Study design and rationale of EXPLORER-CN: a phase III, randomised, double-blind, placebo-controlled clinical study to evaluate the efficacy and safety of mavacamten in Chinese adults with symptomatic obstructive hypertrophic cardiomyopathy

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ABSTRACT

Introduction Hypertrophic cardiomyopathy (HCM) is a primary myocardial disease commonly caused by pathogenic genetic variants encoding sarcomere proteins. Mavacamten, a first-in-class allosteric inhibitor of cardiac-specific myosin, has demonstrated efficacy and safety in international clinical trials of patients with symptomatic obstructive HCM (oHCM) but clinical evidence for mavacamten in the Chinese population is lacking.

Methods and analysis EXPLORER-CN is a multicentre, phase III, randomised, double-blind, placebo-controlled registration trial to evaluate the efficacy and safety of mavacamten in Chinese adults with symptomatic oHCM. The study will enrol approximately 81 participants with symptomatic oHCM. Eligible participants are randomised 2:1 to receive once-daily, oral mavacamten (starting dose 2.5 mg/day), or matching placebo, for 30 weeks, followed by a long-term extension (LTE) period of 48 weeks with active treatment for all subjects. The mavacamten dose will be adjusted by pharmacokinetic (PK)/pharmacodynamic (PD) parameters during the double-blinded, placebo-controlled period and PD-only during the LTE period. The primary efficacy endpoint is change from baseline to week 30 in Valsalva left ventricular outflow tract (LVOT) peak gradient determined by Doppler echocardiography. Secondary efficacy endpoints are change in resting LVOT peak gradient, proportion of participants achieving a Valsalva LVOT peak gradient <30 or < 50 mm Hg, New York Heart Association functional class improvement, change in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score, cardiac biomarkers and left ventricular mass index evaluated by cardiac magnetic resonance. LTE endpoints will characterise the long-term safety and efficacy of mavacamten.

Ethics and dissemination This clinical study has been approved by the Drug Clinical Trial Ethics Committee of the Chinese Academy of Medical Sciences & Peking Union Medical College Hospital (reference number: HS2021089).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This trial will assess mavacamten specifically in a Chinese population, with comprehensive data collection to evaluate its efficacy and safety.
⇒ Dose titration will be based on both pharmacokinetic/pharmacodynamic (PK/PD) parameters during the double blinded, placebo-controlled period and PD-only titration during the long-term extension period.
⇒ The study will provide long-term safety and efficacy data for mavacamten.
⇒ Limited by the fact that peak oxygen consumption by cardiopulmonary exercise testing and postexercise echocardiography data will not be available.
⇒ The study is not powered to detect differences in hard clinical outcomes (eg, major adverse cardiovascular events, death).

Written informed consent will be obtained from each participant. The results will be published in peer-reviewed journals and presented during national and international conferences. Trial registration number NCT05174416.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM), a primary myocardial disease commonly caused by pathogenic genetic variants encoding sarcomere proteins, is a global disease that has been reported in >120 countries on all continents, including the highly populous nation of China.1–3 The prevalence of HCM has been estimated to be 1:200–1:500 in the general adult population without a distinct geographic or ethnic pattern of distribution.2


Received 30 December 2022
Accepted 30 May 2023

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In China, the age-adjusted and sex-adjusted prevalence is approximately 80 per 100,000 adults, equating to at least 1 million cases, which possibly represents the largest HCM population worldwide. Accompanying the increased understanding of HCM, awareness of the disease is now penetrating healthcare systems in China, defining an emerging frontier for diagnosis and management.

HCM is predominantly an obstructive disease, with a large proportion of patients with symptomatic HCM having left ventricular outflow tract (LVOT) obstruction (gradients ≥30 mm Hg) at rest or with provocation. HCM is clinically heterogeneous with presentation varying from asymptomatic to symptomatic, but typically there is a gradual progression of dyspnoea and exercise intolerance, often in the context of obstructive physiology. Therefore, eliminating LVOT obstruction (LVOTO) is one of the primary treatment goals for obstructive HCM (oHCM).

The treatment pattern of oHCM is similar in both China and other countries. Standard pharmacological options for oHCM are β-blockers, non-dihydropyridine calcium-channel blockers (e.g., verapamil, diltiazem) or disopyramide in combination with either class of drugs. In patients with refractory oHCM, septal reduction therapy using surgical myectomy or percutaneous alcohol septal ablation is considered safe and effective in relieving LVOTO. However, the risks of cardiac surgery, lack of experienced centres and the fact that many patients are not amenable to septal reduction, has highlighted the need for alternative approaches. Implantable cardioverter defibrillator placement may also be an option to prevent oHCM-related sudden cardiac death.

Novel pharmacotherapy has attempted to address an important mechanism in HCM. Mavacamten, a first-in-class allosteric inhibitor of cardiac-specific myosin, is designed to target hypercontractility and stiffness associated with oHCM. In the pivotal, global, phase III trial, EXPLORER-HCM (Mavacamten for Treatment of Symptomatic Obstructive Hypertrophic Cardiomyopathy), mavacamten was shown to significantly reduce the LVOT gradient and also improve exercise capacity, New York Heart Association (NYHA) functional class and patient-reported health status in patients with oHCM. Based on robust evidence, the US Food and Drug Administration (FDA) approved mavacamten in April 2022 for the treatment of adults with symptomatic oHCM, to improve functional capacity and symptoms. However, clinical evidence for mavacamten in the Chinese population is lacking and, therefore, a well-designed clinical trial is warranted. This phase III registration 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.

**Methods and analysis**

**Study design**

EXPLORER-CN (ClinicalTrials.gov Identifier: NCT05174416) is a multicentre, phase III, randomised, double-blind, placebo-controlled registration trial to evaluate the efficacy and safety of mavacamten in Chinese adults with symptomatic oHCM.

The study design is shown in **Figure 1**. The trial comprises a screening period of up to 4 weeks followed by a double-blinded, placebo-controlled treatment period of 30 weeks. After completing the 30-week treatment period, eligible participants will continue for a long-term extension (LTE) period of 48 weeks, including double-blinded and open-label LTE phases. The post-treatment follow-up period is 8 weeks, or 20 weeks for poor cytochrome P450 (CYP) 2C19 metabolisers.

**Study organisation**

EXPLORER-CN will be conducted at ~17 experienced HCM sites in China. EXPLORER-CN has been approved by the institutional review boards at participating centres. Written informed consent will be obtained from each participant prior to any study-related procedures. The trial is sponsored and funded by Shanghai LianBio Development Co., Ltd. with IQVIA RDS (Shanghai) Co., Ltd. serving as the contract research organisation to provide monitoring, data and site management. Calyx China Co., Ltd is serving as the imaging core laboratory and is responsible for the independent conduct of the trial under charter of the imaging (both echocardiography and cardiac magnetic resonance (CMR)). Statistical analysis on the final trial data will be performed by the statistical team at IQVIA. An Independent Data Monitoring Committee will provide study oversight by assessing safety. A Clinical Event Adjudication Committee is assembled to independently adjudicate a prespecified set of safety endpoints including, but not limited to, major adverse events. **Figure 1** Study design. *Post treatment follow-up period: 8 weeks (or 20 weeks for poor CYP2C19 metaboliser). FU, follow-up; LTE, long-term extension; PM, poor metabolisers; RCT, randomised, controlled trial.
cardiovascular events (MACEs) and heart failure (HF) events.

The authors are solely responsible for the design and conduct of this study, all study analyses and the drafting and editing of the paper and its final contents.

Study population
EXPLORER-CN will enrol approximately 81 participants with symptomatic oHCM. Full inclusion/exclusion criteria are summarised in online supplemental table 1. Main inclusion criteria are aged ≥18 years old; body weight >45 kg; diagnosed with oHCM consistent with current American College of Cardiology/American Heart Association,7 European Society of Cardiology6 and Chinese Society of Cardiology8 guidelines; LVOT peak gradient ≥50 mm Hg during screening as assessed by echocardiography at rest or after Valsalva manoeuvre (confirmed by echocardiography core laboratory interpretation), with documented resting left ventricular ejection fraction (LVEF) ≥55% by core laboratory read of screening transthoracic echocardiography (TTE) at rest; NYHA functional class II or III symptoms at screening. In addition, premenopausal female subjects, if sexually active, must use an acceptable birth control method.

Main exclusion criteria include known infiltrative or storage disorders causing cardiac hypertrophy that mimics oHCM; history of syncope or sustained ventricular tachyarrhythmia with exercise within 6 months before screening; paroxysmal atrial fibrillation (AF) present at screening; current treatment or planned treatment during the study with disopyramide, cibenzoline, ranolazine or a combination of β-blockers and verapamil or diltiazem, and previous successful treatment with invasive septal reduction (surgical myectomy or percutaneous alcohol septal ablation) within 6 months prior to screening or planned invasive septal reduction during the study.

Subjects who successfully complete the 30-week double-blinded, placebo-controlled treatment period (still on the study drug) and have no active safety concerns (in the judgement of the investigator), will be eligible for the LTE period.

Study treatment
At the start of the 30-week treatment period (day 1), participants are randomised in a 2:1 ratio (mavacamten: placebo) via an interactive response system (IxRS). Randomisation will be stratified according to current treatment with β-blocker (yes or no).

In the 30-week, double-blinded, placebo-controlled treatment period, participants will receive mavacamten or matching placebo. At designated time points (figure 2), the dose of mavacamten will be adjusted via a prespecified dose titration scheme based on echocardiography and predose plasma drug concentration. Permissible doses are 1 mg, 2.5 mg, 5 mg, 10 mg and 15 mg.

