Clinical Study Protocol

An Open-Label, Parallel-Group, Single-Center Phase 1 Clinical Study to Evaluate the Pharmacokinetics of a Single Oral Dose of Mavacamten in Healthy Adult Chinese Subjects

Investigational Drug	Mavacamten Capsules
Protocol No.	LB2001-101
Phase of Development	1
Registration Category	Chemical Drug Category 1
Proposed Indication	Obstructive Hypertrophic Cardiomyopathy
Version and Date	1.0/ 30 Apr 2021
Sponsor	Shanghai LianBio Development Co., Ltd.
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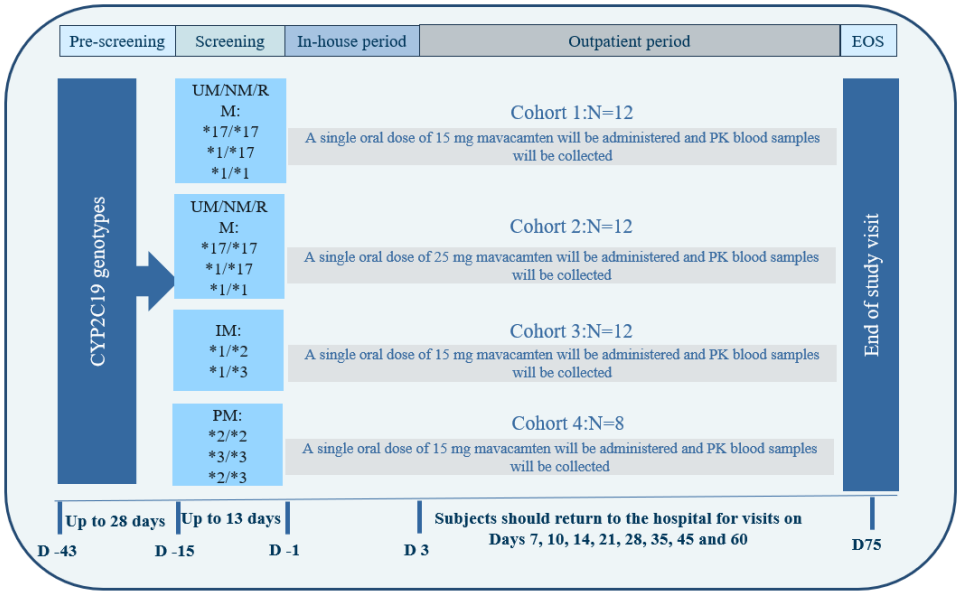
Version History

Version Number	Version Date	Major Amendments and Reason

Synopsis

Title	An Open-Label, Parallel-Group, Single-Center Phase 1 Clinical Study to Evaluate the Pharmacokinetics of a Single Oral Dose of Mavacamten in Healthy Adult Chinese Subjects
Protocol No.	LB2001-101
Sponsor	Shanghai LianBio Development Co., Ltd.
Phase of Development	1
Registration Category	Chemical Drug Category 1
Proposed Indication	Obstructive Hypertrophic Cardiomyopathy (oHCM)
Investigational Drug	Name: Mavacamten Capsules Strength: 10 mg and 15 mg Dosage form: capsules Storage condition: 2℃ to 25℃ (36℉ to 77℉)
Objectives	**Primary:** • To evaluate the pharmacokinetics (PK) of a single oral dose of mavacamten in healthy adult Chinese subjects with different CYP2C19 genotypes. **Secondary:** • To evaluate the safety and tolerability of a single oral dose of mavacamten in healthy adult Chinese subjects with different CYP2C19 genotypes. **Exploratory:** • To evaluate the population PK.
PK Endpoints	**PK endpoints include:** • Area under the curve (AUC) $_{(0\text{-last})}$, $AUC_{(0\text{-inf})}$; • Maximum concentration (C_{max}); • Time to maximum concentration (T_{max}); • Elimination half-life ($T_{1/2}$); • Apparent volume of distribution (V_d/F); • Apparent clearance (CL/F).
Safety Endpoints	**Safety endpoints include:** • Vital signs; • Physical examination findings; • Electrocardiogram (ECG) parameters; • Clinical laboratory tests data, including hematology and blood chemistry, coagulation and urinalysis parameters; • Adverse events (AEs).
Exploratory Endpoint	• Population PK model may be assessed to investigate ethnic differences on key PK parameters including clearance and volume of distribution.
Sample Size	Approximately 44 healthy adult Chinese subjects are expected to be enrolled in this study according to CYP2C19 genotypes into 4 cohorts. • **Cohort 1 and Cohort 2 (n = 12)**: ultra-rapid metabolizer (UM), rapid metabolizer (RM), or normal metabolizer (NM) of cytochrome P450 (CYP) 2C19 to ensure

