled visit 2 weeks later will be arranged to reduce dose (**see Table 5**). To avoid potential bias, the IxRS will randomly select participants from the placebo arm to undergo unscheduled visits (**see Section 6.2**).

At each visit, AEs, concomitant medications, and symptoms will be assessed. ECG, pre-dose PK, and TTE will be performed for ongoing safety monitoring. Compliance with study drug will also be monitored by capsule count at each visit.

The dose titration scheme is provided for IxRS programming. Sites and investigators are not allowed to actively adjust doses during the placebo-controlled treatment period. All dose adjustments will occur in a double-blinded manner via the IxRS, and all participants, whether receiving mavacamten or matching placebo, will undergo assessments that could lead to a blinded dose adjustment. However, the participants who are on placebo will remain on placebo (in blinded fashion) unless the participant meets the criteria of temporary discontinuation as described in **Section 7.4.3** or permanent treatment discontinuation as described in **Section 7.4.4** **and 8.1.3**.

If the dose of mavacamten is decreased at any time, then the participant will continue on the reduced dose during the double-blinded treatment unless safety concerns or intolerability arise requiring further dose reduction or dose discontinuation.

Table 5 PK/PD Criteria for Down-Titration during Double-Blinded Placebo-Controlled Treatment Period

Requires resting LVEF ≥ 50% regardless of Valsalva gradient[a]

Time of Assessment	Pre-dose Mavacamten Plasma Concentration (ng/mL)[a]	Time and Dose[b]
Week 4	700 < Plasma concentration < 1000	Week 6: · Dose reduces from 2.5 mg to 1 mg
Week 6	700 < Plasma concentration < 1000	Week 8: · Dose reduces from 2.5 mg to 1 mg (If dose is reduced at Week 6, it should remain unchanged at Week 8)
Week 8[c]	700 < Plasma concentration < 1000	2 weeks later: · Dose reduces from 5 mg to 2.5 mg or · Dose reduces from 2.5 mg to 1 mg or · Dose reduces from 1 mg to placebo (If dose is reduced at Week 8, it should remain unchanged 2 weeks later)
Week 12	700 < Plasma concentration < 1000	Week 14: · Dose reduces from 5 mg to 2.5 mg or · Dose reduces from 2.5 mg to 1 mg or · Dose reduces from 1 mg to placebo
Week 18	700 < Plasma concentration < 1000	Week 20: · Dose reduces from 10 mg to 5 mg or · Dose reduces from 5 mg to 2.5 mg or · Dose reduces from 2.5 mg to 1 mg or · Dose reduces from 1 mg to placebo
Weeks 24	700 < Plasma concentration < 1000	Week 26: · Dose reduces from 15 mg to 10 mg or · Dose reduces from 10 mg to 5 mg or · Dose reduces from 5 mg to 2.5 mg or · Dose reduces from 2.5 mg to 1 mg or · Dose reduces from 1 mg to placebo
Weeks 26	700 < Plasma concentration < 1000	2 weeks later: · Dose reduces from 15 mg to 10 mg or · Dose reduces from 10 mg to 5 mg or · Dose reduces from 5 mg to 2.5 mg or · Dose reduces from 2.5 mg to 1 mg or · Dose reduces from 1 mg to placebo (If dose is reduced at Week 26, it should remain unchanged 2 weeks later)

Abbreviations: IxRS = interactive response system; LVEF = left ventricular ejection fraction; PD = pharmacodynamics; PK = pharmacokinetics; TTE = transthoracic echocardiography.

a LVEF and pre-dose mavacamten plasma concentration will be communicated directly to the IxRS from the core/central laboratories based on assessments so that it is blinded to the investigator, study site personnel, and the Sponsor. If LVEF < 50%, see Section Treatment Discontinuation. Note: LVEF will not be performed at Week 8 (see also footnote c).

b Dose reduction applies if pre-dose PK criterion is met.

c Week 8 assessment for dose reduction will be based solely on pre-dose mavacamten plasma concentration value, there will be no TTE performed at Week 8, and therefore, no LVEF result.

Table 6 Dose Titration during Double-Blinded Placebo-Controlled Treatment Period

Requires resting LVEF ≥ 50% and pre-dose mavacamten plasma concentration ≤ 700 ng/mL

Time of Assessment	Dose Titration Criteria (based on the LVEF, Valsalva gradient and pre-dose mavacamten plasma concentration)		Dose Titration[a]	Time and Dose[b]
Week 6	LVEF ≥ 55%	Valsalva gradient ≥ 30 mmHg AND plasma concentration < 350 ng/mL	Increase	**Week 8:** · Dose increases from 2.5 mg to 5 mg
	LVEF ≥ 55%	Valsalva gradient < 30 mmHg and plasma concentration < 350 ng/mL OR 350 ≤ plasma concentration ≤ 700 ng/mL (regardless of Valsalva gradient)	No change	**Week 8:** · Dose remains at 2.5 mg or 1 mg
	50% ≤ LVEF < 55%	Regardless of Valsalva gradient and plasma concentration		
Week 12	LVEF ≥ 55%	Valsalva gradient ≥ 30 mmHg AND plasma concentration < 350 ng/mL	Increase	**Week 14:** · Dose increases from 5 mg to 10 mg or · Dose increases from 2.5 mg to 5 mg
	LVEF ≥ 55%	Valsalva gradient < 30 mmHg and plasma concentration < 350 ng/mL OR 350 ≤ plasma concentration ≤ 700 ng/mL (regardless of Valsalva gradient)	No change	**Week 14:** · Dose remains at 5 mg or 2.5 mg or 1 mg
	50% ≤ LVEF < 55%	Regardless of Valsalva gradient and plasma concentration		
Week 18	LVEF ≥ 55%	Valsalva gradient ≥ 30 mmHg AND plasma concentration < 350 ng/mL	Increase	**Week 20:** · Dose increases from 10 mg to 15 mg or · Dose increases from 5 mg to 10 mg or · Dose increases from 2.5 mg to 5 mg
	LVEF ≥ 55%	Valsalva gradient < 30 mmHg and plasma concentration < 350 ng/mL OR 350 ≤ plasma concentration ≤ 700 ng/mL (regardless of Valsalva gradient)	No change	**Week 20:** · Dose remains at 10mg, 5 mg or 2.5 mg or 1 mg
	50% ≤ LVEF < 55%	Regardless of Valsalva gradient and plasma concentration		

Abbreviations: IxRS = interactive response system; LVEF = left ventricular ejection fraction.

[a] Titration adjustments will also be communicated directly to the IxRS based on Week 6, 12 and 16 including measures of peak Valsalva gradient reported by the core laboratory so that blinding is maintained.

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

7.4.2 Dose adjustments during LTE period

During the double-blinded LTE phase:

- Participants who were previously on placebo will start 2.5 mg mavacamten at the end of Week 30, and the dose will be adjusted per a dose titration schedule (**see Table 7**). Scheduled dose decrease may occur at Week 36 if down-titration is met at Week 34 and with opportunities to dose increase at Weeks 42, Week 54 and Week 66 based on their results of resting LVEF and Valsalva gradient determined by TTE at Week 40, Week 52 and Week 64, respectively (**see Table 7**). After Week 66, no dose up-titration will be allowed. The dose titration scheme is provided for IxRS programming. Sites and investigators are not allowed to actively adjust doses during the double-blinded LTE period. All dose adjustments will occur in a double-blind manner via the IxRS.
- Participants previously on mavacamten will continue on the dose received at Week 30 unless the participant meets the criteria of temporary discontinuation as described in **Section 7.4.3** or permanent treatment discontinuation as described in **Section 7.4.4 and 8.1.3**.

During the open-label LTE phase, dose adjustments will base on site-read resting LVEF and LVOT gradient with Valsalva maneuver evaluated by TTE on the day of the visit:

- For participants who were previously on placebo, dose adjustments will occur in an open-label manner via the IxRS guiding by the dose titration schedule (**Table 7**). If safety concern raised, sites and investigators might allow to actively adjust doses (decrease, temporarily discontinue, or remain unchanged even up-titration criteria is met) in conjunction with Sponsor or Sponsor assigned medical monitor. If dose actively adjusted, participants should return to the clinical site 4 weeks later (±7 days) visit with resting and Valsalva TTE assessment, to confirm safety. Based on results and clinical symptoms at follow-up visits, subsequent dose adjustments will be discussed with Sponsor or Sponsor assigned medical monitor.
- For participants previously on mavacamten, dose increase may be considered (if LVEF ≥ 55% and Valsalva gradient ≥ 30 mmHg) during the open-label LTE period (maximum dose 15 mg QD. Skipping dose levels is not allowed.) after discussion with Sponsor or Sponsor assigned medical monitor. For participants who were randomized to mavacamten group but already switched to placebo, a retrial of mavacamten 1 mg might be considered after discussion between investigator and Sponsor or Sponsor assigned medical monitor. If LVEF again falls to <50%, mavacamten will be permanently discontinued. The investigator, in conjunction with Sponsor or Sponsor assigned medical monitor, may also reduce or temporarily discontinue participant's mavacamten dose if safety concern raised. Participants who have had a dose adjustment should return to the clinical site 4 weeks later (±7 days) visit with resting and Valsalva TTE assessment, to confirm safety. Based on results and clinical symptoms at follow-up visits, subsequent dose adjustments will be discussed with Sponsor or Sponsor assigned medical monitor.