At the end of week 30, eligible participants will enter the LTE period. Participants in the mavacamten group will remain on the same dose as at week 30, and those in the placebo group will switch to mavacamten with the dose adjusted via a titration scheme based on echocardiography only (figure 3).

Titration and dose adjustment
The 30-week double-blind, placebo-controlled treatment period includes a 3-step, blinded dose titration scheme with opportunities to increase the mavacamten dose at week 8, week 14 and week 20. Unlike the EXPLORER-HCM trial,12 participants are started on a lower dose, 2.5 mg of oral, once-daily mavacamten or matching placebo on day 1. All dose titrations are blinded and programmed via the IxRS system to remain unchanged, be reduced or be increased, as guided by core laboratory determination of LVEF, Valsalva LVOT gradient, and plasma drug concentration (online supplemental table 2).

During the LTE period, participants who were previously on placebo will start mavacamten 2.5 mg at the end of week 30, and the dose will be adjusted based on resting LVEF and Valsalva LVOT gradient, with opportunities to decrease the dose at week 36 and increase the dose at week 42, week 54 and week 66 (online supplemental table 3). During the double-blinded LTE period, all dose titrations remain blinded and are programmed via the
IxRS system as guided by core laboratory determination of TTE. During the open-label LTE period, all dose titrations will be made by the investigator according to the local measured echocardiography parameters.

In the double-blinded, placebo-controlled treatment period and double-blinded LTE phase, results of TTEs performed at each scheduled visit following randomisation should be kept blinded to the participants, investigator and other blinded study site personnel to maintain blinding. An exception may occur if LVEF ≤30% is measured at the site, then the investigator will be notified at the first moment by the site TTE reporter and study drug will be permanently discontinued. In the open-label LTE treatment phase, TTEs will be site-read and not blinded to the investigator or the site.

Prespecified criteria for temporary discontinuation of study drugs are based on safety parameters of LVEF (<50%) or pharmacokinetics (predose plasma drug concentration >1000 ng/mL, for the double-blind, placebo-controlled treatment period only). If any criteria are met and the study drug is discontinued, participants will return to the site in 2–4 weeks for a reassessment visit. If the parameter(s) return to an acceptable range, the study drug is restarted at a reduced dose. Sham discontinuation alerts are also programmed into the IxRS system to maintain blinding during the double-blinded period.

Background cardiomyopathy therapy (eg, β-blockers, verapamil or diltiazem) is allowed. Participants should be on optimal medical therapy that is well tolerated for at least 2 weeks prior to screening. Background cardiomyopathy therapy should remain unchanged during double-blinded treatment unless safety or tolerability concerns arise. During open-label treatment, investigators should manage background HCM medicines as deemed clinically appropriate.

Endpoints
Details of all study objectives and endpoints are shown in online supplemental table 4.

Primary endpoint
The primary efficacy endpoint is change from baseline to week 30 in Valsalva LVOT peak gradient determined by Doppler echocardiography.

Secondary and exploratory efficacy endpoints
Secondary endpoints are change from baseline to week 30 in resting LVOT peak gradient; the proportion of participants achieving a Valsalva LVOT peak gradient <30 and <50 mm Hg at week 30; the proportion of participants with at least one class improvement in NYHA functional classification from baseline to week 30; change from baseline to week 30 in Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score, serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) and cardiac troponin concentrations, and LV mass index assessed by CMR imaging.

Exploratory endpoints aim to characterise the change from baseline to week 30 for multiple parameters assessing cardiac function, haemodynamics and myocardial structure for mavacamten versus placebo.

Safety endpoints
Safety monitoring will be ongoing during the study. Safety assessments include, but are not limited to, adverse events (AEs), ECG, Holter, TTE, clinical laboratory tests (haematology, chemistry, urinalysis and coagulation test).

Key safety endpoints include incidence of LVEF ≤50% determined by TTE; incidence and severity of treatment-emergent adverse events (TEAEs) and treatment-emergent serious AEs; incidence of MACEs: cardiovascular death, non-fatal stroke and non-fatal myocardial infarction; incidence of HF events including hospitalisation and urgent emergency room/outpatient visits for HF; incidence of new or recurrent AF/flutter; incidence of AEs of special interest: symptomatic overdose, outcomes of pregnancy and LVEF≤30%.

LTE analyses
The safety and effects of mavacamten on clinical symptoms, cardiac biomarkers, health status, echocardiographic

Figure 3 Study schema for the LTE and post-treatment follow-up periods. *For CYP2C19 poor metabolisers, an additional onsite visit will be performed at week 98. Doses listed in the blue boxes refer to possible doses for prior placebo participants. Participants previously receiving mavacamten can receive any permissible dose (1,2.5,5,10, or 15 mg) during the LTE period. LTE, long-term extension; QD, once daily.
measures, and CMR measures over time will be assessed for LTE analyses.

Pharmacokinetics analyses
Plasma concentrations of mavacamten will be summarised descriptively.

Study procedures
Study schema from screening to Week 30 and from LTE to study end are summarised in figures 2 and 3, respectively.

The study includes up to 31 visits with serial assessment of echocardiography, 12-lead ECG, NYHA functional class and laboratory testing, including biomarkers (eg, NT-proBNP and hsTNI). Cardiac rhythm monitoring with 24–48-hour Holter is performed at screening and at weeks 12, 26 and 70. The KCCQ is administered to interrogate per-protocol physical limitations and symptom burden. For CMR-eligible participants, the CMR examination is performed at screening, week 30 and week 78 and submitted to the CMR core laboratory. The primary endpoint will be evaluated at Week 30 by completing the TTE with Valsalva manoeuvre.

Because echocardiographic data are essential for dose titration and assessment of safety and efficacy, all echocardiographic studies are performed by core lab qualified sonographers at clinical sites, following a study-specific image acquisition chart, and analysed at the Imaging Core Laboratory (Calyx China). Screening echocardiogram results, as reported by core laboratories, will be used to confirm eligibility for randomisation.

ECG, Holter, cardiac biomarkers and pharmacokinetic (PK) samples will be collected at study visits and evaluated or tested by central laboratories.

Impact of COVID-19 disease and mitigation strategy
The ongoing conduct of the EXPLORER-CN study was impacted by the COVID-19 pandemic. The nature of the EXPLORER-CN trial, in particular the dose-titration and safety monitoring by core lab measured echocardiography and predose PK, created unique challenges requiring specific mitigation strategies.

For participants restricted by the COVID-19 disease, study visits may be performed by phone or virtually and/or in participants’ home residences by an approved visiting healthcare professional. In addition, study assessments may be performed in a local hospital close to a participant’s home residence. Specifically, NYHA classification may be assessed by the principal investigator via telemedicine, the KCCQ may be completed independently by the participant at home, visiting healthcare professionals may perform ECG, placement and removal of a Holter monitor and blood sample collection. TTE may be performed by a core lab qualified sonographer at a local hospital and submitted to the core lab for interpretation. If impossible, the TTE may be performed and interpreted by a 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 and only be used for safety monitoring to ensure safety.

Participants who are unable to be safely monitored during maintenance of the study drug may be required to temporarily discontinue the study drug (mavacamten or placebo).

Statistical considerations
Based on global data from the EXPLORER-HCM study with a mean change in Valsalva LVOT gradient of −49 (SD 34.4) mm Hg at week 30 in the mavacamten group versus −12 (SD 31.0) mm Hg in the placebo group,12 power calculations show that a sample size of 81 (mavacamten: placebo ratio of 2:1) would provide approximately >90% power to detect a treatment difference of 30 (SD = 35) in change from baseline of Valsalva LVOT gradient at 30 weeks between the active treatment and placebo arms, assuming a dropout rate of 10% and with a one-sided alpha level of 2.5%. Eighty-one participants randomised in a 2:1 ratio, equates to 54 and 27 in the mavacamten and placebo groups, respectively.

The primary endpoint, Valsalva LVOT peak gradient change from baseline to week 30, will be compared between treatment groups using Mixed-Effect Model for Repeated Measures (MMRM). The models will include the baseline LVOT gradient value and stratification factor as a covariate, and treatment, visit and treatment-by-visit interaction as fixed effects, and participants as random effects.

The secondary and exploratory endpoints will be summarised using descriptive statistics without formal statistical testing and thus no multiplicity adjustment.

Continuous variables will be summarised by mean, SD, minimum, median and maximum. Comparison of the means between treatment groups will be analysed by analysis of covariance adjusting for baseline values and stratification factors, or a MMRM, if appropriate. Categorical variables will be summarised by number and percentage within each category, and the relationship with treatment will be analysed by Cochran-Mantel-Haenszel test that takes into account the stratification factor. Point estimate and 2-sided 95% CI for proportion difference between treatment groups will be computed using the stratified Miettinen-Nurminen method.14

Safety data will be analysed using descriptive statistics and will focus on the TEAE period. LTE endpoints and plasma concentrations will also be summarised using descriptive statistics.

Trial status
As of 6 March 2023, the last participant has completed the week 30 visit. The study has entered the LTE period.

Patient and public involvement
None.

Ethics and dissemination
This clinical study will be performed in accordance with ethical principles that have their origin in the Declaration
of Helsinki and are consistent with International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)/Good Clinical Practice (GCP) regulatory requirements. Written informed consent will be obtained from each participant before participation in any clinical research procedure (online supplemental material 1).

The Drug Clinical Trial Ethics Committee of the Chinese Academy of Medical Sciences & Peking Union Medical College Hospital has reviewed and approved the following documents (reference number: HS2021089): study protocol and amendment(s); written Informed Consent Form and consent form updates; participant recruitment procedures/documents (eg, advertisements); written information provided to participants; information about payments and compensation available to participants; and Investigator’s Brochure and available safety information.