	that data will be obtained for at least 10 subjects; • **Cohort 3 (n = 12)**: intermediate metabolizer (IM) of CYP2C19 to ensure that data will be obtained for at least 10 subjects; • **Cohort 4 (n = 8)**: poor metabolizer (PM) of CYP2C19 to ensure that data will be obtained for at least 6 subjects.
Study Design	This is an open-label, parallel-group, single-center Phase 1 clinical study. Healthy adult Chinese subjects with different CYP2C19 genotypes (Cohort 1 and Cohort 2: CYP2C19 UM, RM, or NM; Cohort 3: CYP2C19 IM; Cohort 4: CYP2C19 PM) will be included and administered with a single oral dose of mavacamten to evaluate its PK profile. The doses administered include: 15 mg for cohort 1; 25 mg for Cohort 2; 15 mg for Cohort 3; 15 mg for Cohort 4. Blood samples will be collected from subjects at scheduled time points for PK testing. Series of safety assessments (including but not limited to AEs, laboratory tests, vital signs, and ECGs) will be performed during the whole study at specified time points. 
Inclusion Criteria	Subjects can be enrolled in the study if they meet all of the following criteria: 1. Male or female between the ages of 18 and 60 (inclusive) at screening (one sex not less than 25% each cohort); 2. Subjects who are CYP2C19 UM (*17/*17), CYP2C19 RM (*1/*17), CYP2C19 NM (*1/*1), CYP2C19 IM (*1/*2 or *1/*3) or CYP2C19 PM (*2/*2, *3/*3, or *2/*3) as per central laboratory phenotype interpretation during the pre-screening period; 3. With a body mass index (BMI) between 18 kg/m^2 and 30 kg/m^2 (inclusive) at screening; 4. With a resting left ventricular ejection fraction (LVEF) ≥ 55% by echocardiography at screening; 5. Healthy as determined by medical history, physical examination, vital signs, and laboratory tests (chemistry, hematology, coagulation and urinalysis), and 12-lead ECG at screening and on Day -1. Laboratory values outside the normal range are acceptable if such abnormalities are interpreted as being clinically insignificant. Screening assessments can be repeated for one more time at the investigator's discretion within the screening window; 6. Female subjects shall not be pregnant or breastfeeding and, if sexually active with male partner(s), must adopt one of the following highly effective contraceptive methods from the Screening Visit through 5 months after administration of the investigational medicinal product (IMP):

	• Estrogen and progesterone containing hormonal contraception associated with inhibition of ovulation or progesterone only hormonal contraception associated with inhibition of ovulation by oral, implantable, or injectable routes of administration; • Intrauterine device (IUD); • Intrauterine system (IUS); • Bilateral tubal ligation; • Females who have been surgically sterilized for more than 6 months or postmenopausal for more than 1 year. Permanent sterilization includes hysterectomy, bilateral oophorectomy, bilateral salpingectomy, and/or documented bilateral tubal ligation for at least 6 months prior to screening. Females are considered postmenopausal if they have had amenorrhea for at least 1 year or more following cessation of all exogenous hormonal treatments and their follicle stimulating hormone levels are in the postmenopausal range; 7. Male partners of female subjects must also adopt a contraceptive method (e.g., barrier, condom or vasectomy) from screening through 5 months after administration of the investigational drug; 8. Able to understand and comply with the study procedures, understand the risks involved in this study, and provide written informed consent according to local and institutional guidelines before screening procedure.
Exclusion Criteria	Subjects must not be enrolled in the study if they meet any of the following criteria: 1. History of clinically significant arrhythmia, left ventricular (LV) systolic dysfunction, or coronary artery disease, or QTc >450 ms at screening and on Day -1; 2. History of any type of malignant tumors, other than in situ cervical cancer or surgically excised non melanomatous skin cancers, within 5 years of the Screening Visit; 3. Positive serologic tests at screening for infections with human immunodeficiency virus (HIV) antibody, hepatitis C virus (HCV) antibody or hepatitis B virus (HBV) surface antigen at screening; 4. Vital sign meet any of the following criteria: a) ear temperature was greater than 37.5 ℃; b) heart rate was greater than 100 beats / min or less than 50 beats / min; c) systolic blood pressure was greater than 139 mmHg or less than 90 mmHg; d) diastolic blood pressure was greater than 90 mmHg or less than 50 mmHg at screening and on Day -1; 5. Subjects who have taken prescription medications within 28 days prior to screening or within 5 times of $T_{1/2}$ (if known), whichever is longer; or those who have taken over-the-counter medications (including herbal preparations and nutritional supplements) within 14 days prior to screening or within 5 times of $T_{1/2}$ (if known), whichever is longer (acetaminophen up to 1.5 g per day is allowed); 6. History or evidence of any other clinically significant abnormalities, conditions, or diseases (with the exception of those outlined above) that, in the opinion of the investigator, would pose a risk to the safety of the subject or interfere with study evaluation, procedures, or its completion; 7. Any condition or treatment for a condition that might interfere with the conduct of the trial or might, in the opinion of the investigator, put the subject at risk, including but not limited to, alcoholism, drug dependence or abuse, and psychiatric conditions, if he/she participates in this study; 8. Positive test for alcohol or drug abuse at screening and on Day -1; 9. Use of tobacco exceeding 10 cigarettes per day or nicotine-containing products