Table 7 Dose Titration for Participants Previously on Placebo during LTE

Period

Requires resting LVEF ≥ 50%

Time of Dose Adjustment	Dose Titration Criteria (based on the LVEF and Valsalva gradient)[a]		Dose Titration	Dose[b]
Week 36	LVEF ≥ 50%	Valsalva gradient ≥ 20 mmHg	No change	· Remains at 2.5 mg
	LVEF ≥ 50%	Valsalva gradient < 20 mmHg	Decrease	· Reduces from 2.5 mg to 1 mg
Week 42	LVEF ≥ 55%	Valsalva gradient ≥ 30 mmHg	Increase	· Increases from 2.5 mg to 5 mg or 1 mg to 2.5 mg
	LVEF ≥ 55%	Valsalva gradient < 30 mmHg	No change	· Remains at 2.5 mg or 1 mg
	50% ≤ LVEF < 55%	Regardless of Valsalva gradient		
Week 54	LVEF ≥ 55%	Valsalva gradient ≥ 30 mmHg	Increase	· Increases from 5 mg to 10 mg or · Increases from 2.5 mg to 5 mg or · Increases from 1 mg to 2.5 mg
	LVEF ≥ 55%	Valsalva gradient < 30 mmHg	No change	· Remains at 5 mg or 2.5 mg or 1 mg
	50% ≤ LVEF < 55%	Regardless of Valsalva gradient		
Week 66	LVEF ≥ 55%	Valsalva gradient ≥ 30 mmHg	Increase	· Dose increases from 10 mg to 15 mg or · Dose increases from 5 mg to 10 mg or · Dose increases from 2.5 mg to 5 mg or · Dose increases from 1 mg to 2.5 mg
	LVEF ≥ 55%	Valsalva gradient < 30 mmHg	No change	· Remains at 10 mg or 5 mg or 2.5 mg or 1 mg
	50% ≤ LVEF < 55%	Regardless of Valsalva gradient		

Abbreviations: LTE = long-term extension; LVEF = left ventricular ejection fraction.

a During the double-blinded LTE phase, dose titration will be based on LVEF and Valsalva gradient measured 2 weeks before, i.e., Week 34, 40, 52, 64, respectively. During open-label LTE phase, dose titration will be based on LVEF and Valsalva gradient measured on the date of dose adjustment, i.e., Week 36, 42, 54, 66, respectively.

b 15 mg once daily is the maximum allowable dose of mavacamten. If dose is planned to increase to 15mg during open-label LTE phase, investigator is encouraged to discuss with medical monitor.

* If the mavacamten dose is decreased at any time during the double-blinded LTE due to LVEF < 50%, then the participant will continue on the reduced dose to the end of double-blinded treatment unless safety concerns or intolerability arise requiring further dose reduction or dose discontinuation.

7.4.3 Dose adjustments leading to temporary discontinuation

In addition to the dose adjustments described above at any time (T) during the treatment period, dosing may be temporarily discontinued in the case of systolic dysfunction (LVEF < 50%) or higher than expected plasma concentration.

- **Double-blinded, placebo-controlled treatment period**

The treatment should be temporarily discontinued if a participant meets at least one of following criteria:

1) Resting LVEF < 50% (determined by TTE) by core laboratory
2) Pre-dose plasma drug concentration ≥ 1000 ng/mL by central laboratory

It will be communicated to the investigator and Sponsor that a criterion for temporary discontinuation has been met. Upon receipt of this information, once the participant meets the temporary treatment discontinuation criteria, the 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.

At the follow-up visit (T+ 2 to 4 weeks), plasma drug concentration and TTE assessments will be repeated and another unscheduled visit will be planned for 2 weeks later (T+4 to 6 weeks; drug dispensing visit only if performing as unscheduled visit). If the plasma drug concentration is < 700 ng/mL and resting LVEF ≥ 50%, participants shall restart the treatment at a lower dose (If follow-up visit [T+2 to 4 weeks] occurs beyond Week 30, only TTE will be repeated. In this situation, only LVEF ≥ 50% is required for restarting the treatment at a lower dose).

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

- **Double-blinded LTE phase**

The treatment should be temporarily discontinued if a participant meets the following criterion:

1) Resting LVEF < 50% (determined by TTE) by core laboratory

It will be communicated to the investigator and Sponsor that the criterion for temporary discontinuation has been met. Upon receipt of this information, once the participant meets the temporary treatment discontinuation criterion, the 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.

At the follow-up visit (T+2 to 4 weeks), TTE assessments will be repeated and another unscheduled visit will be planned for 2 weeks later (T+4 to 6 weeks). If the resting LVEF ≥ 50%, participants shall restart the treatment at a lower dose. If follow-up visit (T+2 to 4 weeks) occurs during open-label LTE period, additional visit 2 weeks later

(T+4 to 6 weeks; drug dispensing visit only if performing as unscheduled visit) is not required. Dose will be adjusted at follow-up visit (T+2 to 4 weeks).

If resting LVEF are still out of range (< 50%) at the follow-up visit, then study drug will be switched to placebo.

If the mavacamten dose is decreased at any time due to LVEF < 50% during the double-blinded LTE period, then the participant will continue on the reduced dose to the end of double-blinded treatment unless safety concerns or intolerability arise requiring further dose reduction or dose discontinuation.

- **Open-label LTE phase**

The treatment should be temporarily discontinued when participates meet the following criterion:

1) Resting LVEF < 50% (site-read TTE).

Upon receipt of this information, once the participant meets the temporary treatment discontinuation criterion, the investigator will instruct the participant to discontinue study drug on the day of visit 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.

At the follow-up visit (T+2 to 4 weeks), TTE will be repeated to confirm if resting LVEF is ≥ 50%. If resting LVEF is ≥ 50% at this visit, then study drug may be restarted at a lower dose.

If at the follow up visit (T+2 to 4 weeks), resting LVEF is < 50%, the participants will be permanently discontinued. Participants will be followed until LVEF ≥ 50%, stabilization, or the participant is considered lost to follow-up.

At any time during the treatment period, dosing would be permanent discontinued in the case of LVEF ≤ 30% and new or worsening heart failure (see **Section 7.4.4**).

7.4.4 Management in the specific case

- **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 blinded study site personnel during placebo-controlled and double-blinded LTE phase. 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 professional (other qualified sonographer or unblinded clinician/cardiologist) who is not the blinded investigator (i.e., primary investigator and sub-primary investigator). If the result is confirmed (LVEF ≤ 30%), then the blinded 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. It should be subsequently managed as described in **Section**

8.1.4. Participants will be followed until LVEF ≥ 50%, stabilization, or the participant is considered lost to follow-up.

- **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 (e.g., 5 to 10 µg/kg/min dobutamine infusion) should be considered. Additional supportive measures, e.g., 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 and should be subsequently managed as described in Section 8.1.4.

7.5 Hepatotoxicity stopping and re-challenge rules

Participants with abnormal hepatic laboratory values (e.g., 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.

7.5.1 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:

1) TBL > 2 × upper limit of normal (ULN) or international normalized ratio > 1.5.
2) AND increased AST or ALT, if the baseline value was < ULN and AST or ALT elevation is > 3 × ULN.
3) 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 (e.g., 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 (e.g., indinavir, atazanavir, irinotecan) or herbal or dietary supplements.

- Heritable disorders causing impaired glucuronidation (e.g., 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.

7.5.2 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:

1) Elevation of either AST or ALT, regardless of baseline AST or ALT value, if:
   1. > 8 × ULN at any time.
   2. > 5 × ULN and < 8 × ULN for ≥ 2 weeks.
   3. > 5 × ULN and < 8 × ULN and unable to adhere to enhanced monitoring schedule.
2) 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.
3) 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. Re-challenge may be considered if an alternative cause, such as acute hepatitis B infection, is discovered and the

laboratory abnormalities resolve to normal or baseline.

7.5.3 Criteria for re-challenge of study drug after potential hepatotoxicity

The decision to re-challenge the participant should be discussed and unanimously agreed by the investigator and Sponsor and Sponsor assigned medical monitor.

If signs or symptoms recur with re-challenge, then study drug will be permanently discontinued. Participants who clearly meet the criteria for permanent discontinuation should never be re-challenged.

7.6 Overdose

An overdose is defined as taking more capsules of study drug than directed. An overdose may be suspected by the investigator or spontaneously reported by the participant. An overdose may be symptomatic or asymptomatic and may reflect enhanced on-target PD effects of mavacamten. Only symptomatic overdoses should be reported as AEs.

In the event of symptomatic overdose or in the presence of significant symptoms and/or clinical compromise, including depressed cardiac contractility or asystole, the investigator should promptly contact the medical monitor. No further treatment should be administered until the cause for the event is fully understood, the participant has returned to a stable clinical state and the medical monitor of Sponsor has approved the restart of study drug.