The results will be published in peer-reviewed journals and presented during national and international conferences.

**DISCUSSION**

Mavacamten is a novel, cardiac-specific myosin inhibitor for the treatment of patients with symptomatic oHCM, a condition with a significant unmet medical need, with the goals of eliminating LVOT gradient, improving cardiac function, functional capacity and symptoms. The clinical benefit of mavacamten in patients with oHCM has been demonstrated in the global phase III EXPLORER-HCM trial and phase III VALOR-HCM trial. However, Asian subjects had very low representation in EXPLORER-HCM (accounting for only 2.4% of participants) and no Chinese sites were included in the study. Therefore, a study evaluating mavacamten in Chinese subjects with oHCM is needed.

The proposed primary endpoint in EXPLORER-CN is the change from baseline to week 30 in Valsalva LVOT peak gradient. LVOTO is a key pathophysiological feature of oHCM and is associated with symptoms, complications and prognosis. LVOTO is also a strong predictor of AF development and progression to advanced HF. Patients with LVOTO progress to NYHA class III–IV at an annual rate of 3.2%–7.4%, compared with 1.6% in patients with no LVOTO. LVOTO has also been associated with an increased risk of all-cause mortality, HCM-related mortality and sudden cardiac death in several large studies. Meanwhile, successfully eliminating the LVOT gradient improves subjects’ outcomes. A large study has shown that abolition of LVOT by surgical septal myectomy is associated with long-term survival. Thus, relief of LVOTO has been the most important target and change in LVOT gradient after treatment is a clinically meaningful endpoint which has been used as a primary endpoint in several other studies, including studies with/without mavacamten.

Using Valsalva manoeuvre as the primary provocation method in the current study is mainly based on feasibility. Although exercise-provoked LVOT gradient was used in EXPLORER-HCM and the exercise test is a method of physiological provocation, it is considered to be a relative contraindication for oHCM and is not recommended in patients with a resting LVOT gradient >50 mm Hg in China. Consequently, the exercise test is not suitable for all subjects with oHCM and experience using the exercise test in patients with oHCM is generally lacking at most Chinese sites. In a prospective study, Kumar et al demonstrated that the mean peak LVOT gradient with Valsalva manoeuvre is comparable with exercise among patients with HCM. Valsalva manoeuvre is a practical, effective, time-efficient and cost-efficient method of provoking LVOTO.

An array of secondary, exploratory and safety endpoints will be collected, including NYHA class, KCCQ, biomarkers, CMR, AE and events of clinical interest. These comprehensive efficacy and safety data will help to further define the safety profile and effect of mavacamten in Chinese individuals with oHCM and provide similar data to bridging global data.

After 30 weeks in the placebo-controlled treatment period, eligible participants will be entered into the LTE period. The total treatment duration for the mavacamten arm will be ~2 years and participants in the placebo group will have the opportunity to receive mavacamten for an additional 48 weeks during the LTE period. During this LTE period, the efficacy and safety of mavacamten will be assessed to determine long-term outcomes in participants receiving mavacamten.

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 response parameters and avoiding excessive pharmacologic effects. Both an EXPLORER-HCM-like titration scheme, using a PK/pharmacodynamic (PD) approach, and an FDA posology-approved scheme, using a PD-only approach, will be examined in the current EXPLORER-CN study.

The major difference in the current dose titration scheme compared with EXPLORER-HCM and FDA-approved dosing is the use of a lower mavacamten starting dose, 2.5 mg once daily, with 1 mg being available for subjects not able to tolerate mavacamten 2.5 mg. Based on previous clinical studies and PK modelling, once-daily mavacamten 5 mg is considered to be a safe starting dose, even in subjects with reduced clearance due to poor CYP2C19 metabolism (one of the main enzymes responsible for mavacamten metabolism), or other factors. However, considering that mavacamten has not previously been studied in Chinese subjects with HCM and the incidence of poor CYP2C19 metabolisers is higher, and average body weight is lower, in this patient population, we have adopted a conservative approach. Consequently, the mavacamten starting dose in EXPLORER-CN is 2.5 mg once daily, with an additional one up-titration opportunity (3-step scheme) to allow titration to a maximum of...
15 mg once daily. Dose titration is designed to be stepwise and participants are not allowed to skip dose levels.

A CMR substudy was designed for EXPLORER-HCM to examine the effect of mavacamten versus placebo on cardiac structure and function. The CMR substudy included a total of 35 subjects (mavacamten, n=17; placebo, n=18) and the results demonstrated a favourable impact of mavacamten on cardiac remodelling in HCM, including significant reductions in LV mass index, maximum LV wall thickness and left atrial volume index. To evaluate the effect of mavacamten on cardiac function and structure assessed by CMR in Chinese patients, the design of the EXPLORER-CN study includes CMR secondary and exploratory endpoints which are consistent with the global substudy. In order to collect more CMR data in Chinese patients, all clinical sites are required to pass the CMR qualification and qualified to perform CMR assessment according to CMR-related manuals. All eligible patients will undergo CMR testing.

There are some limitations in EXPLORER-CN study. First, exercise test and postexercise echocardiography will not be performed due to limited experience and feasibility in Chinese hospitals. Therefore, peak oxygen consumption by cardiopulmonary exercise testing and post-exercise echocardiography data will not be available. Second, this study is not powered to detect differences in hard clinical outcomes (eg, MACE, death). Further studies in a larger population and with a longer follow-up period are needed to demonstrate the effect of mavacamten on clinical outcomes.

In conclusion, this study will provide clinical data on the efficacy, safety and dosage of mavacamten in Chinese adults with oHCM—a population which has not been studied previously in clinical trials. We anticipate that EXPLORER-CN will launch a new era of targeted therapy for Chinese individuals with oHCM.

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Acknowledgements We thank all investigators and the individuals who are participating in this trial and their families. Under the supervision of the authors, editorial support was provided by Robert A Furlong PhD and David P Figgitt PhD, ISMPP CMPt; Content Ed Net, with funding from Shanghai LianBio Development Co., Ltd.

Contributors ZT wrote the first draft of the manuscript; SYZ is the national principal investigator for EXPLORER-CN; ZT, YLH, FW, WJ, QZ, JMZ, PY and GW are study investigators. All authors, including investigators and PWH and JS, contributed to the study design. All authors critically evaluated and commented on the manuscript and have given final approval of the manuscript.

Funding This work was supported by Shanghai LianBio Development Co., Ltd. (Grant/Award Number, N/A).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES


Information sheet and consent form

Study 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

Study protocol No.: LB2001-301

Study drug: Mavacamten Capsules, referred throughout the document as the "study drug"

Sponsor of the study: Shanghai LianBio Development Co., Ltd.

Site Name: <Site Name>

Investigator: <Investigator's Name>

Introduction

You are invited to take part in 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 (oHCM).

"Phase III" means this study is at a late stage of drug development where the safety and efficacy of the drug in human have been preliminarily evaluated in Phase I, Phase II, or other prior Phase III studies. Phase III studies usually serve as the major source of clinical evidence to support the marketing approval of a drug. Randomized means you will be put into a group by chance; like rolling a coin, you do not know which side will face ground. Double-blinded means neither you nor your study doctor will know which group you are in. A placebo is a "dummy treatment", which looks like the genuine medicine but contains no active ingredient. In this you will be assigned to take either the study drug or the placebo, but in addition to this you will still receive standard oHCM therapies as per study protocol regardless of your assignment (so named background treatment, see "What will you have to do?" below). The background treatment is not supplied by the sponsor. To help you decide if you want to take part, you should understand the study and what it will involve for you. To make an informed decision to take part – you should know the purpose of the study, the procedures, the benefits and risks of the study, the discomforts and the precautions taken. This process is called 'informed consent’. Please take the time to read the following information carefully and discuss it with others. Please ask your study doctor if there is anything that is not clear or if you would like more information.

The potential clinical benefit of mavacamten in this study is to provide therapeutic effect in participants with symptomatic oHCM. It cannot be promised the study will help you but in the future the information we get from this study may help improve the future treatment of people with the same condition.

Once you have decided if you want to take part, you will be asked to sign the informed consent form. You will have a copy of the signed form to keep, and the original will stay at the study center.

The study drug, mavacamten, is being developed for the treatment of obstructive hypertrophic cardiomyopathy (oHCM). The oHCM is a condition where the muscular wall of the heart (ventricles) becomes thicker than normal and blocks blood flow out of the heart. The study drug is a novel small-molecule drug. It selectively inhibits the cardiac myosin ("cardiac myosin" is a type of protein in the cardiac muscle building block and plays a critical role in cardiac muscle contraction; "selectively" means this drug mainly target cardiac myosins). A number of clinical studies have been conducted in patients and healthy subjects: as of August 5th 2022, 22 global clinical studies (not including China studies) have been initiated, of which 15 have been completed. Available clinical data observed from these studies have demonstrated the efficacy and safety of the study drug in non-Chinese symptomatic oHCM patients. This study will specifically look at the efficacy and safety of the study drug in Chinese symptomatic oHCM patients. The conduct of this study has been approved by National medical Products Administration (NMPA) and site Ethics Committee. Approximately 81 subjects will take part in this study. According to the information revealed in the Investigators Brochure (Version 10, date October 31st 2022), mavacamten is approved for the treatment of adults with symptomatic New York Heart Association (NYHA) class 2-3 obstructive hypertrophic cardiomyopathy (HCM) to improve functional capacity and symptoms in the United States (US, April 28th 2022) and for the same indication in Australia (September 19th 2022).
Expenses and payment
There will be no cost to you for taking part in this study. You will be provided with all study drugs and examinations related to the study at no cost to you. You will be paid CNY 200 for each visit in total (including required unscheduled visits) as reimbursement for travel costs and other expenses. Nutrition costs will be covered by a fixed allowance of CNY 300 for each PK sample collection. (These blood samples will be used to find out the concentration of study drug in your body by checking how much of the study drug is in your bloodstream at a particular point in time. This type of research is known as "pharmacokinetics" or "PK"). You will receive your reimbursement [every xx month or at each visit] from [Institution or Investigator] in [Cash or bank transfer] during study conduct.