	of equivalent amount within 28 days prior to screening; 10. Hypersensitivity to mavacamten or any of the components of its formulation (Inactive ingredients are silicon dioxide, mannitol, hypromellose, croscarmellose sodium, and magnesium stearate (non-bovine). The capsule contains gelatin, titanium dioxide, black iron oxide, red iron oxide, and yellow iron oxide); 11. Prior exposure to mavacamten; 12. Prior exposure to the investigational drug (or current use of an investigational device) within 30 days prior to screening, or at least 5 times of $T_{1/2}$ (if known), whichever is longer; 13. Unable to comply with the study restrictions/requirements, including the number of required visits to the clinical site; 14. Had donated over or lost 400 mL blood in 60 days or plasma in the last 2 weeks prior to the screening visit; 15. Infection of coronavirus disease 2019 (COVID-19) (i.e., positive for polymerase chain reaction) within 6 months prior to screening; 16. Unsuitable to participate in the study as judged by the investigator.
Study Procedures	This study will consist of the following 5 periods: • **Pre-screening period (Day -43 to Day -15, up to 28 days)** Subjects who sign the pre-screening informed consent form (ICF) will enter the pre-screening period to determine their CYP2C19 genotypes. • **Screening period (Day-14 to Day -2, up to 13 days):** After determining their genotypes, subjects who sign the main ICF will enter the screening period to complete screening examinations. • **In-house period (Day -1 to Day 3, total 4 days):** Eligible subjects will be divided into 4 parallel cohorts based on their CYP2C19 genotypes (Cohort 1 and Cohort 2: CYP2C19 UM, RM, or NM; Cohort 3: CYP2C19 IM; Cohort 4: CYP2C19 PM). Subjects will be admitted to the clinical research unit (CRU) the day before dosing (Day -1), and receive a single oral dose of mavacamten on Day 1 (Cohort 1: 15 mg; Cohort 2: 15 mg; Cohort 3: 15 mg; Cohort 4: 15 mg). They will remain in the CRU until Day 3 (48 hours after administration of mavacamten) for PK and safety assessments. • **Outpatient period (Day 4 to Day 75, total 72 days):** Subjects who have finished the examinations on Day 3 will enter the outpatient period. Outpatient visits will occur on Days 7, 10, 14, 21, 28, 35, 45 and 60 to collect blood samples and perform safety assessments. • **End of study visit (Day 75)** End of study (EOS) Visit will occur on Day 75 to complete the final safety examination and obtain the last blood samples for PK assessment.
Dosing Regimen and Routes of Administration	• **Dosing Regimen** Subjects will receive a single dose of mavacamten on Day 1. Cohort 1: 15 mg (15 mg capsules × 1); Cohort 2: 25 mg (10 mg capsules x 1 and 15 mg capsules x 1); Cohort 3: 15 mg (15 mg capsules × 1); Cohort 4: 15 mg (15 mg capsules × 1); • **Route of Administration** The drug is to be administered orally. Subjects should fast overnight (for at least 8 hours) before taking mavacamten with 240 mL water, and should not eat any food until 3 hours after dosing. Water will be allowed except for 1 hour before and after dosing.