The participant should be closely monitored clinically for AEs/SAEs, with supportive measures undertaken as clinically indicated. There is no specific antidote for mavacamten. In acute overdose or toxic ingestion, gastrointestinal decontamination should be considered. If necessary, corrective measures, as described in the 2013 American College of Cardiology Foundation/American Heart Association Guideline for the Management of Heart Failure (Yancy et al., 2013) , in the 2016 European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (Ponikowski et al., 2016) and in the 2018 Guidelines for Diagnosis and Treatment of Chinese Adult Patients with Heart Failure (Chinese Society of Cardiology, 2018) should be implemented.

Based on its almost exclusive hepatic metabolism through the CYP2C19 and CYP3A4 enzymes, avoidance of inhibitors of these enzymes (e.g., omeprazole) is important and administration of inducers of CYP2C19 and CYP3A4 may be helpful. The efficacy of other measures of elimination has not been established.

7.6.1 Reporting and follow-up of overdose

Symptomatic overdose is an AESI. If a participant should experience symptomatic overdose, the investigator will report the symptomatic overdose to the medical monitor and complete the required information in the Overdose Reporting Form/SAE form within 24 hours of study staff becoming aware of the overdose. Follow-up on the participant's condition will be conducted by the investigator and study staff.

7.7 Prior and concomitant therapy

7.7.1 Prior therapy

At the time of signing the ICF, participants will be asked about their medication history over the previous 28 days, including prescription and nonprescription medications, herbal medications, vitamins, and minerals. Prior medications were those with a stop date within 28 days prior to the first dose of study drug of analysis interest.

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

7.7.2 Background HCM therapy

Background cardiomyopathy therapy (e.g., beta-blocker, verapamil, or diltiazem) is allowed. Participants should be on optimal medical therapy as determined by the primary physician and informed by HCM treatment guidelines. The treatment should be well tolerated for at least 2 weeks prior to screening, and the site investigator should maintain this treatment unchanged (i.e., at a stable dose) until the end of the double-blinded treatment unless safety or tolerability concerns arise and agreed by both investigator and Sponsor or Sponsor assigned medical monitor.

In open-label LTE phase, investigators should manage background HCM medicines as clinically appropriate. The treatment may be adjusted or stopped as determined by the investigator in conjunction with the Sponsor or Sponsor assigned medical monitor.

Any change in HCM medications must be entered into the eCRF with the rationale for the change.

7.7.3 Concomitant therapy

Concomitant medications are those with a stop date on or after the first dose of study drug of analysis interest or were ongoing at the end of the analysis period.

Concomitant therapy will be collected at all clinic visits from the first dose until the end of the study. Document all concomitant therapies on the appropriate eCRF, whether prescription or over-the-counter, vitamin and/or mineral supplements, herbs, and medications taken for an event or procedure (e.g., biopsy). Include start/stop dates, dose, route, and indication.

7.7.4 Prohibited therapy

Prior or concomitant treatment with cardiotoxic agents such as doxorubicin or similar is prohibited. Use of disopyramide, cibenzoline or ranolazine is prohibited from 14 days before screening to the EOS.

Additional prohibited medications are listed in **APPENDIX 2.**

8. Treatment Discontinuation and Withdrawal from Study

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.

8.1 Treatment discontinuation

8.1.1 Temporary treatment discontinuation

Temporary treatment discontinuation

- Will be implemented when a predefined safety threshold has been met (see Section 7.4.3)
- 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 8.1.3).

If a temporary treatment discontinuation was caused by a safety threshold being met, treatment will be resumed approximately 2 to 6 weeks later, either at a lower dose or with switch to placebo or discontinuation, transmitted via IxRS (see Section 7.4.3).

In the case of discontinuation for an AE/SAE, the investigator should make a best effort to resume study drug as soon as practically possible, assuming there are no safety concerns (i.e., 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.

8.1.2 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.

All permanent treatment discontinuation should be recorded in the eCRF.

8.1.3 Permanent treatment discontinuation criteria

The following reasons will lead to permanent treatment discontinuation or withdraw from study:

1) If all the criteria are met for possible DILI.
2) Pregnancy.
3) LVEF ≤ 30% as determined by site laboratory.
4) New or worsening HF associated with systolic dysfunction.
5) Any breaking of the study blind requested by the investigator.
6) Continued administration of study drug is considered by the investigator to be detrimental to the participant's safety or well-being.
7) The participant requests to discontinue study drug.
8) The Sponsor requests that the participant permanently discontinues study drug.

8.1.4 Management of participants after permanent treatment discontinuation

There may be situations in which it is necessary for a participant to permanently discontinue study drug. In all cases, participants should be encouraged to discuss stopping study drug with the investigator/designee so that questions can be addressed, and concomitant therapy can be adjusted if needed. Investigators should contact the Sponsor or Sponsor assigned medical monitor prior to permanent study drug discontinuation to discuss the situation.

If a participant permanently discontinues treatment prior to Week 30, the participants will be asked to undergo an ET visit as soon as possible after stopping study drug and be encouraged to participate post-treatment visits (phone visit and the onsite visits, using the procedure outlined in **Table 1**) and Week 30 visit.

If permanent treatment discontinuation occurs during LTE period. The participants will be asked to undergo an ET visit, phone visit and the onsite post-treatment visits, using the procedure outlined in **Table 2**.

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 (e.g., 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 (e.g., number of attempts and dates of attempted telephone contact or receipt for sending a registered letter).

8.2 Withdrawal from study

8.2.1 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. Permanent treatment discontinuation described above should be distinguished from withdrawal of consent for ongoing study participation.

Participant who withdraws 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 endpoint.

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

8.2.2 Replacement of participants who withdraw from the study

Participants who withdraw from the study after randomization will not be replaced.

9. Study Assessment

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, 2**. When several assessments are to be conducted at the same time point, the preferred order of assessments is ECG, vital signs, pre-dose PK, and then TTE all prior to study drug dosing. The order of assessments may vary slightly at specific time points to facilitate the most contemporaneous performance of the required assessments (e.g., TTE might be prior to pre-dose PK). Unscheduled or additional safety assessments may be performed if necessary, in the opinion of the investigator. Whenever possible discussion with the Sponsor or Sponsor assigned 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.

9.1 Efficacy assessment

9.1.1 Echocardiography

In the double-blinded, placebo-controlled treatment period and double-blinded LTE phase, all echocardiography data will be sent to a central imaging; pre-specified echocardiography results from multiple visits will be transmitted to the IxRS to confirm eligibility and to maintain blinding.

In the open-label LTE treatment phase, echocardiograms will be site-read and not blinded to the investigator or the site. Echocardiography data used for dose titration will be sent to the IxRS. Echocardiograms will also be sent to a core laboratory for data analysis.

Echocardiography assessments will take place as described in **Table 1, 2**.

- **Resting transthoracic echocardiography**

Resting TTE will be assessed prior to dosing during onsite visits as described in **Table 1, 2**. Instantaneous peak LVOT gradient at rest and provoked peak LVOT gradient (Valsalva maneuver) will be assessed. The investigator should confirm during screening that participant can adequately perform the Valsalva maneuver. Care should be taken to select the best window and angle when obtaining Doppler signal to assess the LVOT gradient and to avoid contamination by MR jet if present. Left ventricular ejection fraction (2-dimensional LVEF) and left ventricular fractional shortening will also be analyzed along with a variety of other echocardiographic measures.

TTE results (at least, the LVEF and peak LVOT gradient value) performed at each scheduled visit following randomization during the placebo-controlled period and

double-blinded LTE phase should be kept blinded to the investigators, except the unblinded site personnel (sonographer and unblinded clinician/cardiologist). During the open-label LTE phase, resting TTE will be assessed at clinical site study visits and also read by core laboratory.

9.1.2 New York heart association functional classification

The NYHA Functional Classification of HF assigns participants to 1 of 4 categories based on the participants' symptoms. HF classification will be assessed by the investigator at every study visit and recorded as indicated in the clinical database.

Table 8 NYHA Functional Classification of HF

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

9.1.3 Kansas City Cardiomyopathy Questionnaire (23-item version)

The KCCQ (23-item version) is a patient-reported questionnaire that measures the impact of patients' CV disease or its treatment on 6 distinct domains using a 2-week recall: symptoms/signs, physical limitations, quality of life, social limitations, self-efficacy, and symptom stability (Green et al., 2000). In addition to the individual domains, 2 summary scores can be calculated from the KCCQ: the overall summary score (includes the total symptom, physical limitation, social limitations and quality of life scores) and the clinical summary score (combines the total symptom and physical limitation scales). Scores range from 0 to 100, with higher scores reflecting better health status. The KCCQ will be administered to participants as indicated. The KCCQ, 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.

9.1.4 Cardiac magnetic resonance imaging

Qualified participants will participate in the cardiac CMR assessments. Participants will undergo CMR at baseline (during screening period), Week 30, ET, Week 78 to evaluate changes in LV mass, myocardial fibrosis, cellular hypertrophy, and cardiac structure and function. Refer to the CMR related manual for additional details.

9.1.5 Pharmacokinetic assessments

Blood samples will be collected for pre-dose mavacamten plasma concentration assessments prior to dosing at post-Day 1 most onsite visits during the placebo-controlled treatment period, and at the visits of Week 78/ET. In additional, a PK sample will be collected 0.5 to 3 hours post-dose at selected visits (**See Table 1-2**). PK sample will also be collected at post-treatment onsite visits. Unscheduled or additional PK samples may be collected if appropriate in the opinion of the investigator and/or Sponsor (also see Section 7.4.3).

