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 titration during the long-term extension period. The study will provide long-term safety and efficacy data for mavacamten.

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).

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. 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.
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 (eg, verapamil, diltiazem) or diisopropylpyramide 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-blind, 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-blind 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

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 supplement 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, European Society of Cardiology and Chinese Society of Cardiology 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, 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 supplement 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

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**Figure 2** Study schema from screening to week 30. Doses listed in the blue boxes refer to possible doses for participants who are in the mavacamten and placebo groups. During the LTE lead-in period, participants will visit every 8 weeks. LTE, long-term extension; QD, once daily.
IxRS system as guided by core laboratory determination of TTE. During the open-label LTE period, all dose titrations will 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
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 (e.g., 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, NHYA 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 safety 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.8 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.17 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.17-19 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.20 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.21-25

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-HCM12 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.8 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.24

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.13,25 However, considering that mavacamten has not previously been studied in Chinese subjects with HCM and the incidence of poor CYP2C19 metabolisers is higher,26-28 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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