What will you have to do?
• You will have to go to the study visits and finish study assessments as instructed by the study doctor. You should take study drugs per the instructions the doctors give you. At all onsite visits days you should take the drug at the study center after all relevant assessments are done. You should also return your drug containers to the study center.

• You should comply with the restrictions defined in study protocol. For example, you should refrain from intensive exercise, abstain from blood/plasma donation, and refrain from grapefruit or grapefruit juice-containing products, within specific periods during the study. Your study doctor will give you detailed instruction.

• You must not take part in any other studies while you are taking part in this study.

• If you are a woman of childbearing potential, you and your male partner must use effective methods of birth control or practice true abstinence.

• You must tell your doctor all drugs and treatments you are taking. If you cannot remember drug name, please bring the pill box to your doctor. If at the time of signing the consent form you have been on stable optimal standard HCM therapy as determined by your primary doctor and the standard therapy meets the specific requirements defined in study protocol, you should maintain your standard therapy unchanged during the study. If during the study it is needed to adjust the standard hypertrophic cardiomyopathy (HCM) therapy it should be adjusted by your study doctor. There are some drugs and therapies that you should not take during this study. For example, concomitant use of omeprazole or esomeprazole is prohibited. The study staff will give you more information on this.

• You should not participate in the study if you plan to have implantable cardioverter-defibrillator (ICD) placement or septal reduction therapy over the study periods.

• You should inform your study doctor in a timely manner any symptoms or medical problems you have including any inpatient hospitalization, and should let the study doctor know if you think you and your partner may have become pregnant.

The study will consist of 4 periods:
• A screening period of up to 4 weeks which is to screen eligible subjects for the study. After signing this ICF, you will undergo a variety of general, cardiac and laboratory examinations to assess your eligibility, and only the eligible subjects could enter the treatment period.

• A 30-week double-blinded, placebo-controlled treatment period. Your possibility of being assigned to the active drug group versus placebo group is 2:1. During this period, you will take the treatment (active drug or placebo) orally once a day, and receive examinations and assessments at schedules discussed in below sections. The starting dose is 2.5 mg once daily (or placebo). Based on your results of echocardiography (refer to below for explanations on this examination) and PK tests, your dose may be adjusted according to prespecified rules. But as has been mentioned above, this period treatment is double blinded, so neither you nor your study doctor will know whether you are taking the active drug or the placebo, nor will you know the exact dose you are taking. Although the treatment assignment is not made known to you, the dose will be strictly determined and your safety will be monitored according to the study protocol. In special cases, when the protocol pre-defined safety criteria is met, you will be timely instructed to temporarily or permanently stop the treatment to protect your safety. In case of permanent discontinuation, an
early termination (ET) visit will be scheduled for you as soon as possible, which will include a series of heart function examinations to ensure your safety. If early discontinuation, you will be required for a phone visit at 4 weeks visit and an onsite follow-up visit at 8 weeks (If you are CYP2C19 poor metabolizer, an additional onsite visit will be performed 20 weeks later; please refer to below for explanation of CYP2C19 and its relation with your treatment), and attending the week 30 visit. Please follow your doctor's instruction so that your safety will be well monitored.

- The 48-week Long-term extension (LTE) period. Subjects 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 subjects will receive active study drug (mavacamten) for a duration of 48 weeks during the LTE period. Subjects who were previously in mavacamten group will continue to receive dose at Week 30. Subjects who were previously in placebo group will receive mavacamten 2.5 mg, once daily as starting dose. Your dose may be adjusted based on your response to the treatment (eg, your echocardiography). The LTE period will first be double-blinded until all subjects complete the 30-week placebo-controlled treatment period, after which it will be open-label. "Open-label" means both you and your study doctor know your treatment and dose, as opposed to "double-blinded".

- The post treatment follow-up period. After you complete the LTE period (or discontinue the study at an earlier stage) you will be contacted by phone 4 weeks later and return to the study center 8 weeks later. If you are CYP2C19 poor metabolizer, an additional onsite visit will be performed 20 weeks later.

Your study doctor will give you detailed instruction about the study procedures and requirements for you.

You will take below procedures for various purposes during the whole study and the frequency of the procedures can be referred to the tables listed as below as well.

- You will read, review this main informed consent form and if you choose to be considered for this study you need to sign and date on it.
- The study doctor will review the entry criteria with you to find out whether or not you are eligible for this study.
- You will be asked about your personal information, eg., age, sex, and race.
- You will be asked about how you are feeling, your medical history and any medicine you are currently taking.
- Your vital signs (temperature, heart rate, breathing rate, and blood pressure) will be measured. At some visits only the heart rate and blood pressure are required. Blood pressure should be taken after resting for at least 5 minutes.
- You will have a physical examination. A complete physical examination includes assessments of general appearance, skin, head and neck, mouth, lymph nodes, thyroid, abdomen, and muscle and bones, heart, neurological, and breathing systems. A brief physical examination includes heart and breathing systems. Details can be referred to below table annotation.
- Your height and weight will be measured and your body mass index will be calculated.
- You will have an electrocardiogram (ECG). This is a painless, non-invasive test that shows how your heart works (captures the electrical activity of your heart). To have the ECG, you will lie on a bed/couch for few minutes with sensors called electrodes taped to your arms, legs, and chest.
- At certain visits you will be asked to wear a Holter monitor for approximately 24-48 hours. The Holter monitor basically functions like an ECG – it tracks the electric activities in your heart and it is also non-invasive. Different than the ECG, the Holter monitor is a portable device for continuous monitoring for 24-48 hours.
- You will have an echocardiography which is an imaging test to determine your heart function utilizing ultrasound. In this study a modality of echocardiography named "transthoracic echocardiogram" is used, which is non-invasive, painless. The probe is placed on the chest wall.
(or thorax) of the subject, and images are taken through the chest wall. The echocardiography will be taken when you are at rest as well as when you are asked to perform the “Valsalva maneuver”. The Valsalva maneuver is an easily performed maneuver in which you will expel the air out with your best effort as if blowing up a balloon. This maneuver has some physiological effects so it can be used to aid accurate echocardiographic assessment for your oHCM. Since the echocardiography result is critical to blinding maintenance, you and your study doctor will not be informed of post-randomization echocardiography data during the 30-week placebo-controlled treatment period and in double-blind LTE phase. However, core lab will review your echocardiography data. and if pre-defined safety criteria is met, your doctor will be notified. In some case, if needed, an unblinded physician might review your echocardiography data to ensure your safety. In some cases, if needed, you may be asked to take unblinded echocardiography (eg, in case of an adverse event, if needed, an echocardiography will be taken and will inform your doctor of the results to facilitate medical interpretation and treatment).

- The cardiac magnetic resonance (CMR) imaging will be taken. It is a medical imaging technology for non-invasive assessment of the function and structure of the heart. Only suitable subjects will be taken the CMR imaging. Under certain circumstances, for example if you are experiencing atrial fibrillation (a kind of irregular beating of the upper chambers of the heart) or you have a CMR contraindication eg, pacemaker, you will not take this examination. Your study doctor will check your eligibility before the examination.

- If you have an implantable cardioverter-defibrillator (ICD), your data will be downloaded from ICD at specific visits.

- The study doctor will assess how your physical activity is limited by the heart problem according to the New York Heart Association (NYHA) functional classification criteria. You will be classified to 1 of 4 categories based on your symptoms.

- You will be asked to answer a questionnaire, namely the Kansas City Cardiomyopathy Questionnaire (KCCQ). The KCCQ (23-item version) is a patient reported questionnaire that measures the impact of patients’ heart disease or its treatment using a 2-week recall.

- Your blood samples will be collected for the below tests:
  - Test to determine different cell components of your blood (hematology),
  - Test to determine your general health and body function (biochemistry),
  - Tests to measure components that help in blood clotting,
  - Follicle stimulating hormone (FSH) test only in postmenopausal women to confirm postmenopausal status,
  - Pregnancy test in women who are able to have children. Blood pregnancy test will be performed at screening, and urine pregnancy tests will be performed at all other onsite visits. A blood test will be performed if any urine test is positive.
  - Test to check for HIV (a virus that can cause the acquired immune deficiency syndrome [AIDS]), and Hepatitis B and Hepatitis C (viruses that can cause liver damage). Positive results for hepatitis or HIV will be reported to health authorities as per the local requirements,
  - Test to measure how much of the study drug is in your blood (PK blood sample),
  - Test to measure the concentration of molecules in your blood which may reflect how good or bad the heart is working (cardiac troponin and NT-proBNP) and the extent of cardiac muscle impairment,
  - Test to analyze the DNA sequence of your CYP2C19 gene. A gene is a chain of DNA. The sequence of DNA within a gene is like a code that instructs how a corresponding protein is produced. Any alterations in the sequence can have a consequence on the structure and function of the protein. This gene codes the enzyme CYP2C19, which plays a major role in metabolizing the study drug (removing it from the blood by processing it in the liver).
Therefore, the gene sequence of the enzyme may change the time the drug remains in the blood, and thus affect the concentration of the study drug in the body.