PK Sampling	• **PK Sampling Schedule** 3 mL whole blood will be collected at each of the following time points for PK analysis: pre-dose (within 60 min before dosing), 10 min, 20 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 8 h, 12 h, 24 h and 48 h, and on Days 7, 10, 14, 21, 28, 35, 45, 60 and 75 after dosing of mavacamten.
Statistical Methods	Approximately 44 subjects will be enrolled in this study. ● **Datasets** ➢ **Pharmacokinetic Set** (PKS): All subjects exposed to mavacamten and with at least one plasma concentration will be included in the PKS. ➢ **Safety Analysis Set** (SAS): All subjects exposed to mavacamten, regardless of the doses administered, will be included in the SAS. ● **Statistical Analysis** ➢ **PK Analyses:** Individual plasma concentration-time data of mavacamten will be displayed and summarized graphically on the linear and semi-log scales. PK parameters, including $AUC_{(0\text{-last})}$, $AUC_{(0\text{-inf})}$, C_{max}, T_{max}, $T_{1/2}$, V_d/F, CL/F will be calculated using a non-compartmental model. The concentration-time data for each cohort will be summarized and the mean concentration-time curve will be plotted on the linear and semi-log scales by cohort. Descriptive statistical analysis for parameters will be performed by cohort. Statistics include the number of subjects, arithmetic mean, geometric mean (GM), standard deviation (SD), and coefficient of variation (CV), minimum (min), median, and maximum (max). ➢ **Safety Analyses:** Safety analyses will be based on descriptive statistics (summary tables) as well as individual data for AEs, clinical laboratory values, vital signs, and ECG parameters. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be monitored throughout the study to determine their severity and their potential relationship to the investigational drug. The number of subjects who experience AEs after dosing (from single dose administration to the EOS) will be summarized by cohort. ➢ **Population PK (PopPK) Analysis**: PopPK analysis will be conducted with the pooled data from the current study LB2001-101 and other mavacamten studies. Additional details on PopPK model development and analysis will be provided in a separate PopPK data analysis plan (DAP), and the results of PopPK analysis will be reported in a separate clinical study report (CSR). *Note: PopPK analysis will be performed only after approval by relevant regulatory authorities and within the approved scope.*

Table 1 Study Flow Chart

Weeks	Pre-screening	Screening Period	In-house Period				Outpatient Period								End of study visit
Days	D-43 to D-15	D-14 to D-2	D-1	D1	D2	D3	D7	D10	D14	D21	D28	D35	D45	D60	D75
Visit Window (day)							±1	±1	±1	±1	±1	±1	±1	±1	±1
Signing the pre-screening ICF[1]	X														
Demographics[2]	X														
CYP2C19 genotyping	X														
Signing the main ICF		X													
Inclusion/exclusion criteria		X	X												
Assign subject number	X	X	X												
Medical history		X													
Vital signs[3]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[4]		X	X			X									X
Weight, height[5]		X													X
12-lead ECG[6]		X	X	X		X					X			X	X
Echocardiography		X													
Hematology[7]		X	X								X				X
Blood chemistry[8]		X	X			X					X				X
Urinalysis[9]		X	X								X				X
Coagulation[10]		X	X			X					X				X
FSH[11]		X													
Serum pregnancy test[12]		X													X
Urine Pregnancy test[12]			X								X			X	
Hepatitis B, C, and HIV virology		X													
Alcohol or drug abuse test[13]		X	X												
Investigational drug[14]				X											
PK blood sampling[15]				X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate

aminotransferase; BP = blood pressure; CK = creatine kinase; CYP = cytochrome P450; ECG = electrocardiogram; EOS = end of study; FIB = fibrinogen; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; HR = heart rate; ICF = informed consent form; INR = international normalized ratio; PK = pharmacokinetic; PT = prothrombin time; QD = once daily; RBC = red blood cell; SAE = serious AE; TT = thrombin time; WBC = white blood cell.

Note: safety laboratory tests (hematology, blood chemistry, coagulation, urinalysis) are not required to be repeated on Day -1 if the latest results are within 7 days from Day -1. 12-lead ECG test is not required to be repeated on Day -1 if the latest result is within 3 days from Day -1.

1. Signing the pre-screening ICF: after signing of the pre-screening ICF, test for determining CYP2C19 genotypes could be performed.

2. Demographics: including age, gender and ethnicity.

3. Vital signs: including temperature, heart rate, respiratory rate, and systolic and diastolic BP in a supine position after 5 minutes of rest. While the subject is in the CRU, vital signs will be taken upon rising in the morning. On Day 1, vital signs should be collected before IMP dosing.

4. Physical examination: a complete physical examination will be conducted at screening and the EOS Visit, while abbreviated physical examinations on other visits. A complete physical examination includes assessments of general appearance, skin, head and neck, mouth, lymph nodes, thyroid, abdomen, and musculoskeletal, cardiovascular, neurological, and respiratory systems. Brief physical examination included cardiovascular and respiratory examinations.

5. Height, weight: weight (kg) will be measured at screening and the EOS Visit. And height (cm) will be measured at screening.

6. 12-lead ECG: it will be performed after 10 minutes of rest at screening, on Day -1, Day 1 (pre-dose: within 3h before dosing, and post-dose: 2 h±30min after dosing), Day 3, Day 28, Day 60, and at the EOS Visit. When the 12-lead ECG is completed, a 10-second paper ECG will be obtained as the subject's source documentation. If clinical symptoms or clinical indications occur accordingly, the investigator may consider increasing the frequency of test.