At all visits from Day 1 through Week 78, study drug will be administered at the investigational site to facilitate collection of pre-dose PK samples. The date and time of dosing will be documented. All PK samples will be sent to a central laboratory for processing and pre-dose PK results will be transmitted to the IxRS.

9.1.6 Pharmacogenetic assessment

Blood will be drawn preferably on Day 1 for CYP2C19 genotyping.

9.1.7 Cardiac biomarkers

9.1.7.1 NT-proBNP and cardiac troponin

Blood samples will be collected for NT-proBNP and cardiac troponin concentrations at screening and most post-screening onsite visits (**Table 1-2**). Serum concentrations of NT-proBNP and cardiac troponin will be included in the data package provided for the periodic IDMC meetings. Unscheduled or additional blood samples may be collected if appropriate in the opinion of the investigator (e.g., for medical management of HF) and/or Sponsor. Whenever possible, discussion with the Sponsor or Sponsor assigned medical monitor is encouraged.

9.2 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.

Safety data will be monitored on an ongoing basis by the study Sponsor, comprised of individuals with specialized expertise in Cardiology, Pharmacology and PV.

9.2.1 Medical history

A complete medical history will be recorded at screening visit, which will include evaluation (past or present) of the following: general, head and neck, eyes, ears, nose, throat, chest/respiratory, heart/CV, 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).

9.2.2 Physical examination

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

Height (cm) and body weight (kg) will be measured, 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.

9.2.3 12-lead ECG

12-lead ECG evaluations will be performed after 10 minutes of rest at screening and at all onsite study visits. On visits during the treatment period ECGs will be taken prior to dosing. All ECG data will be sent to a core laboratory.

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.

9.2.4 Holter monitor

At 4 time points during the study, participants will wear a Holter monitor to collect continuous HR and rhythm data for approximately 24-48 hours (**Table 1-2**). The Holter monitor uses surface electrodes, internal electronics to capture a continuous ECG waveform, removable memory card to store data, 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.

9.2.5 Vital signs

Vital signs are to be assessed at each onsite study visit. At selected visit, 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 participants 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 laboratory related manual for additional details.

9.2.6 Other safety assessments

Refer to **Section 10** for information on AE assessment and **Section 7.7** for concomitant therapy.

Safety laboratory results will be assessed in an ongoing manner. Essential laboratory parameters are provided in **Appendix 1**.

Serum pregnancy testing will be performed at screening, urine pregnancy at remaining visits throughout the whole study period for all females of childbearing potential. Confirmatory serum testing will be performed if any urine test is positive.

9.3 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 (e.g., 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
- 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 (e.g., tonic water)

Contraception requirements are discussed in Section 11.

9.4 Study procedures by visit

Study procedures are presented by visit in **Table 1-2**. 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 Sponsor or Sponsor assigned medical monitor before conducting an unblinded TTE if possible. And best effort should be made that unblinded clinician/cardiologist review the TTE prior to the investigator, to decide whether to report the TTE result to investigator or which data to report (e.g., based on unblinded clinician/cardiologist's clinical judgement,not report LVEF or LVOT gradient to investigator is acceptable). All information collected from unscheduled visits will be recorded on the eCRF and included in the clinical database.

9.5 Visit scheduling

All visits after Day 1 should occur within the visit window (**see Table 1-2**). If an evaluation is missed, reschedule and perform it as close as possible to the original date.

10. Evaluation, Recording and Reporting of Adverse Events

10.1 Definitions

10.1.1 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 (e.g., tachycardia, enlarged liver, clinically important or abnormal laboratory result), participant-reported symptom (e.g., 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 (e.g., invasive procedures such as biopsies).

For Sponsor to collect additional information about clinically important laboratory results or diagnostic tests (e.g., 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 (e.g., >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 following additional points should be considered for AEs:

- Preplanned medical or surgeries or procedures

  - Preplanned surgeries or procedures that were scheduled prior to signing of informed consent are not considered AEs. However, if a planned procedure is performed early (e.g., as an emergency) due to worsening of a preexisting condition, the worsening of the condition should be captured appropriately as an AE.

- Hospitalization for elective surgeries or procedures

- Elective procedures performed for which there is no change in the participant's medical condition should not be recorded as AEs.

- A hospitalization that was planned prior to the study or was scheduled during the study when the elective surgery or procedure became necessary because of the expected normal progression of the disease should not be recorded as AEs.

- Insufficient clinical response (lack of efficacy)

- Insufficient clinical response, efficacy, or pharmacologic action should not be recorded as an AE. The investigator must make the distinction

- Overdose

- Cases of overdose with any medication without manifested side effects are not considered AEs.

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

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 (e.g., 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

10.1.2 Serious adverse event

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

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

10.2 Collection and reporting of adverse event

10.2.1 Collection periods

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.

10.2.2 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 (e.g., anemia, not low hemoglobin). However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

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

10.2.3 Start date/time and stop date/time

The date (and time, if eligible) that the AE started and the date (and time, if eligible) that the event ended will be recorded. For events that continue for long periods of time, recording the end date as the day the event stabilized will be acceptable.

10.2.4 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?"

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

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

For SAEs, causal relationship will also be assessed for other medications and study procedures. Note that, for SAEs that could be associated with any study procedure, the

causal relationship is implied as “yes.”

10.2.5 Intensity

Record the intensity or severity of the AE 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 interventional indicated.
- Fatal: event led to death.

10.2.6 Seriousness

Record SAE criteria described in **Section 10.1.2** 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 (**see Section 10.2.5**), whereas seriousness is defined by the criteria in **Section 10.1.2**.

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.

10.2.7 Outcome

Record the outcome of the event based on the options provided on the eCRF. Outcome of the SAE should be recorded in SAE form.

10.3 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 EOS regardless of causality will be reported by the investigator or designee to Sponsor/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 will be provided in separate materials for site reference.

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

updating the SAE form with this information.

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

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

10.4 Reporting adverse events of special interest

Symptomatic overdose, outcomes of a pregnancy, and LVEF ≤ 30% as determined by local site read echocardiogram are considered AESI.

AESIs are required to be reported by the investigator to the Sponsor within 24 hours.

10.5 Follow-Up of adverse events and serious adverse events

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

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.

The Sponsor 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.

10.6 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 5 months after the last dose of study drug. The investigator is responsible for informing Sponsor within 24 hours of knowledge of the pregnancy even if no AE has occurred per the reporting guidelines. The participant will be asked to provide information on the outcome of the pregnancy through 6 months after birth or details of premature termination. Spontaneous miscarriage and congenital abnormalities will be reported as SAEs. Consent to report information regarding pregnancy and pregnancy outcomes should be obtained from the partner of the male participant.

Pregnancy of a participant or partner of a male participant should be entered on the Pregnancy Notification CRF. Pregnancy follow-up should be documented on a follow-up form and report to Sponsor or designee within 24 hours.

Any SAE experienced by a participant during pregnancy must be reported on SAE form and be reported within 24 hours.

10.7 Safety reporting to investigators, institutional review boards, independent ethics committees, and regulatory authorities

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

SUSARs are SAEs that qualify for mandatory expedited reporting to regulatory authorities when the SAE is suspected to be caused by the study drug and is considered unexpected (i.e., not defined as expected in the current investigator's brochure [IB], clinical study protocol, or approved labeling for marketed products). In this case, Sponsor/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 IRB/IEC of the SUSAR as required by local regulatory authorities and in accordance with their IRB/IEC policy.

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

11. Risks and Precautions

11.1 General risks

Based on nonclinical data and the available clinical data, four important risks have been described: heart failure due to systolic dysfunction defined as symptomatic LVEF < 50%, teratogenicity, QT prolongation, and increased risk of heart failure due to interaction with CYP2C19 and potent CYP3A4 inhibitors. Refer to **Section 1.3** for details of general risks.

11.2 Pregnancy

11.2.1 Avoidance of pregnancy

Women of childbearing potential must use appropriate methods of birth control. Women of non-childbearing 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 follicle stimulating hormone (FSH) levels are in the postmenopausal range.

11.2.2 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 5 months after the last dose of study drug, female participants should practice true abstinence or use effective means of contraception as follows:

- Estrogen- and progestogen-containing hormonal contraception associated with inhibition of ovulation or progestogen-only hormonal contraception associated with inhibition of ovulation by oral, implantable, or injectable route of administration.
- IUD.
- 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 FSH are in the postmenopausal range.

In addition to the above contraceptive requirements for female participants, male partners must also use a contraceptive (e.g., barrier, condom or vasectomy).

11.2.3 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 5 months after the last dose of study drug. The investigator is responsible for informing Sponsor within 24 hours of knowledge of the pregnancy even if no AE has occurred per the reporting guidelines. The participant will be asked to provide information on the outcome of the pregnancy through 6 months after birth or details of premature termination. Spontaneous miscarriage and congenital abnormalities will be reported as SAEs.