Volume of blood collected for each test are described in detail in Section “What will happen to any samples you give?”.

- Your urine samples will be collected during the study for following tests:
  - Routine laboratory examinations,
  - Pregnancy test in women who are able to have children.
- You will also be asked if you have had any illness or injury since your last visit and if there have been any changes in the medications you take.

Following tables show what examinations you will take at each visit. Table 1 outlines the schedule of activities from screening to Week 30 (ie, the end of double-blind treatment period). Table 2 outlines the schedule for the LTE and post-treatment follow-up period.
Table 1 Schedule of Study Procedures: Screening to Week 30

<table>
<thead>
<tr>
<th>Visit</th>
<th>Screening</th>
<th>Double-blinded, Placebo-controlled Treatment Period</th>
<th>ET</th>
<th>Post-treatment Visits*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>V0</td>
<td>V1 V2 V3 V4 V5 V6 V7 V8 V9 V10 V11</td>
<td>4 weeks from ET/W 30</td>
<td>/</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 1 W 4 W 6 W 8 W 12 W 14 W 18 W 20 W 24 W 26 W 30</td>
<td>8 weeks from ET/W 30</td>
<td>/</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phone visit Site visit Site visit</td>
<td>20 weeks from ET/W 30</td>
<td>/</td>
</tr>
<tr>
<td>Day/Week</td>
<td>Day -28 to Day -1</td>
<td>Day 1 W 4 W 6 W 8 W 12 W 14 W 18 W 20 W 24 W 26 W 30</td>
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<td></td>
</tr>
</tbody>
</table>

Assessment:

**General procedures**
- Informed consent X
- Medical history X
- Demographics X
- Inclusion/exclusion criteria X X
- Roll into LTE X
- Randomization X
- Physical examinationa X X X X X X X X X X X X
- Body height, weight 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 X X
- Vital signs X X X X X X X X X X X

**Cardiac Assessments**
- 12-lead ECG X X X X X X X X X X X
- Holter X X
- Resting and Valsalva TTE X X X X X X X X X X
- CMR X X

**Laboratory Assessments**
- Hepatitis panel and HIV test X
- PK sampling (pre-dose) X X X X X X X X X X

Main ICF_V3.0CHN01_24Feb2023 Protocol LB2001-301
## Screening

Double-blinded, Placebo-controlled Treatment Period

<table>
<thead>
<tr>
<th>ET</th>
<th>Post-treatment Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 weeks from ET/W 30</td>
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<tr>
<td></td>
<td>8 weeks from ET/W 30</td>
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<tr>
<td></td>
<td>20 weeks from ET/W 30</td>
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<tr>
<td>V0</td>
<td>Day -28 to Day -1</td>
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<td>V10</td>
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<tr>
<td>V11</td>
<td></td>
</tr>
</tbody>
</table>

| PK sampling (post-dose) | X | X | X | X |
| Coagulation test       | X | X | X | X | X | X | X | X | X |
| Chemistry              | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Hematology             | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Urinalysis             | 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 |
| NT-proBNP              | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| FSH                    | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Pregnancy test (β-hCG) | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Pharmacogenetics       | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

### Symptom Assessments

| NYHA functional classification | 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 | X | X | X | X |

### Investigational Medical Product

| IMP QD | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| IMP administered at site      | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| IMP compliance                | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

*a If a subject does not proceed to the LTE period or ET occurs, the subject 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.

*b At screening, ET and Week 30, a complete physical examination will be conducted. At other visits will be an abbreviated physical examination on cardiopulmonary.

*c 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.

Main ICF_V3.0CHN01_24Feb2023
Protocol LB2001-301
Table 2 Schedule of Study Procedures: LTE and Post Treatment Follow-up Period

<table>
<thead>
<tr>
<th>Week</th>
<th>LTE Period</th>
<th>ET</th>
<th>Post-treatment Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>34&lt;sup&gt;d&lt;/sup&gt;</td>
<td>36</td>
<td>40&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>/</td>
<td>4 weeks from ET/W</td>
<td>Phone visit</td>
</tr>
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</table>

**Assessment**

**General Procedures**

- Physical examination<sup>b</sup>  
  X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X
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<td>36</td>
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<tr>
<td>IMP administered at site</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>IMP compliance</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

<sup>a</sup>The onsite visit at 20 weeks after ET/Week 78 visit is only for CYP2C19 poor metabolizer.

<sup>b</sup>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.

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

<sup>d</sup>Week 34, 40, 46, 54, 62, 70, 78: During open-label LTE phase, only these visits are required for prior mavacamten participants.
What will happen to any samples you give?

In this study, the hematology, blood biochemistry, coagulation, virology screen, FSH, blood/urine pregnancy testing, and urinalysis will be carried out in the local laboratory of each study center. After testing, the samples will be destroyed in accordance with the standard procedure of the study center. The PK sample analysis, cardiac troponin and NT-proBNP measurements, and CYP2C19 gene analysis will be conducted at central laboratories contracted with the Sponsor so that it can be analyzed with the same standard method. The PK analysis and cardiac troponin and NT-proBNP measurements will be conducted at Q2 Solutions (Beijing) Co., Ltd., and the CYP2C19 gene analysis will be conducted at Beijing Prohealth Clinical Laboratory.

Each central laboratory will transport, store, test your samples, and complete analysis and report in accordance with national regulations, standard procedures, and project requirements. For the cardiac troponin and NT-proBNP tests, remaining sample will be destroyed within 7 days after test is completed. Your samples for PK analysis and the CYP2C19 gene analysis will be stored at center lab until the study is completed and passes the inspection conducted by Health Authority. Your sample(s) will be retained for longer if the Health Authority has active questions about the study, in which case sample(s) will be stored until the Health Authority's questions have been addressed.

The volume of blood sample required for each test is summarized in Table 3. A total of approx. 27 mL blood (about 6 teaspoons) will be required for the screening period. A total of approx. 112 mL blood (about 23 teaspoons) will be required for the 30-week double-blinded placebo-controlled treatment period. For the 48-week LTE period a maximum of 103 mL (21 teaspoons) may be collected. Approx. 17 mL blood (4 teaspoons) will be collected in the ET visit period. Approx. 17 mL blood (4 teaspoons) will be collected in the follow-up period (33 mL (7 teaspoons) for CYP2C19 poor metabolizer). Throughout the whole study collectively, a subject will be drawn a maximum of approx. 276 mL (56 teaspoons) over 90 weeks (292 mL (59 teaspoons) for CYP2C19 poor metabolizer).

<table>
<thead>
<tr>
<th>Test</th>
<th>Volume per test (approximately)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis panel and HIV</td>
<td>5 mL</td>
</tr>
<tr>
<td>PK sampling</td>
<td>3 mL</td>
</tr>
<tr>
<td>Coagulation test</td>
<td>3 mL</td>
</tr>
<tr>
<td>Chemistry</td>
<td>5 mL</td>
</tr>
<tr>
<td>Hematology</td>
<td>3 mL</td>
</tr>
<tr>
<td>Cardiac troponin and NT-proBNP</td>
<td>2.5 mL</td>
</tr>
<tr>
<td>CYP2C19 genotyping</td>
<td>2 mL</td>
</tr>
<tr>
<td>FSH</td>
<td>4 mL</td>
</tr>
<tr>
<td>Pregnancy test</td>
<td>4 mL</td>
</tr>
</tbody>
</table>

Your samples will only be used for the purpose as defined in this informed consent form, and will not be used for other purpose. For carrying out any new analysis on the samples not connected to this study, your permission will be required – you will be asked to sign a new consent form to allow further use of the samples. You have the right to refuse.

All above blood sample will only be collected after the Human Genetic Resource Administration of China (HGRAC) approval is received. You can check related information via below Reference Link: http://most.gov.cn/bszn/new/rlyc/fwzn/.

What alternative treatments are available?

Taking part in this study is voluntary – you do not have to take part to be treated for your condition. Your study doctor will discuss with you any other treatments or investigational drugs that may be available, and will also discuss their risks and benefits. If you decide not to take part in this study, it will not affect your ability to receive medical care.
What are the possible disadvantages or risks of taking part?

Possible side effect and risk of the study drug

Like all research, the treatment and procedure may lead to unknown risk. Any medication may have temporary, permanent, or unforeseen side effects.

It is possible that the symptoms of your condition will not improve during the study. Treatment with this study drug may also involve risks to your future health that we currently don’t know about. Treatment or procedures in this study may or may not induce side effects. The side effects may be mild, moderate, or even severe, and differ in people having such experience. We will monitor closely and carefully for any side effects reported by participants in this study. Below are the information regarding side effects:

Possible side effect of the study drug

The safety of mavacamten was evaluated in two other Phase 3 studies (EXPLORER-HCM and VALOR-HCM). In a total of 179 subjects who received 2.5 mg, 5 mg, 10 mg or 15 mg mavacamten, the most commonly reported adverse drug reaction with mavacamten were dizziness, dyspnoea, systolic dysfunctions, and syncope.

There may be other side effects or risks of taking mavacamten that are not yet known. If you suffer any side effects or you think you are experiencing a side effect, during this study, please tell your study doctor immediately (see ‘Who should you contact for more information?’). Any side effects or other health issues occurring during the study will be followed up by the study doctor. Notably, like all other medications, please store your study drug in safety places where children are unable to reach.

Possible risk of the study drug

Based on the previous study of the study drug, heart failure due to systolic dysfunction (defined as symptomatic left ventricular ejection fraction [LVEF] <50%) has been identified as an important risk. Teratogenicity and increased exposure to mavacamten due to drug interactions (with CYP2C19 inhibitors or with moderate to strong CYP3A4 inhibitors) have been identified as potential risks.