7. Hematology: including hematocrit, hemoglobin, RBC count, WBC count and differential, platelet count.

8. Blood chemistry: including albumin, total protein, direct bilirubin, total bilirubin, ALP, ALT, AST, creatinine, urea nitrogen, uric acid, CK, chlorine, potassium, sodium, calcium, magnesium, and glucose.

9. Urinalysis: including urine glucose, urine ketone bodies, urine pH, urine protein, urine specific gravity, urine leukocyte esterase, urine WBC and urine RBC.

10. Coagulation: including PT, INR, APTT, FIB, and TT.

11. FSH: FSH test will be performed at screening for postmenopausal women to confirm their postmenopausal status (serum pregnancy test at screening). If the result of FSH test shows that the subject is not postmenopausal, a pregnancy test (serum or urine) is required to be performed at another visit to ensure that the subject is not pregnant.

12. Pregnancy test: it will be performed in women of childbearing potential only. Serum pregnancy test will be performed at screening and the EOS Visit. Urine pregnancy test will be performed on Day -1, Day 28 and Day 60.

13. Alcohol or drug abuse test: a combination drug detection kit (colloidal gold method) will be used for this test to detect the amount of morphine, ketamine, tetrahydrocannabinic acid, methamphetamine, 3,4-Methylenedioxymethamphetamine and cocaine in human urine.

14. Investigational drug: administered orally on Day 1.

15. PK blood sampling: blood samples will be obtained at pre-dose (within 60 min before dosing), 10 min, 20 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 8 h, 12 h, 24 h and 48 h, and on Days 7, 10, 14, 21, 28, 35, 45, 60, and 75 after dosing of mavacamten to determine its plasma concentrations.

16. AEs: during the pre-screening and screening period, only study procedure -related AEs (e.g., blood sampling) will be collected.

Table 2 PK Sampling Schedule

	In-house Period			Outpatient Period								End of study visit
Days	**D 1**	**D 2**	**D 3**	**D 7**	**D 10**	**D 14**	**D 21**	**D 28**	**D 35**	**D 45**	**D 60**	**D 75**
Visit Window (day)	**0**	**0**	**0**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**
Collection time points	Pre-dose (within 60 min before dosing) 10 min±2 min 20 min±2 min 30 min±2 min 45 min±2 min 1 h±2 min 1.5 h±3 min 2 h±3 min 3 h±3 min 4 h±3 min 8 h±5 min 12 h±5 min	24 h ± 1 h post-dose	48 h ± 1 h post-dose	Outpatient visits: 144 h ± 24 h post-dose on Day 1	Outpatient visits: 216 h ± 24 h post-dose on Day 1	Outpatient visits: 312 h ± 24 h post-dose on Day 1	Outpatient visits: 480 h ± 24 h post-dose on Day 1	Outpatient visits: 648 h ± 24 h post-dose on Day 1	Outpatient visits: 816 h ± 24 h post-dose on Day 1	Outpatient visits: 1056 h ± 24 h post-dose on Day 1	Outpatient visits: 1416 h ± 24 h post-dose on Day 1	EOS Visit: 1776 h ± 24 h post-dose on Day 1

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Abbreviations	Definitions
AE	Adverse event
AESI	Adverse events of special interest
AF	Atrial fibrillation
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
APTT	Activated partial thromboplastin time
AUC	Area under the curve
BIL	Bilirubin
BMI	Body mass index
BP	Blood pressure
β-hCG	Beta human chorionic gonadotropin
cGMP	Current Good Manufacturing Practice
CDE	Center for Drug Evaluation
C_{max}	Maximum concentration
CK	Creatine kinase
CL/F	Apparent clearance
CRU	Clinical research unit
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CSP	Clinical study protocol
CSR	Clinical study report
CV	Cardiovascular
CV	Coefficient of variation
CYP	Cytochrome P450
DAP	Data analysis plan
DSUR	Development Safety Update Report
EC	Ethics committee; refers to an IRB or IEC or equivalent
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data collection
EOS	End of study
ET	Early termination
FAS	Full analysis set
FIB	Fibrinogen
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GM	Geometric mean
HB	Hemoglobin
HBV	Hepatitis B virus
HBsAb	hepatitis B surface antibody
HCV	Hepatitis C virus
HCM	Hypertrophic Cardiomyopathy
HOCM	Hypertrophic obstructive cardiomyopathy
hERG	Human ether-à-go-go-related gene
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
ICD	Implantable cardioverter defibrillator
ICF	Informed Consent Form