12. Statistical Analyses

12.1 General considerations

A comprehensive SAP will be prepared and finalized before first patient in (FPI) and any subsequent amendments will be documented, with final amendments completed prior to database lock.

12.2 Sample size determination

Approximately 81 participants will be randomized with a ratio of 2:1. The sample size should provide adequate power to determine the superiority of mavacamten in improving Valsalva LVOT gradient relative to placebo. The power calculation assumes a true difference of 30 with a standard deviation of 35 in change from baseline of Valsalva LVOT gradient at 30 weeks between the active treatment arm and the placebo arm. The proposed sample size will provide > 90% power with a 1-sided 2.5% alpha level. Considering the estimated 10% dropout rate, the final sample size would be 81 patients (54 mavacamten: 27 placebo).

12.3 Study endpoints

The analyses will be performed at the end of the 30-week placebo-controlled treatment period and the end of study. The 30-week placebo-controlled treatment period is randomized, two-arm double-blinded, and the conceptual analytical approach is to compare the mavacamten treatment arm with the placebo arm. The goal of the LTE analysis is to access extension follow-up efficacy and safety with all participants receiving mavacamten treatment, to summarize the data from the first administration of mavacamten in the study, by the randomized (treatment) group and, if appropriate, for overall.

- **Primary efficacy endpoint**

- Change from baseline to Week 30 in Vaslalva LVOT peak gradient.

- **Secondary efficacy endpoint**

- Change from baseline to Week 30 in resting LVOT peak gradient.
- Proportion of participants achieving a Valsalva LVOT peak gradient < 30 mmHg at Week 30.
- Proportion of participants achieving a Valsalva LVOT peak gradient < 50 mmHg at Week 30.
- Proportion of participants with at least 1 class improvement in NYHA functional classification from baseline to Week 30.

- Change from baseline to Week 30 in KCCQ CSS.
- Change from baseline to Week 30 in NT-proBNP.
- Change from baseline to Week 30 in cardiac troponin.
- Change from baseline to Week 30 in LV mass index assessed by CMR imaging.

- **Exploratory efficacy endpoints**

- Proportion of participants achieving NYHA Class I and LVOT peak gradient < 30 mmHg for resting and Valsalva gradients at Week 30.
- Change from baseline to Week 30 in echocardiographic indices of cardiac structure and systolic and diastolic function.
- Change from baseline to Week 30 in myocardial fibrosis by CMR imaging.
- Change from baseline to Week 30 in cellular hypertrophy, cardiac structure and function by CMR imaging.
- Change from baseline to Week 30 in Total Symptom Score and Overall Summary Score from KCCQ.

- **Safety endpoints**

- Incidence of LVEF < 50% determined by transthoracic echocardiography TTE.
- Incidence and severity of TEAEs, and treatment-emergent SAEs.
- Incidence of MACEs (CV death, non-fatal stroke, non-fatal myocardial infarction).
- Incidence of hospitalizations (due to CV and non-CV events).
- Incidence of HF events including HF hospitalizations and urgent emergency room/outpatient visits for HF.
- Incidence of atrial fibrillation/flutter (new from screening, and recurrent).
- Incidence of ICD therapy and resuscitated cardiac arrest.
- Incidence of ventricular tachyarrhythmias including ventricular tachycardia, ventricular fibrillation, and Torsades de Pointe.

- Incidence of AESIs (symptomatic overdose, outcomes of pregnancy, LVEF ≤ 30%).

- **Long-term extension endpoints**

- Change from baseline in NYHA class, echocardiographic and CMR parameters, cardiac biomarkers, and KCCQ results through EOS.
- Incidence of safety events, including: LVEF < 50%; TEAEs and treatment-emergent SAEs; MACEs; hospitalizations; HF events; atrial fibrillation/flutter; ICD therapy and resuscitated cardiac arrest; ventricular tachyarrhythmias; or AESIs.

- **Pharmacokinetic endpoint**

- Mavacamten plasma concentration over time.
- PK parameters using a population PK approach.

12.4 Definitions of analysis sets

12.4.1 Intention-to-treat population

All randomized participants regardless of whether they receive study drug, with analyses conducted according to the randomized treatment assignment.

12.4.2 Per-protocol population

All randomized participants who reached Week 30 visit, completed all efficacy assessments and have no important protocol deviation affecting primary efficacy endpoint, with analyses conducted by actual treatment received.

12.4.3 Safety analysis population

All randomized participants who receive at least 1 dose of study drug, with analyses conducted by actual treatment received.

12.4.4 PK analysis population

All randomized participants who receive at least 1 dose of mavacamten and have at least 1 detectable mavacamten plasma drug concentration.

12.5 Method of analysis

Descriptive summary statistics for continuous variables will include the number of participants, mean, SD, median, first quartile, third quartile, minimum, and maximum. Categorical variables will be summarized using counts and percentages.

12.6 Disposition of participants

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

12.7 Demographics, baseline characteristics

Demographic and baseline characteristics will be summarized descriptively.

12.8 Extent of study treatment exposure and compliance

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

The duration of study drug exposure is defined as last dose date – first dose date + 1 day, regardless of intermittent discontinuations. Adjusted duration will also be derived by taking protocol-defined interruptions into account.

A given administration will be considered noncompliant if the 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 exposure and compliance will be summarized descriptively (number [n], mean, SD, median, minimum, and maximum). The compliance of participants with compliance < 80%, 80%~120%, > 120% will be summarized.

12.9 Efficacy analyses

All efficacy analyses will be performed on the ITT population. Supplementary analysis of primary endpoint will also be performed on the Per Protocol population.

12.9.1 Primary endpoint analysis

The primary endpoint of Valsalva LVOT peak gradient change from baseline at Week 30 will be summarized using descriptive statistics and compared between treatment groups using Mixed-Effect Model for Repeated Measures (MMRM). The models will include baseline LVOT gradient value and stratification factor as a covariate (current treatment with beta-blocker or not), and treatment, visit and treatment-by-visit interaction as fixed effects, and participants as random effects. The within-participant covariance between visits will be estimated via an unstructured covariance matrix. In case of convergence problems, alternative covariance structures will be considered in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR (1) with separate participant random effect. The normality assumption will be assessed graphically by a QQ plot of residuals versus the expected quantiles of the standard normal distribution. If normality assumption appears to be violated, other methods might be considered. More detailed statistical analysis strategies will be documented in SAP.

12.9.2 Secondary endpoints analysis

The general analytical approaches of the secondary efficacy endpoints are the following

(The p-values generated for secondary endpoints will be considered as descriptive purpose and thus no multiplicity adjustment will be applied):

- Continuous variables will be summarized with descriptive statistics, including mean, standard deviation, minimum, median, and maximum, and the comparison of the means between treatment groups will be analyzed using analysis of covariance that adjusts for the baseline value and stratification factor, or MMRM if appropriate.
- Categorical variables will be summarized with number and percentage within each category, and the relationship with treatment will be analyzed by Cochran-Mantel-Haenszel test that takes into account of the stratification factor. Point estimate and 2-sided 95% CI for proportion difference between the treatment groups will be computed based on the "stratified Miettinen-Nurminen" method.

12.9.3 Exploratory endpoints analysis

The exploratory endpoints will be summarized using descriptive statistics. Additional details will be specified in the SAP.

12.10 Safety analysis

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

- The safety analysis performed for the 30-week placebo-controlled period will focus on comparing the mavacamten and placebo, and data will be summarized by the treatment received.
- The baseline value is defined as the last available value before the first administration of study drug of analysis interest (i.e., the first dose of randomized drug in the analysis for double blind period).
- For quantitative safety parameters based on 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 and within first 30-week treatment.

12.10.1 Adverse events

AEs will be mapped to system organ classes (SOC) 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 SOC and PT in descending 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, all TEAEs leading to permanent treatment discontinuation, and AESI.

- ***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 group.
- Death in nonrandomized participants or randomized and not treated participants.
- TEAE leading to death (death as an outcome on the AE eCRF page as reported by the investigator) by primary SOC and PT showing number and percent of participants sorted by descending order of count.

- ***Pregnancy***

The following pregnancy summaries will be generated:

- Number of participants or partners of participant who became pregnant summarized by treatment group.
- Outcomes of the pregnancies and analysis of the outcomes.
- TEAE experienced during the pregnancy by primary SOC, and PT showing the number and percent of participants sorted by SOC and PT.

· ***Overdose***

The following summaries for reports of overdose will be generated:

- Number of participants who experienced overdose summarized by treatment group
- Analysis of the cause and occurrence of the overdose
- TEAE experienced during the overdose by primary SOC and PT showing the number and percent of participants sorted by SOC and PT.

12.10.2 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***

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

Fridericia's Correction:

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

· ***ECG numeric variables***

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

· ***Categorical analysis***

The incidence count and percentage of participants with any post dose QTcF values of > 450 msec, > 480 msec, > 500 msec, > 520 msec, and > 550 msec will be tabulated for all participants. Participants with QTcF values > 500 msec will be listed with corresponding baseline values, ΔQTcF, and baseline and treatment HR. The incidence count and percentage of participants with QTcF increase from baseline of > 30 msec and > 60 msec will be tabulated.

· ***Morphology findings***

ECG morphologies for each participant will be listed.