- Cardiac Failure and Systolic Dysfunction

  Heart failure due to systolic dysfunction defined as symptomatic LVEF less than 50%: In the mavacamten program, systolic dysfunction associated with mavacamten was observed with LVEF < 50% with or without symptoms of left heart failure.

  As of the data cut of 31-May-2022, a total of 11 mavacamten treated subjects experienced at least one of the following events of interest: SAE of cardiac failure (Standardized MedDRA Queries [SMQ] [narrow]), SAE of systolic dysfunction, and adverse event of special interest (AESI) of LVEF ≤ 30%. Four mavacamten-treated subjects experienced more than one of these events of interest.

  Clinical data has shown that dose-dependent, reductions in LVEF have been monitorable with use of echocardiograms, reversible with temporary or permanent discontinuation of the study drug. Therefore, throughout the study subjects’ cardiac function will be extensively monitored by echocardiograms. Also, since dose adjustment will be made in a gradual manner based on individual response, the possibility of overdose can be minimized.

- Drug interactions

  Possibly increased risk of heart failure due to interaction with CYP2C19 or moderate to strong CYP3A4 inhibitors (such as omeprazole or esomeprazole). Mavacamten is primarily metabolized by CYP2C19 and CYP3A4. Starting or increasing the dose of any CYP2C19 or moderate to strong CYP3A4 inhibitor may increase the risk of systolic dysfunction. Stopping or decreasing dose of a CYP2C19 or moderate to strong CYP3A4 inhibitor may lead to a loss of therapeutic response to mavacamten. To overcome this, study doctor will periodically check the medications you are taking. If you have a condition that requires any medication, please tell the primary doctor about your participation in this clinical study, and inform and inquire the study doctor in advance.
wherever possible.

- **Teratogenicity:**

  For female subjects, based on pregnant animal studies mavacamten may cause fetal harm. No clinical data exists on the safety of mavacamten during pregnancy, this means the effects of study drug on a pregnancy, fetus or a breast-fed infant are not well established. Female subjects who have childbearing potential and their male spouse must take birth control measures following study doctor's instructions, see below Contraception requirements section for detail. If you are or become pregnant, please tell your study doctor immediately.

**Allergic reaction**

Sometimes people have allergic reactions to drugs. You may have an allergic reaction to your study drug. Symptoms of an allergic reaction may include hives, rash, itching, flushing, swelling around the mouth, lips, tongue, throat, or eyes, having a hard time breathing, shortness of breath, wheezing, a sudden drop in blood pressure (making you feel dizzy or lightheaded). You may experience other symptoms. Severe allergic reactions (called anaphylaxis) can be life threatening and may require emergency treatment or hospitalization.

Contact your study doctor (see 'Who should you contact for more information?') immediately, if you think you may be having an allergic reaction to study drug.

**Contraception requirements**

If you are a woman who is able to have children, a pregnancy test will be done at screening, and if the result is positive, you will not be able to continue in the study. Also, If you are a woman who is able to have children, you must practice true abstinence or use highly effective form of birth control consistently from screening visit through **5 months** after the study drug is last administered, and your male partners must also use a contraceptive (eg, barrier, condom or vasectomy) during the same period. 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. The acceptable highly effective birth control methods include the follows. The study doctor will discuss methods of birth control with you if needed.

- Estrogen- and progesterone- (a hormone involved in the menstrual cycle, pregnancy, and embryogenesis) containing hormonal birth control associated with inhibition of ovulation, or progesterone-only hormonal birth-control associated with inhibition of ovulation by oral, implantable, or injectable route of administration. (Both estrogen and progesterone are hormones. The estrogen is the sex hormone responsible for the development and regulation of the female reproductive system and secondary sex characteristics, and progesterone is a hormone involved in the menstrual cycle, pregnancy, and embryogenesis).
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion.
- Female surgically sterile for 6 months or postmenopausal for 1 year.

If you become pregnant or you think you may be pregnant during the study or within 5 months after the last study drug administration, contact the study doctor's office immediately. You may be asked to withdraw from the study. You must not be breast feeding an infant during the study.

The study doctor must follow-up and keep a record of the course and the outcome of all pregnancies, even if you withdraw from the study or if the study has finished. If you becomes pregnant during the study, the study doctor or his/her staff will ask to contact you/your partner and your doctor for information about the pregnancy and the child until 6 months after the birth.
Male contraception in study subjects is not required as the risk of teratogenic effects caused by mavacamten transferred by seminal is negligible. However, the pregnancy information of your partner would be necessary to further complete the investigated drug’s safety information. If your partner becomes pregnant or thinks she may be pregnant while you are in the study or within 5 months after the last study drug administration, contact the study doctor’s office immediately. Your female partner(s) will be invited to sign a consent form to allow medical follow-up. The Sponsor may also request you and your female partner’s consent to collect confidential information about her health and that of the baby. The study doctor must follow-up and keep a record of the course and the outcome of all pregnancies.

Possible risks of study procedures and assessments

Blood samples: Blood samples will be taken from a vein in your arm during the study. The risks of taking blood via a needle include temporary discomfort from the needle in your arm, bruising, clotting, swelling at the needle site, and, in rare instances, infection. In rare case, you may also experience dizziness, nausea or fainting during blood taking. Please tell the study doctor or study staff if you do not feel well after having your blood taken.

Blood pressure: An inflatable cuff will be placed on your arm and a machine will measure your blood pressure after you have rested for 5 minutes. You may experience mild discomfort in your arm while the cuff is inflated.

Electrocardiogram (ECG): Small electrodes will be stuck to your chest, arms and legs and a machine will measure the electrical activity of your heart. These electrodes may cause some slightly local uncomfortable.

The holter is a safe and painless procedure. The patches that the study staff will stick to your chest and other areas of your body to monitor your heart may irritate your skin and cause itching and/or redness. The study staff might need to shave your body hair so that they can stick the pads to your skin only if necessary. The shaving may cause some irritation. If you are allergic to the material in the patches, a local allergic reaction could occur. When the sticky patches are removed, it might sting for a few seconds. Holter will monitor your heart for approximately 24-48 hours.

Echocardiography: Cardiac ultrasound is a non-invasive and painless examination. The medical ultrasonic couplant will be smeared to your chest skin. And then, an ultrasound probe will be used to examine your heart. Medical ultrasonic couplant are gel-like substances that are non-toxic to humans but may cause local irritation and may be uncomfortable. You will be required to perform Valsalva maneuver. The Valsalva maneuver requires you to expel the air out with your best effort as if blowing up a balloon. It is a very safe maneuver, but you may feel transient discomfort. In rare case, Valsalva maneuver might cause fainting due to a low heart rate.

During an CMR (Cardiac Magnetic Resonance) scan, you may feel anxious because of the enclosed space (claustrophobia). MRIs cannot be performed in the presence of metal, if you have a pacemaker, artificial heart valve, dental braces, internal hardware, or if you are pregnant, you must tell your doctor. In some cases you are not eligible for the CMR. For the scans, you will receive the magnetic resonance contrast material. This is given in your vein using a indwelling needle. You will not receive the CMR scan if you are known to be allergy to the contrast material or if you have abnormal kidney function. You may feel local warmth/pain in the area where the needle was inserted. You may also have nausea/vomiting or headache. Serious allergic reactions related to MRI contrast material may be life-threatening but are very rare. In rare cases extravasation of contrast medium may occur which can cause skin injury or phlebitis.

What happens when the research study stops?

During the study you will receive the study drug free of charge. The study drug may not be available as a prescription paid for by the health care system immediately after the end of the study. There is no guarantee that you will continue to receive this particular drug or treatment when you have finished taking part in the study. The care you receive after the study has ended may involve a different drug or treatment, which the hospital, together with your study doctor, considers to be the most suitable alternative.

If you have a reaction to the study drug, your participation may be stopped at any time by the study doctor or sponsor without your consent.
If the study is stopped, you will be told, and your study doctor will make suggestions or arrangements for your subsequent therapies.

**What if you have a question?**
If you have a question, concern or complaint about any part of this study, you should ask to speak to the study doctor or a member of the research team, who will do their best to help (see ‘Who should you contact for more information?’).

If you have any questions about your rights as part of the research, or any concerns or complaints about the research that you do not want to discuss with the study doctor or research team, see ‘Who should you contact for more information?’.

If you suffer a serious illness or injury during this study, please contact your study doctor immediately (see ‘Who should you contact for more information?’).

**Compensation for study related injury**
The sponsor should take appropriate measures to ensure the compensation or the payment available to subjects and investigators.

The Sponsor should provide investigators and clinical trial institutions with legal and economic insurance or guarantees related to trials, which should be adaptive to the nature and degree of risk of the trials. The damage caused by the fault of the investigator and the clinical trial institution themselves is not included.

The Sponsor should be responsible for the diagnosis and treatment expenses of the subjects’ damage or death related to the trial, and the corresponding compensation. The sponsor and the investigator should promptly pay the compensation or payment for the subjects.

The compensation approach provided by the sponsor to the subjects shall be complied with relevant laws and regulations.

The Sponsor should provide the investigational product to the subjects free of charge and should pay the medical testing fees related to the trials.

**What if new information about the study drug becomes available?**
Sometimes new information about the study drug is received. You will be told if any relevant new information becomes available that may affect your willingness to carry on taking part in the study. If this happens, your study doctor will contact you as soon as possible, and will discuss whether you should continue in the study. If you decide not to carry on, your study doctor will make arrangements for your care to continue. If you decide to continue in the study, you may be asked to sign a new consent form.