Abbreviations	Definitions
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IM	Intermediate metabolizer
IME	Important medical events
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
IUD	Intrauterine device
IUS	Intrauterine system
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
LVOT	Left ventricular outflow tract
LVOTO	Left ventricular outflow track obstruction
MedDRA	Medical Dictionary for Regulatory Activities
MR	Mitral regurgitation
nHCM	Non-obstructive hypertrophic cardiomyopathy
NM	Normal metabolizer
NMPA	National Medical Products Administration
oHCM	Obstructive Hypertrophic Cardiomyopathy
pH	Pondus hydrogenii
PK	Pharmacokinetics
PKS	Pharmacokinetics set
PopPK	Population pharmacokinetics
PM	Poor metabolizer
PT	Preferred term
PT	Prothrombin time
PPS	Per-Protocol set
QD	Once daily
QTc	Corrected QT interval
QTcF	QT Interval corrected by heart rate using Fridericia's formula
RBC	Red blood cell
RM	Rapid metabolizer
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SCD	Sudden cardiac death
SD	Standard deviation
SOC	System Organ Class
SRT	Septal reduction therapy
SS	Safety analysis set
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Elimination half-life
TEAE	Treatment-emergent adverse events
TT	Thrombin time
T_{max}	Time to maximum concentration
UM	Ultra-rapid metabolizer
ULN	Upper limit of normal
V_d/F	Apparent volume of distribution
WBC	White blood cell

1. Introduction

1.1 Background

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder defined by left ventricular (LV) hypertrophy that cannot be explained by other cardiac or systemic diseases. HCM is a chronic, progressive disease of the cardiomyocyte, and largely involves the cardiac sarcomere, with a diverse clinical presentation and course. Over time, HCM results in tissue remodeling characterized histologically by myocyte hypertrophy and disarray, microvascular remodeling, and fibrosis [1]. Approximately 40% of patients with sporadic HCM and 60% of those with a family history of HCM have a mutation in one or more sarcomeric structural genes [2-5]. Mutations in cardiac myosin and other sarcomeric proteins appear to increase net power generation by the sarcomere [6-8], consistent with the generally hypercontractile state and impaired compliance of the myocardium observed clinically in HCM. Recent estimates of the prevalence of HCM using information from large administrative databases indicate that the prevalence of clinically diagnosed HCM ranges from 3 to 7 per 10,000 [9 to 12]. It is estimated that there are around 1 million adults affected by HCM in China [13].

Two HCM phenotypes are recognized based on the peak left ventricular outflow tract (LVOT) gradient, namely obstructive hypertrophic cardiomyopathy (oHCM, also known as hypertrophic obstructive cardiomyopathy [HOCM]) and non-obstructive hypertrophic cardiomyopathy (nHCM), where obstruction is defined as a peak LVOT gradient ≥30 mmHg at rest or with provocation [3]. Approximately 70% of individuals diagnosed with HCM have oHCM [14]. Based on this, the prevalence rate of oHCM is likely between 2 and 5 per 10,000, based on the recent estimates of HCM. The precise mechanism of LVOT obstruction is unknown, but the combination of the abnormal ventricular geometry caused by septal hypertrophy, reduced ventricular cavity size, and the pathologic elongation of the mitral valve leaflets are considered as contributing factors [15]. Outflow tract obstruction can produce increased LV systolic pressure and an array of subsequent abnormalities, including prolongation of ventricular relaxation, elevation of LV diastolic pressure, mitral regurgitation (MR), atrial fibrillation (AF), myocardial ischemia, and decreased forward cardiac output [16]. The presence of LVOT obstruction is an important prognostic factor in HCM, and is associated with an increased risk of progressive disease, congestive heart failure, stroke, and death [17, 18]. The risk of sudden cardiac death (SCD), which is one of the most common non-traumatic causes of death in young adults and sometimes the first manifestation of HCM, is also increased in the presence of LVOT obstruction [3,19,20].

The current guideline-recommended drugs for HCM mainly depend on the empirical use of drugs for cardiovascular (CV) disease, including beta-blockers, verapamil, diltiazem, and disopyramide [3,2,2]. These drugs cannot alter the natural course of HCM and only have modest effect on peak LVOT gradient. In oHCM, septal reduction therapy (SRT) may reduce obstruction and improve LV outflow, and an implantable cardioverter-defibrillator (ICD) may prevent SCD, but both involve invasive procedures and require specialized operators and experienced clinical centers, and may not be applicable to all patients [23]. Cardiac transplant is the only option when pharmacologic options fail to adequately manage oHCM. None of these treatment options address the underlying etiology of HCM. Because of the huge unmet clinical need for the treatment of HCM, an urgent need for innovative drug development emerges. The Class 1 new drug of mavacamten to be evaluated in this trial boasts a breakthrough mechanism, and is being investigated in multiple clinical studies worldwide, showing good prospects for its clinical application in the treatment of HCM. Brief description will be made in the next section.