· ***Concentration-QTc analyses***

A concentration-QTc regression analysis, based on data collected from the ECG recordings after drug administration and pre-dose 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.

12.10.3 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 participant 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 number and percentage of participant with elevated liver function tests (based on safety laboratory data) during the TEAE period will be summarized by categories of elevation (> 3 × ULN, > 5 × ULN, > 10 × ULN, > 20 × ULN for ALT and AST, > 1.5 × ULN for ALP, and > 1.5 × ULN and > 2 × ULN for TBL). Potential Hy's law cases will be investigated by summarizing the number of participants with elevated ALT or AST (> 3 × ULN) and with elevated TBL (> 2 × ULN) where transaminase elevation coincides with or precedes bilirubin elevation.

12.10.4 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.

12.10.5 Concomitant medications

Concomitant medications will be summarized.

12.10.6 Other safety analyses

Abnormal physical examination results will be listed.

12.11 Long-term extension analysis

The efficacy and safety endpoints of long-term extension will be summarized using descriptive statistics. Additional details will be specified in the SAP.

12.12 Pharmacokinetics analysis

Plasma concentration will be summarized.

In addition, a population PK analysis may be performed and will be reported in separate report. Data from previously conducted mavacamten studies might be added for the population PK model development, simulation PK/PD and/or exposure-response analysis. This analysis will only be done after related local regulatory approval.

13. Data Collection and Management

13.1 Data confidentiality

All records identifying the participant will be kept confidential and, in accordance with the applicable laws and/or regulations, will not be made publicly available. Participant names will not be supplied to the Sponsor. Only the screening or randomization number will be recorded on the eCRF. If the participant's name appears on any other document or trial materials, then that information must be redacted before a copy of the document is supplied to the Sponsor. Trial data stored on a computer will be stored in accordance with local data protection laws and regulations. Participants will be informed in writing that representatives of the Sponsor, IRB/IEC/REB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws and regulations.

If the results of the trial are published, the participants' identity will remain confidential.

The investigator will maintain a list to enable participants' records to be identified in accordance with applicable laws and regulations.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Either year of birth or exact date of birth (depending on local privacy regulations) will be recorded to establish that the participant satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

13.2 Study center monitoring

Before study initiation, at a study center initiation visit or at an investigator's meeting, Sponsor (or designated CRO) will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the study center regularly to check the completeness of participant records, the accuracy of entries on the eCRFs, the adherence to the protocol and to Good Clinical Practice (GCP), the progress of enrollment, and to ensure that study drug is being stored, dispensed, and counted appropriately according to specifications by site staff. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information recorded on eCRFs must be traceable to source documents in the participant's file. The investigator must also keep the original

signed ICF (a signed copy is given to the participant).

The investigator must give the field monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Sponsor's monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study specific monitoring plan.

13.3 Data collection

The designated investigator staff will enter the data required by the protocol into the eCRFs. The eCRFs have been built using fully validated secure web-enabled software. The investigator and site staff will not be given access to the electronic data capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and allow modification or verification of the entered data by the investigator's staff.

The principal investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

PK and cardiac biomarker samples and imaging scans obtained during the course of the study will be collected from the study centers and analyzed by a Sponsor designated laboratory. Designated study center staff will enter the information required by the protocol into the appropriate eCRF and/or designated laboratory requisition forms. Field monitors will review the eCRFs and laboratory paper requisition forms for accuracy and completeness and instruct site personnel to make any required corrections or additions. One copy of the requisition form will be forwarded to each analytical laboratory with the respective sample(s) by the designated study center staff; and one copy will be retained at the study center.

13.4 Database quality assurance

Quality assurance and quality control systems will be implemented and maintained per Standard Operating Procedures (SOP) by Sponsor or Sponsor contracted CRO, as appropriate, to ensure that this clinical study is conducted and data are generate d, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 GCP: Consolidated Guidance and the applicable regulatory requirement.

13.5 Study documentation, record keeping and retention of documents

Each participating study center will maintain appropriate medical and research records for this trial, in compliance with section 4.3 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of participants. As part of participating in sponsored study, each study center will permit authorized representatives of the Sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality

assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).Examples of these source documents, data and records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

14. Study Compliance and Ethical Considerations

14.1 Compliance statement

This clinical study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/ GCP, applicable regulatory requirements.

14.2 Informed consent

The ICFs used for the study must comply with the ICH GCP guidelines, and 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, to ensure 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 an impartial witness, must give informed consent in writing.

Prior to participation in any study-related procedures, participants must sign and date an Ethics Committee (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.

14.3 Ethics committee

The term EC used in this document refers to an IRB or 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 (e.g., 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), including the documents reviewed, such as informed consent, and date of the review. The investigator has the responsibility to provide Sponsor with the written EC approval prior to initiating any study-related procedures.

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

- All SUSARs (as described in **Section 10.7**)
- 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 Sponsor.

15. Administrative Procedure

15.1 Sponsor's responsibilities

Sponsor reserves the right to terminate the study at any time. Sponsor and the investigators will assure that adequate consideration is given to the protection of the participants' interests. Sponsor retains the right to terminate the study and remove 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

15.1.1 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 IMP used in this study. These data will be processed with adequate precautions to ensure confidentiality according to applicable laws.

Sponsor 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 participant.

Sponsor, 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 Sponsor and will have the right to rectify erroneous or inaccurate data up until database lock.

15.1.2 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.

15.1.3 Ongoing communication of safety information during the study

Sponsor will provide the investigator(s) with documentation of SUSARs from this study and other studies. The investigator(s) must forward this documentation to the EC as per EC's requirement or local regulation.

Sponsor 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.

15.1.4 Study monitoring

Sponsor 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 (e.g., pharmacy, diagnostic laboratories).

15.1.5 Study auditing and inspecting

Sponsor 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 Sponsor, EC, government regulatory authority, and Sponsor's quality assurance personnel or its designees by providing direct access to source data/documents after appropriate notification from Sponsor.

15.2 Investigator's responsibilities

15.2.1 Screening log

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

15.2.2 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 return/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 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.

15.2.3 Reporting and recording of study data

Data will be captured and compiled using procedures developed by Sponsor or designee. EDC technology will be used for this study. Clearly record all requested study data on the eCRF and other forms as required. Whenever possible, record the reason for missing data in the source document. Only individuals who are identified on the study delegation 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 (i.e., 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.

15.2.4 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, phone)
- Documentation verifying participant eligibility (i.e., 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.

15.2.5 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.

15.2.6 Records retention

Sponsor 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 Sponsor, the investigator agrees to keep records, including the identity of all participants (i.e., 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 Sponsor.

15.2.7 Protocol deviations

Unless there is a safety concern, no protocol deviations will be allowed or waived 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 participant without prior EC approval. Immediately after the implemented deviation or change, the investigator must report and explain the reasons

for the protocol deviation to sponsor and EC as per EC's requirement. The medical monitor will review the protocol deviation and notify the study monitor of the response.

15.2.8 Blood sample collection/storage

Blood samples that are collected as part of protocol procedures will be stored and analyzed for PK, PD and CYP2C19 genotype analyses.

15.3 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.

15.4 Protocol amendments and study administrative letters

Study procedures will not be changed without the approval of Sponsor.

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

The amendment/addendum 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/addendum requires a change to the ICF, the EC will need to approve the revised ICF before the revised form is used.

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

15.5 Administrative consideration

- **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 into 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 collect ECG, echocardiographic, Holter and CMR data from digital equipment used by clinical site personnel
- IxRS will be used to dispense IMP and transfer data in double-blinded manner

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.

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

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

- **Study records**

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

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

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

16. Publication Policy

The data and results of the study will be owned by Sponsor and shall be confidential information of Sponsor, participant to the investigator's publication rights, all as outlined in the agreement between the investigator/institution and Sponsor regarding the conduct of the clinical study (the "Clinical Study Agreement"). It is understood by the investigator that Sponsor may use the information developed in this study in connection with the development of Sponsor 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 Sponsor.

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 Sponsor's intention to prevent publication of the data generated in the study; rather, Sponsor 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.

17. Reference

Alfares AA, Kelly MA, McDermott G, Funke BH, Lebo MS, Baxter SB, et al., Result of clinical genetic testing of 2912 probands with hypertrophic cardiomyopathy: expanded panels offer limited additional sensitivity. Genet Med. 2015; 17: 880-8.

Anderson RL, Trivedi DV, Sarkar SS, et al., Deciphering the super relaxed state of human β-cardiac myosin and the mode of action of Mavacamten from myosin molecules to muscle fibers. Proc Natl Acad Sci U S A. 2018;115(35): E8143-E8152.

Autore, CP, Bernabo P, Barilla CS, Bruzzi P, Spirito P. The prognostic importance of left ventricular outflow obstruction in hypertrophic cardiomyopathy varies in relation to the severity of symptoms. J Am Coll Cardiol. 2005;45: 1076-80.

Chinese Society of Cardiology, et al. Guidelines for Diagnosis and Treatment of Chinese Adult Patients with Hypertrophic Cardiomyopathy. Chin J Cardiol.2017;45(12):1015-1032.