Also, if new information becomes available, your study doctor may stop your participation without your consent. If this happens the reasons will be explained, and arrangements made for your care to continue.

**What will happen if you don’t want to carry on with the study?**
You can stop taking part in the study at any time without giving any reason. This will not affect your future treatment or your relationship with your study doctor. If you stop taking part, please tell your study doctor immediately. When you withdraw from the study, please cooperate with your doctor to finish the Early Termination visit as soon as possible and then you will get a phone visit 4 weeks later and you will be requested to be onsite to get a follow-up visit 8 weeks later (if you are CYP2C19 poor metabolizer, an additional onsite visit will be performed 20 weeks later). In addition, if you withdraw during the double-blind treatment period, your study doctor will schedule the Week 30 assessments for you. We strongly recommend you to follow your doctor’s instruction to finish the follow-up visit required as it aims to make safety assessment and ensure your safety to be protected.

**Will your taking part in this study be kept confidential and how will your personal information be used?**
The study doctor and research team will collect, record and use personal information about you for the study purposes. Your personal information collected during the study may include sensitive information about your physical or mental health or condition, and health information about you in medical records, and other personal information such as date of birth, sex, nationality. Your privacy and your personal information will be protected using measures which follow the requirements applicable in China for the
protection of your personal information. Any information about you that is collected during this study will remain confidential. To ensure privacy and the scientific integrity of the study, your name and address will not be disclosed outside the hospital and you will only be identified by a code. This code will be attached to records or samples released to the Sponsor and the service providers associated with the study.

Your personal information will be stored and used for medical, statistical, and regulatory purposes related to the research. Representatives of the sponsor and regulatory authorities in China and other countries may use your personal information to verify the research. If your personal information is reviewed by one of these people, then they may need your entire medical record. The information obtained during the study may be published or sent to regulatory authorities or health insurers in China or other countries where regulatory approval or payment for the study drug is required. Your identity will not be released except with your permission, unless necessary for your safety.

Your personal information may be accessed by the Research Ethics Committee, the Sponsor and its affiliates, research partners, other participating study centers, and representatives assisting with the research (such as the contract research organization, study monitors, auditors), central laboratory and regulatory authorities in China or other countries and health insurers.

By signing this consent form, you are giving permission for processing of your personal information in a database and transferring of this information or any part of it to people and organizations in the manner as described above, including transferring to people or organizations outside China, where personal data protection laws may be less strict but your information will be adequately protected.

You may use your rights under your local data protection laws to access and correct your personal information or ask for it to be deleted. You can object to any further processing of your information by contacting the study doctor.

According to legal requirements, your personal data will be stored in the study databases and/or paper files for 15 years after the study ends. In case local regulations or institutional policies require a longer retention period, the data will be stored as required.

All subjects participated in China will be able to search the study related information on the Web site www.chinadrugtrials.org.cn This Web site will not include information that can identify you.

The results of this study will be used to make informed clinical decisions for developing this new drug. If you want the results to be made available to you, please talk to your study doctor.

Who has reviewed the study?
All research studies are reviewed by an independent group of people, called a research ethics committee to protect your safety, rights, well-being and dignity. This study has been reviewed and has been given a favorable opinion by Research Ethics Committee.

The Sponsor, Regulatory Authorities or the Ethics Committee may stop the study at any time where there is good reason, e.g., unsatisfactory participant enrollment with regard to quality or quantity, significant or numerous deviations from study protocol requirements, the incidence or severity of safety findings in this or other studies indicating potential health hazard caused by the study drug.

Who should you contact for more information?
For more information about the study, please contact your study doctor or study staff:

Name: <insert name of Investigator or Study staff>
Address: <insert address>
Phone: <insert number>

If you have any questions about your rights as a research subject please contact here.

Name: <insert name of Ethics Committee>
Address: <insert address>
Phone number: <insert phone number>

Thank you for reading this and considering if you will take part in this study.
Consent form

Study 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

Study protocol: LB2001-301

Study drug: Mavacamten Capsules, referred throughout the document as the “study drug”

Sponsor of the study: Shanghai LianBio Development Co., Ltd.

Site Name: <Site Name>

Investigator: <Investigator’s Name>

I confirm the following:

- I have read and understand the information sheet for the above study, and have had enough time to think about taking part.
- I have had enough time to ask questions and I am satisfied with the answers given to all of my questions.
- I voluntarily agree to be part of this research study, to follow the study procedures and to provide the information the study doctor, nurses or other staff members ask from me.
- I understand that I am free to withdraw from this study at any time without giving a reason and without my medical care or rights being affected.
- I have received a signed copy of this information sheet and consent form to keep for myself.
- I agree, if my study doctor is not my doctor, my doctor may be told about my taking part in this study and asked for medical information about me.
- I agree to my samples being taken and used as described in this information sheet.
- I give permission for my personal information collected as part of this clinical study to be:
  - identified only with my subject ID number;
  - reviewed, processed and transferred by and to the Sponsor and its authorized representatives for the purposes described in the study protocol;
  - reviewed and audited by appropriately authorized organizations;
  - published and sent to regulatory authorities or health insurers in China or other countries; and
  - transferred if required to any country, where data protection laws may be less strict.
- I understand I may also be contacted at a later date(s) for my permission in connection with this.

- <The following text is only used for study centers that had previously received ethics committee approval for the informed consent form from Shanghai Jsure Health Technology CO., Ltd. If previously the informed consent form from Shanghai Jsure Health was not approved by ethic committee, the following text will be deleted.>

  The personal information collected by Shanghai Jsure Health Technology CO., Ltd. (hereafter referred to as "Jsure Health"), including name, ID number, mobile phone number, and address, will be used by Jsure Health to provide you with reimbursement for additional expenses caused by participating the study. Whether or not to provide personal information to Jsure Health does not impact continuous participation in this study.

  At any time while Jsure Health is providing you the services, you have the right to contact Jsure Health to terminate the service and request Jsure Health to delete or withdraw the personal information you provided.

  The contact information is stated below:
  Shanghai Jsure Health Technology CO., Ltd.
  Address: Room 2-A, Building 4, No. 315, Guangyuan West Road, Xuhui District, Shanghai
  E-mail: finance@jsure.com
  Tel: (86 21) 31229190

  Personal information will be deleted immediately after the reimbursement fee is transferred to you via bank card/WeChat payment code (after confirming not rejected or returned).
Please tick "√" in the box below □ to indicate whether you agree or not the personal information to be handled by Jsure Health.
If you agree and sign this consent, Jsure Health will consider you agree with their process regarding your personal information. If you do not agree to let Jsure Health handle your personal information, Jsure Health will delete your personal information collected previously and will no longer process any of your personal information after signing this consent.

□ I agree
□ I disagree

By signing this document, I give agree to take part in this study, as set out in the information sheet and consent form.

For Subject

Printed Name of Subject:

_________________________________________   ____________________
Signature of Subject:     Date and time:
For Impartial Witness (If Applicable)

Printed Name of Impartial Witness: ________________________________

Signature of Impartial Witness: __________________ Date and time: ________

Investigator/ Authorized Designee:

• I have fully and carefully explained the study to the person named above and confirm that, to the best of my knowledge, they clearly understand the nature, risks and benefits of taking part in this study.
• I confirm that I gave them all opportunities to ask questions about the study, and that I answered all the questions they asked correctly and to the best of my ability.
• I confirm that they have not been forced into giving consent, and that they have given their consent freely and voluntarily.
• I confirm they have been given a copy of this information sheet and consent form.

Printed name of Investigator/Designee: ________________________________

Signature of Investigator/Designee: __________________ Date and time: ________
## Supplemental Table 1. Full inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Is at least 18 years old at screening.</td>
<td>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.</td>
</tr>
<tr>
<td>2) Body weight is greater than 45 kg at screening.</td>
<td>2) Known infiltrative or storage disorder causing cardiac hypertrophy that mimics oHCM, such as Fabry disease, amyloidosis, or Noonan syndrome with LV hypertrophy.</td>
</tr>
<tr>
<td>3) Has adequate acoustic windows to enable accurate TTEs (refer to echocardiography related manual).</td>
<td>3) Has a history of syncope within 6 months prior to screening or sustained ventricular tachyarrhythmia with exercise within 6 months prior to screening.</td>
</tr>
<tr>
<td>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):</td>
<td>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.</td>
</tr>
<tr>
<td>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</td>
<td>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.</td>
</tr>
<tr>
<td>B. Has LVOT peak gradient ≥50 mmHg during screening as assessed by echocardiography at rest or after Valsalva manoeuvre (confirmed by echocardiography core laboratory interpretation).</td>
<td>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).</td>
</tr>
<tr>
<td>5) Has documented LVEF ≥55% by echocardiography core laboratory read of screening TTE at rest.</td>
<td>7) Previously participated in a clinical study with mavacamten.</td>
</tr>
<tr>
<td>6) Has a valid measurement of Valsalva LVOT peak gradient at screening as determined by echocardiography core laboratory.</td>
<td>8) Hypersensitivity to any of the components of the mavacamten formulation.</td>
</tr>
<tr>
<td>7) Has NYHA Class II or III symptoms at screening.</td>
<td>9) Current treatment (within 14 days prior to screening) or planned treatment during the study with disopyramide, cibenzoline, or ranolazine.</td>
</tr>
<tr>
<td>8) Has documented oxygen saturation at rest ≥90% at screening.</td>
<td>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.</td>
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<tr>
<td>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).</td>
<td>11) For individuals on beta-blockers, verapamil, or diltiazem, any dose adjustment of that medication within 14 days prior to</td>
</tr>
</tbody>
</table>
a) Oestrogen- 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.

<table>
<thead>
<tr>
<th>No.</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>12</td>
<td>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 &gt;6 months prior to screening may be enrolled if study eligibility criteria for LVOT gradient criteria are met).</td>
</tr>
<tr>
<td>13</td>
<td>ICD placement within 2 months prior to screening or planned ICD placement during the study.</td>
</tr>
<tr>
<td>14</td>
<td>Has QTcF &gt;500 msec when QRS interval &lt;120 msec or QTcF &gt;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).</td>
</tr>
<tr>
<td>15</td>
<td>Has documented obstructive coronary artery disease (&gt;70% stenosis in one or more epicardial coronary arteries) or history of myocardial infarction.</td>
</tr>
<tr>
<td>16</td>
<td>Has known moderate or severe (as per investigator’s judgment) aortic valve stenosis, constrictive pericarditis, or clinically significant congenital heart disease at screening.</td>
</tr>
<tr>
<td>17</td>
<td>Has any acute or serious comorbid condition (e.g., major infection or haematologic, 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.</td>
</tr>
<tr>
<td>18</td>
<td>History of malignant disease within 10 years of screening:</td>
</tr>
<tr>
<td>a)</td>
<td>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.</td>
</tr>
<tr>
<td>b)</td>
<td>Participants with other malignancies who are cancer free for more than 10 years</td>
</tr>
</tbody>
</table>
before screening can be included in the study.

19) Has safety laboratory parameters (chemistry, haematology, 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 $< 3 \times$ the upper limit of the laboratory reference range.
c) The body size–adjusted estimated glomerular filtration rate is $\geq 30$ 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 cardiotoxic 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.
### Supplemental Table 2. Blind dose adjustments during the Double-Blinded Placebo-Controlled Treatment Period

#### PK/PD Criteria for Down-Titration (requires resting LVEF ≥50% regardless of Valsalva gradient*)

<table>
<thead>
<tr>
<th>Time of Assessment</th>
<th>Pre-dose Mavacamten Plasma Concentration (ng/mL)*</th>
<th>Time and Doseb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>700 &lt; Plasma concentration &lt; 1000</td>
<td>Week 6: Dose reduces from 2.5 mg to 1 mg</td>
</tr>
<tr>
<td>Week 6</td>
<td>700 &lt; Plasma concentration &lt; 1000</td>
<td>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)</td>
</tr>
<tr>
<td>Week 8c</td>
<td>700 &lt; Plasma concentration &lt; 1000</td>
<td>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)</td>
</tr>
<tr>
<td>Week 12</td>
<td>700 &lt; Plasma concentration &lt; 1000</td>
<td>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</td>
</tr>
<tr>
<td>Week 18</td>
<td>700 &lt; Plasma concentration &lt; 1000</td>
<td>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</td>
</tr>
<tr>
<td>Week 24</td>
<td>700 &lt; Plasma concentration &lt; 1000</td>
<td>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</td>
</tr>
<tr>
<td>Week 26</td>
<td>700 &lt; Plasma concentration &lt; 1000</td>
<td>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)</td>
</tr>
</tbody>
</table>

At Week 6, Week 12 and Week 18: if PK/PD criteria for down-titration are not met, potential dose up-titration may proceed as follows: Dose Titration (requires resting LVEF ≥ 50% and pre-dose mavacamten plasma concentration ≤ 700 ng/mL)

<table>
<thead>
<tr>
<th>Time of Assessment</th>
<th>Dose Titration Criteria (based on the LVEF, Valsalva gradient and pre-dose mavacamten plasma concentration)</th>
<th>Dose Titration*</th>
<th>Time and Dosec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 6</td>
<td>LVEF ≥ 55% Valsalva gradient ≥ 30 mmHg AND plasma concentration &lt; 350 ng/mL</td>
<td>Increase</td>
<td>Week 8: Dose increases from 2.5 mg to 5 mg</td>
</tr>
<tr>
<td></td>
<td>LVEF ≥ 55% Valsalva gradient ≥ 30 mmHg AND plasma concentration ≤ 350 ng/mL OR 350 ≤ plasma concentration ≤ 700 ng/mL (regardless of Valsalva gradient)</td>
<td>No change</td>
<td>Week 8: Dose remains at 2.5 mg or 1 mg</td>
</tr>
<tr>
<td></td>
<td>50% ≤ LVEF &lt; 55% Regardless of Valsalva gradient and plasma concentration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>LVEF ≥ 55%</td>
<td>Valsalva gradient ≥ 30 mmHg AND plasma concentration &lt; 350 ng/mL</td>
<td>Increase</td>
</tr>
<tr>
<td>---------</td>
<td>------------</td>
<td>---------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>LVEF ≥ 55%</td>
<td>Valsalva gradient &lt; 30 mmHg and plasma concentration &lt; 350 ng/mL OR 350 ≤ plasma concentration ≤ 700 ng/mL (regardless of Valsalva gradient)</td>
<td>No change</td>
</tr>
<tr>
<td>50% ≤ LVEF &lt; 55%</td>
<td>Regardless of Valsalva gradient and plasma concentration</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 18</th>
<th>LVEF ≥ 55%</th>
<th>Valsalva gradient ≥ 30 mmHg AND plasma concentration &lt; 350 ng/mL</th>
<th>Increase</th>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LVEF ≥ 55%</td>
<td>Valsalva gradient &lt; 30 mmHg and plasma concentration &lt; 350 ng/mL OR 350 ≤ plasma concentration ≤ 700 ng/mL (regardless of Valsalva gradient)</td>
<td>No change</td>
<td>Week 20: Dose remains at 10 mg, 5 mg, 2.5 mg or 1 mg</td>
</tr>
<tr>
<td>50% ≤ LVEF &lt; 55%</td>
<td>Regardless of Valsalva gradient and plasma concentration</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

* 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. Note: LVEF will not be performed at Week 8 (see also footnote c).

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

* 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.

* 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.

* If the mavacamten dose is decreased at any time during the study, then the participant will continue on the reduced dose to Week 30 unless safety concerns or intolerability arise requiring further dose reduction or dose discontinuation.
Supplemental Table 3. Dose Titration during the LTE Period for Participants Previously on Placebo (requires resting LVEF ≥50%)

<table>
<thead>
<tr>
<th>Time of Dose Adjustment</th>
<th>Dose Titration Criteria (based on the LVEF and Valsalva gradient)*</th>
<th>Dose Titration</th>
<th>Doseb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 36</td>
<td>LVEF ≥ 50% Valsalva gradient ≥ 20 mmHg</td>
<td>No change</td>
<td>Remains at 2.5 mg</td>
</tr>
<tr>
<td></td>
<td>LVEF ≥ 50% Valsalva gradient &lt; 20 mmHg</td>
<td>Decrease</td>
<td>Reduces from 2.5 mg to 1 mg</td>
</tr>
<tr>
<td>Week 42</td>
<td>LVEF ≥ 55% Valsalva gradient ≥ 30 mmHg</td>
<td>Increase</td>
<td>Increases from 2.5 mg to 5 mg or 1 mg to 2.5 mg</td>
</tr>
<tr>
<td></td>
<td>LVEF ≥ 55% Valsalva gradient &lt; 30 mmHg</td>
<td>No change</td>
<td>Remains at 2.5 mg or 1 mg</td>
</tr>
<tr>
<td></td>
<td>50% ≤ LVEF &lt; 55% Regardless of Valsalva gradient</td>
<td>No change</td>
<td>Remains at 2.5 mg or 1 mg</td>
</tr>
<tr>
<td>Week 54</td>
<td>LVEF ≥ 55% Valsalva gradient ≥ 30 mmHg</td>
<td>Increase</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>LVEF ≥ 55% Valsalva gradient &lt; 30 mmHg</td>
<td>No change</td>
<td>Remains at 5 mg or 2.5 mg or 1 mg</td>
</tr>
<tr>
<td></td>
<td>50% ≤ LVEF &lt; 55% Regardless of Valsalva gradient</td>
<td>No change</td>
<td>Remains at 5 mg or 2.5 mg or 1 mg</td>
</tr>
<tr>
<td>Week 66</td>
<td>LVEF ≥ 55% Valsalva gradient ≥ 30 mmHg</td>
<td>Increase</td>
<td>Increases from 10 mg to 15 mg or 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</td>
</tr>
<tr>
<td></td>
<td>LVEF ≥ 55% Valsalva gradient &lt; 30 mmHg</td>
<td>No change</td>
<td>Remains at 10 mg or 5 mg or 2.5 mg or 1 mg</td>
</tr>
<tr>
<td></td>
<td>50% ≤ LVEF &lt; 55% Regardless of Valsalva gradient</td>
<td>No change</td>
<td>Remains at 10 mg or 5 mg or 2.5 mg or 1 mg</td>
</tr>
</tbody>
</table>

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

* 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 the 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 the dose is planned to increase to 15 mg during the open-label LTE phase, the investigator is encouraged to discuss this with the 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.
## Supplemental Table 4. Study objectives and endpoints

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
</tr>
<tr>
<td>• <strong>Primary Efficacy</strong></td>
<td></td>
</tr>
<tr>
<td>To compare the effect of a 30-week course of mavacamten with placebo on Valsalva LVOT gradient peak as determined by Doppler echocardiography</td>
<td>• Change from baseline to Week 30 in Valsalva LVOT peak gradient</td>
</tr>
<tr>
<td><strong>Secondary Efficacy</strong></td>
<td></td>
</tr>
</tbody>
</table>
| 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** | |

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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 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