Chuan P, Sivaramakrishnan S, Ashely EA, Spudich JA. Cell-intrinsic functional effects of the α-cardiac myosin Arg-403-Gln mutation in familial hypertrophic cardiomyopathy. Biophys J. 2012;102: 2782-2790.

Elliott PM, Gimeno JR, Thaman R, Shah J, Ward D, Dickie S, et al., Historical trends in reported survival rates in patients with hypertrophic cardiomyopathy. Heart. 2006;92: 785-91.

Elliott PM, Anastasakis A, Borger MA, et al., 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy. Eur Heart J. 2014;35(39):2733-2779.

Firoozi S, Elliott PM, Sharma S, et al., Septal myotomy-myectomy and transcoronary septal alcohol ablation in hypertrophic obstructive cardiomyopathy: a comparison of clinical, haemodynamic and exercise outcomes. Eur Heart J. 2002;23(20):1617-1624.

Frey N, Luedde M, and Katus HA. Mechanisms of disease: hypertrophic cardiomyopa thy, Nat Rev Cardiol. 2011;9: 91-100.

Gersh BJ, Maron BJ, Bonow RO, et al., 2011 ACCF/AHA Guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2011;58: e212-260.

Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol. 2000;35: 1245-1255.

Heart Failure Committee of Chinese Medical Doctors Association, et al., Chinese guidelines for the management of hypertrophic cardiomyopathy. Chin J Heart Fail & Cardiomyopathy.2017; 1(2): 65-86.

Heart Failure Group of Chinese Society of Cardiology, et al., Chinese guidelines for the diagnosis and treatment of heart failure 2018. Zhonghua Xin Xue Guan Bing Za Zhi. 2018; 46(10): 760-789.

Heitner SB, Jacoby D, Lester SJ, Owens A, et al., Mavacamten treatment for obstructive hypertrophic cardiomyopathy a clinical trial. Annals of internal medicine. 2019;170(11):741-748.

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

Hua TR, Zhang SY. Cardiomyopathies in China: A 2018-2019 state-of-the-art review, Chronic Dis Transl Med.2020; 6(4): 224-238.

Ho CY, Sweitzer NK, McDonough B, Maron BJ, Casey SA, Seidman JG, et al., Assessment of diastolic function with Doppler tissue imaging to predict genotype in preclinical hypertrophic cardiomyopathy. Circulation. 2002;105: 2992-7.

Ho CY, Day SM, Ashley EA, Michels M, Pereira AC, Jacoby D, et al., Genotype and Lifetime Burden of Disease in Hypertrophic Cardiomyopathy: Insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe). Circulation.2018;138: 1387-98.

Kim LK, Swaminathan RV, Looser P, Minutello RM, Wong SC, Bergman G, et al., Hospital volume outcomes after septal myectomy and alcohol septal ablation for treatment of obstructive hypertrophic cardiomyopathy: US Nationwide Inpatient Database, 2003-2011. JAMA Cardiol. 2016;1: 324-32.

Maron BJ, Rowin EJ, Casey SA, Link MS, Lesser JR, et al., Hypertrophic cardiomyopathy in adulthood associated with low cardiovascular mortality with contemporary management strategies. J Am Coll Cardiol. 2015;65(18):1915–1928.

Maron MS. Clinical utility of cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Cardiovasc Magn Reson. 2012; 14:13.

Maron MS, Olivotto I, Zenovich AG, Link MS, Pandian NG, Kuvin JT, et al., Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. Circulation.2006; 114(21):2232–2239.

Maron MS, Olivotto I, Betocchi S, Casey SA, Lesser JR, Losi MA, Cecchi F, Maron BJ. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med. 2003;348(4): 295–303.

Maron, MS, Rowin EJ, Olivotto I, Casey SA, Arretini A, Tomberli B, et al., Contemporary natural history and management of nonobstructive hypertrophic cardiomyopathy, J Am Coll Cardiol. 2016;67: 1399-409.

Mckenna WJ, Maron BJ, Thiene G, et al., Classification, epidemiology, and global burden of cardiomyopathies. Circ Res. 2017;121(7): 722-730.

McKenna WJ, Judge DP. Epidemiology of the inherited cardiomyopathies. Nat Rev Cardiol. 2020; 18(1):22-36.

Moravsky G, Ofek E, Rakowski H, Butany J, Williams L, Ralph-Edwards A, Wintersperger BJ, Crean A. Myocardial fibrosis in hypertrophic cardiomyopathy: accurate reflection of histopathological findings by CMR. JACC Cardiovasc Imaging. 2013; 6: 587-596.

Moon I, Lee SY, Kim HK, Han KD, Kwak S, Kim M, Lee HJ et al., Trends of the prevalence and incidence of hypertrophic cardiomyopathy in Korea: A nationwide population-based cohort study. PLoS One. 2020; 15: e0227012.

Olivotto I, Oreziak A, Barriales-Villa R, Abraham TP, Masri A, Garcia-Pavia P, Saberi S, Lakdawala NK, et al, Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet.2020; 396(10253):759–769.

Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, Evanovich LL, Hung J, Joglar JA, Kantor P, Kimmelstiel C, Kittleson M, Link MS, Maron MS, Martinez MW, Miyake CY, Schaff HV, Semsarian C, Paul S. 2020 AHA/ACC Guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: executive summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2020; 76(25):3022-3055.

Ponikowski P, Voors AA, Anker SD, et al., 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2016 May 20;37(27):2129-2200.

Pujades-Rodriguez M, Guttmann OP, Gonzalez-Izquierdo A, Duyx B, O'Mahony C, Elliott P, et al., Identifying unmet clinical need in hypertrophic cardiomyopathy using national electronic health records. PLoS One. 2018;13: e0191214.

Quarta G, Aquaro GD, Pedrotti P, Pontone G, Dellegrottaglie S, Iacovoni A, Brambilla P, Pradella S, et al., Cardiovascular magnetic resonance imaging in hypertrophic cardiomyopathy: the importance of clinical context. Eur Heart J Cardiovasc Imaging. 2018;19: 601-610.

Sedehi D, Finocchiaro G, Tibayan Y, et al., Long-term outcomes of septal reduction for obstructive hypertrophic cardiomyopathy. J Cardiol. 2015;66(1):57-62.

Sherrid MV, Gunsburg DZ, Moldenhauer S, Pearle G. Systolic anterior motion begins at low left ventricular outflow tract velocity in obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2000;36: 1344-54.

Sommese RF, Sung J, Nag S, et al., Molecular consequences of the R453C hypertrophic cardiomyopathy mutation on human beta-cardiac myosin motor function. Proc Natl Acad Sci USA. 2013;110: 12607-12612.

Sung J, Choe E, Elting M, et al., Single molecule studies of recombinant human α- and β-cardiac myosin to elucidate molecular mechanism of familial hypertrophic and dilated cardiomyopathies. Biophysical J. 2012;102(3 suppl 1):613a-614a.

Teekakirikul P, Zhu W, Huang HC, Fung E. Hypertrophic Cardiomyopathy: an overview of genetics and management. Biomolecules. 2019;9(12):878.

Yancy CW, Jessup M, Bozkurt B, et al., 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62(16): e147-239.

Zou Yubao, Song Lei, Wang Zhimin, Ma Aiqun, Liu Tangwei, Gu Huimin, et al., Prevalence of idiopathic hypertrophic cardiomyopathy in China: A population-based echocardiographic analysis of 8080 adults. AM J Med. 2004;116(1):14-8.

Appendix 1: Laboratory Assessment

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

Hematology/Coagulation	Biochemistry	Urinalysis[a]
•WBC count, including differential count	• Sodium	• Specific gravity
• Platelet count	• Potassium	• pH
• Hemoglobin	• Chloride	• Protein
• Hematocrit	• Calcium	• Glucose
• RBC count	• Magnesium	• Ketones
• APTT	• Creatinine	• RBC
• INR	• eGFR	• WBC
• FIB	• ALP	
• PT	• ALT	
• TT	• AST	
	• CK	
	• Glucose	
	• Total protein	
	• Albumin	
	• Total bilirubin	
	• Direct bilirubin	
	• Uric acid	

ALT = alanine aminotransferase; ALP = alkaline phosphatase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CBC = complete blood count; CK = creatine kinase; eGFR = estimated glomerular filtration rate; FIB = fibrinogen; INR = international normalized ratio, RBC = red blood cells; TT = thrombin time; WBC = white blood cells.

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

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

The following nonsafety laboratory parameters will be measured at Screening:

- Hepatitis panel (HBV and HCV)
- HIV test
- FSH (only for postmenopausal women)
- Pregnancy test (β hCG) (for all females of childbearing potential)

Appendix 2: Prohibited Medications

Cardiotoxic Agents

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

Disopyramide, cibenzoline or ranolazine

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

Moderate and Potent CYP2C19 Inhibitors and Potent CYP3A4 Inhibitors

Potent and moderate CYP2C19 inhibitors and potent CYP3A4 inhibitors are prohibited from 14 days before Screening through the EOS. Examples are listed below. For any medication in question, ask the medical monitor.

CYP2C19 inhibitors

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

CYP3A4 inhibitors

- Boceprevir (antivirals)
- Ceritinib (kinase inhibitors)
- Clarithromycin (antibiotics)
- Cobicistat (GS-9350)
- Conivaptan (diuretics)
- Grapefruit juice (food products)
- Idelalisib (kinase inhibitors)
- Indinavir (protease inhibitors)
- Itraconazole (antifungals)
- Josamycin (antibiotics)
- Ketoconazole (antifungals)

- LCL161 (cancer treatments)
- Mibefradil (calcium channel blockers)
- Mifepristone (antiprogestins)
- Nefazodone (antidepressants)
- Nelfinavir (protease inhibitors)
- Posaconazole (antifungals)
- Ribociclib (kinase inhibitors)
- Ritonavir (protease inhibitors)
- Saquinavir (protease inhibitors)
- Telaprevir (antivirals)
- Telithromycin (antibiotics)
- Tipranavir (protease inhibitors)
- Troleandomycin (antibiotics)
- Tucatinib (kinase inhibitors)
- Viekira Pak (antivirals)

St. John's Wort

Use of St. John's Wort is prohibited from 14 days before Screening to EOS.

Biotin Supplements

Biotin supplements are prohibited from 14 days prior to screening through the end of study visit. Multivitamins that contain <1000 mg QD of biotin are allowed during the study but must be stopped 24 hours prior to each study visit.

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 (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 sponsor as an SAE within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded).

The appropriate CRF (e.g., AE CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities are to be completed and sent to sponsor.

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

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, 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 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: NASH, hypoxic/ischemic hepatopathy, and biliary tract disease
- Obtain gastroenterology or hepatology consult
- Perform appropriate liver imaging or biopsy if clinically indicated; strongly consider these tests in cases of concurrent transaminase and TBL elevation.
- Follow the participant until all laboratory abnormalities return to baseline or normal. The “close observation period” is to continue for a minimum of 4 weeks after investigational product(s) or protocol-required therapies discontinuation

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

Appendix 4 Management of Participants Who Are Unable to Attend Onsite Study Visits with Unavoidable Circumstances (e.g., COVID-19 or other pandemics or natural disasters)

If participants are not able to visit the study site due to unavoidable circumstances (e.g., COVID-19 or other pandemics or natural disasters), the following provisions may be made:

- Study visits may be performed by phone/virtually.
- Study visits may be performed in participants' home residence by a visiting health care professional assigned by Primary Investigator and approved by sponsor.
- Study assessments may be performed in a local hospital close to participants' home residence with Sponsor's approval.
- Participants who are unable to "be safety monitored during maintaining the study drug" (see below) may be required to temporarily discontinue study drug (mavacamten or placebo).

The visiting health care professional or local hospital must be confirmed as qualified and approved by the investigator and Sponsor before performing study assessments.

If possible, training will be provided to ensure assessments' quality and reduce discrepancy between on-site and remote assessments.

Remote Health Assessment

Protocol-specified assessments listed below may be conducted in the participant's home by a visiting health care professional or via telemedicine:

- NHYA classification may be assessed by the principal investigator via telemedicine
- The KCCQ may be completed independently by the participant at home
- ECG may be acquired by visiting health professional
- Holter monitor may be applied and removed at participant's home by a visiting healthcare professional.
- Blood sample collection may be done by a visiting health care professional

All above also can be done in a local hospital close to participants' home residence with Sponsor's approval with similar method.

In addition, physical examination may be performed by the local hospital. TTE may be performed by a qualified sonographer who has been certified by the echocardiography core lab at a local hospital and submitted to the core lab for interpretation. If impossible, the TTE may be performed and interpreted by sonographer in the local hospital according to his/her routine clinical practice. The TTE will not be submitted to the core lab or used for data analysis. These TTE will only be used as safety monitoring to ensure the safety (i.e., LVEF not less than 50%) during maintaining the study drug (and the dose). Please refer to the study-related documents for details.

Drug Dispensation

In certain circumstances, it may be necessary to ship study drug directly to participants. When study drug is shipped directly to the participants, a qualified individual who is contracted by the Sponsor or CRO will open the package of study drug, review temperature monitoring data, and confirm receipt. Study sites should contact participants by telephone to confirm study drug delivery. The study drug bottle(s) from the previous study visit will be returned to the site by the designee.

Temporary Discontinuation of Study Drug

Participants in 30-week Placebo-controlled Period (Day 1 to Week 30)

Under unusual circumstances such as a Pandemic or Natural Disaster, if participants in the placebo-controlled dosing period of the study, cannot "be safety monitored during maintaining the study drug" (i.e., at a minimum, TTE to be performed for safety assessment) within 1 week over their scheduled study assessment window, as they cannot be seen at the site, local hospital or by a home healthcare provider, the participant will be contacted by the site at the end of the 1-week overdue period and instructed to temporarily discontinue study drug (mavacamten or placebo). Participants who discontinue study drug should be contacted by the site every 4 weeks from the time of discontinuing study drug to assess for AEs and to document concomitant medications.

If participants can return to the study site for visit or "be safety monitored during maintaining the study drug" within 6 weeks of discontinuation of study drug and prior to the "Week 20" visit (including "Week 20" visit), the study drug could be resumed at the site or under the remote guidance of the site (i.e., resume the study drug and the dose received prior to discontinuation) at scheduled or unscheduled visit. For example, if participants cannot return to the study site for the "Week 8" visit, the site will instruct them to discontinue the study drug and conduct a remote visit during this period. If participants can return to the study site after 3 weeks, unscheduled visit ("Week 11") will be performed and the study drug will be resumed, and subsequent scheduled visits will be completed according to the protocol. If participants can return to the study site after 6 weeks, the study drug will be resumed at the "Week 14" visit (scheduled visit).

If the study drug is resumed at "Week 6", "Week 12" or "Week 18" visit, the dose will

not be up-titrated at “Week 8”, “Week 14” or “Week 20” regardless of TTE parameters and pre-dose PK results (dose remain unchanged). Dose adjustments at subsequent visits will comply with Table 5 and Table 6. If the study drug is resumed at “Week 8”, “Week 14” or “Week 20” visit, an unscheduled TTE should be performed to assess participants’ safety.

If participants cannot return to the study site for visit or “be safety monitored during maintaining the study drug” within 6 weeks of discontinuation of study drug OR prior to the “Week 20” visit (including the “Week 20” visit), the "post-treatment visit" will be performed (remote visit; participants will be followed up to 8 weeks after the last dose, 20 weeks for poor CYP-2C19 metabolism). When the participant can return to the study site and the study is still in the participants’ enrollment, under sponsor’s approval, the participant may receive a new participant ID and undergo rescreening to re-enter the study (Prior to re-screening, the treatment should be discontinued for at least 8 weeks, 20 weeks for poor CYP-2C19 metabolism). All screening assessments need to be repeated. Participants must meet the inclusion and exclusion criteria (the exclusion criteria #7 is no longer applicable):

- Participants will restart study drug (mavacamten 2.5 mg or placebo, consistent with the drug that the participant was randomized to at the beginning of the study, before temporary discontinuation) at Day 1 and resume study visits from Day 1.

- Participants who do not qualify based on re-screening assessments may be scheduled for repeat screening at a later time.

Participants in LTE Period

Under unusual circumstances such as a Pandemic or Natural Disaster, if participants in the LTE period, cannot “be safety monitored during maintaining the study drug” (i.e., at a minimum, TTE to be performed for safety assessment) within 4 weeks over their scheduled study assessment window, as they cannot be seen at the site, local hospital or by a home healthcare provider, the participant will be contacted by the site at the end of the 4-week overdue period and instructed to stop taking study drug (mavacamten). Sites should conduct “post-treatment visit” (remote visit; participants will be followed up to 8 weeks after discontinuation of treatment, 20 weeks for participants with poor CYP-2C19 metabolism) to assess AEs and record concomitant medications.

Sponsor signature page

Authorization of the Sponsor

A Phase III, Randomized, Double-blinded, Placebo-controlled Clinical Study with A Long-term Extension to Evaluate the Efficacy and Safety of Mavacamten in Chinese Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy.

The clinical study protocol has been reviewed and approved by the representative of MyoKardia, Inc.

Printed Name	**Signature**
Title	**Date (mm-dd-yyyy)**

Investigator's signature page

I have read and understood the contents of the clinical protocol, A Phase III, Randomized, Double-blinded, Placebo-controlled Clinical Study with A Long-term Extension to Evaluate the Efficacy and Safety of Mavacamten in Chinese Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy, and I agree to the following:

I have reviewed this protocol and agree to implement this protocol in compliance with the ethical principles deriving from the Declaration of Helsinki, Good Clinical Practice of International Conference on Harmonization, and the requirements of any regulatory authority and/or institutional review committee/independent ethics committee (IRB/IEC).

I agree to allow the Sponsor's representatives and relevant regulatory authorities to access my participant study records so that they can verify the data I or my designee have entered into the CRF. I understand the responsibilities as a Principal Investigator.

I understand that the Sponsor may decide to suspend or prematurely terminate this study at any time for any reasons; such decisions will be communicated to me in writing. Conversely, if a decision is made to withdraw my center from this study, I will immediately notify the Sponsor in writing.

Printed Name	**Signature**
Title	**Date (mm-dd-yyyy)**