1.2 Overview of Mavacamten

1.2.1 Basic Information

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

1.2.2 Clinical Experience with Mavacamten

To date, 18 clinical studies have been initiated to investigate the safety and tolerability of mavacamten. Please refer to the Investigator's Brochure (IB) for detailed information of these studies. The most relevant data to this study are the results from MYK-461-011 and MYK-461-012, which are briefly described below:

- **Study MYK-461-011**

The MYK-461-011 study was a phase 1, single-center, prospective, open-label, parallel-group clinical study to evaluate the PK profile of mavacamten administered by a single oral dose to healthy Japanese and Caucasian subjects. The study enrolled 20 healthy Japanese subjects and 8 healthy Caucasian subjects whose cytochrome P450 (CYP) 2C19 genotypes were ultra-rapid metabolizer (UM), rapid metabolizer (RM), normal metabolizer (NM) or intermediate metabolizer (IM). Three sequential cohorts (Cohort 1-3) of healthy Japanese subjects received a single dose of mavacamten ranging from 5 mg, 15 mg to 25 mg. To compare the PK profile between Japanese and Caucasian subjects, healthy Caucasian subjects (Cohort 4) received a single dose of 25 mg mavacamten. The results showed that mavacamten was rapidly absorbed with a median T_{max} of 0.5 hours. The exposure of mavacamten was increased in an almost dose-proportional manner between 5 and 15 mg. The geometric means (GM) of maximum concentration (C_{max}), area under the curve $(AUC)_{(0\text{-last})}$ and $AUC_{(0\text{-inf})}$ in Japanese and Caucasian subjects were similar. The results of Caucasian subjects showed slightly higher variability. The Japanese and Caucasian subjects also showed similar mean elimination half-lifes ($T_{1/2}$) of approximately 155 hours. The mean volume of distribution (V_d/F) and $V_{d,z}/F$ were comparable between Japanese and Caucasian subjects. The results indicated no significant differences in the PK data between Japanese and Caucasian subjects. Therefore, dose modifications based on PK were not required for subjects of different ethnicities.

There were no deaths, SAEs or AEs of moderate severity. All treatment-emergent adverse events (TEAEs) (n = 4) were mild in severity. One TEAE was considered as related to the investigational drug (headache in a Japanese subject who received 15 mg mavacamten). Other TEAEs were judged to be unrelated to the investigational drug (1 upper respiratory tract infection, 1 viral upper respiratory tract infection, and 1 hypoaesthesia).

- **Study MYK-461-012**

MYK-461-012 was a single-center, open-label, parallel-group, phase 1 clinical trial evaluating the PK profile of mavacamten administered by a single dose (15 mg) to 16 healthy Asian subjects (8 CYP2C19 NM, 8 CYP2C19 PM).

Following a single dose of 15 mg mavacamten to subjects of CYP2C19 PM, the C_{max} was 489.9 ng/mL; median T_{max} occurred at 0.75 hours post-dose, with a $T_{1/2}$ of 552.8 hours; the $AUC_{(0\text{-last})}$ and $AUC_{(0\text{-inf})}$ were 35,310 and 42,800 h·ng/mL, respectively; and the CL/F and V_z/F were 350.5 mL/h and 279,500 mL, respectively. Overall exposure of mavacamten was higher in CYP2C19 PM subjects compared to CYP2C19 NM subjects.

No SAEs, deaths, or AEs leading to study discontinuation occurred during the study. All TEAEs (n=11) were mild in severity. One subject of CYP2C19 NM experienced two TEAEs of chest discomfort, one of which was judged to be related to mavacamten, and the other was unrelated to mavacamten. Additional 3 TEAEs were judged to be investigational drug-related (1 palpitations in a subject of CYP2C19 NM, 1 constipation and 1 diarrhea in 2 subjects of CYP2C19 PM). Others were judged to be unrelated to the investigational drug (3 upper respiratory tract infections, including 1 cough, 1 oropharyngeal pain and 1 upper-airway cough syndrome).

The PK data from MYK-461-011 and MYK-461-012 were illustrated below:

Table 3 Summary of PK Parameters from Study MYK-461-011 and Study MYK-461-012

Study		MYK-461-011				MYK-461-012
Parameter	Statistic	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 2
		5 mg	15 mg	25 mg	25 mg	15 mg
		Japanese Subjects	Japanese Subjects	Japanese Subjects	Caucasian Subjects	Asian Subjects
		IM	IM	UM/RM/ NM	UM/RM/ NM	PM
		N=4	N=8	N=8	N=8	N=8
C_{max} (ng/mL)	GM (gCV %)	141.3 (15.5)	289.0 (19.8)	504.0 (18.3)	515.8 (28.6)	489.0 (31.4)
T_{max} (h)	Median	1.5	1.0	1.5	1.5	0.750
$AUC_{(0\text{-last})}$ (h*ng/mL)	GM (gCV %)	5897 (28.8)	14660 (25.4)	16890 (30.8)	18820 (49.6)	35310 (13.6)
$AUC_{(0\text{-inf})}$ (h*ng/mL)	GM (gCV %)	6277 (28.7)	15410 (27.4)	17370 (34.0)	19280 (53.2)	42800 (20.3)
$T_{½}$ (h)	Mean (CV %)	222.2 (24.6)	221.5 (23.0)	153.8 (50.5)	155.7 (48.2)	571.6 (24.5)
CL/F (mL/h)	Mean (gCV %)	821.3 (29.5)	1006 (29.2)	1505 (30.6)	1425 (40.6)	357.1 (22.1)
$V_{d,z}/F$ (mL)	Mean (gCV %)	251200 (16.4)	310900 (26.0)	306800 (30.8)	276600 (26.1)	282300 (14.9)

1.3 Known and Potential Benefits and Risks

There is no clinical benefit for the healthy subjects enrolled in the current study.

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

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

Data across nonclinical toxicology studies have shown that doses of mavacamten exceeding therapeutic levels can lead to reduced cardiac function, decreased blood pressure, compensatory increases in heart rate, and death. Clinical data has shown that dose-dependent, on-target reductions in LVEF have been monitorable with use of echocardiograms, reversible

with temporary or permanent discontinuation of treatment, and observed in the setting of mavacamten treatment alone or with concomitant conditions frequently observed in HCM, such as atrial fibrillation.

In patients with HCM, mavacamten's on-target mechanism of action reduces LVEF and may cause systolic dysfunction with LVEF < 50% with or without symptoms of left heart failure. Patients with a serious intercurrent illness or arrhythmia (e.g., atrial fibrillation or other uncontrolled tachyarrhythmia) may be at greater risk of systolic dysfunction. Data from MYK-461-006, conducted in subjects with nHCM, demonstrated that those who experienced decreases in LVEF returned to normal levels after interruption or discontinuation of study treatment. In the EXPLORER-HCM study (Study MYK-461-005), 7 subjects (5.7%) in the mavacamten group and 2 subjects (1.6%) in the placebo group experienced reversible reductions in LVEF < 50% while on treatment. In all 7 subjects treated with mavacamten, LVEF recovered following temporary interruption of dosing or was diagnosed at the end of the 30-week treatment period and recovered at Week 38. All subjects with an event of LVEF < 50% completed the study, with favorable changes from baseline in at least one key efficacy endpoint.

- **Teratogenicity**

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

- **QT Prolongation**

Across all clinical studies in HCM patients, there has been no indication of a mavacamten-induced QTc prolongation and/or of a concentration-dependent increase in QTc. In the EXPLORER-HCM study, baseline QTc interval was 440 ms in the mavacamten group and 443 ms in the placebo group. 22 (17.9%) patients in the mavacamten group and 20 (15.6%) patients in the placebo group had a change from baseline in QTcF interval of > 30 ms, the majority of whom did not have an ICD/pacemaker. This included 2 (1.6%) patients in the mavacamten group and 3 (2.3%) in the placebo group with a change > 60 ms. For 1 (0.8%) patient in the mavacamten group and 2 (1.6%) in the placebo group, maximum changes from baseline were > 15%.

Prolonged exposure to mavacamten in healthy animals resulted in a moderate prolongation of the QTc interval. Animal studies have suggested that such QTc prolongation occurs as a normal electrophysiological adaptation of healthy ventricles to the induced sustained mechanical changes, as mavacamten shows negligible direct (blockade) and/or indirect (trafficking) effects on human ether-a-go-go related gene (hERG) channels at the cellular level.

Consistent with non-clinical findings, in clinical studies involving healthy volunteers, sustained exposure to mavacamten led to marked depression of systolic dysfunction, which was associated with moderate concentration-dependent QTc prolongation (> 10 ms). No acute QTc changes have been observed at comparable (or higher) exposures during single-dose studies.

Safety testing in other mammalian species has shown that dose-limiting toxicities are associated with exaggerated pharmacological effect rather than off-target effects.

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

Mavacamten is primarily metabolized by CYP2C19 and CYP3A4. Starting or increasing the dose of any CYP2C19 or potent CYP3A4 inhibitor may increase the risk of systolic dysfunction. Stopping or decreasing dose of a CYP2C19 or potent CYP3A4 inhibitor may lead to a loss of therapeutic response to mavacamten. The potential for drug interactions with a CYP 2C19 inhibitor, including over-the-counter medications (such as omeprazole or esomeprazole), must be considered prior to and during mavacamten therapy. A list of prohibited medications for subjects in mavacamten clinical trials are utilized for screening and monitoring of subjects in the program.

Notably, clinical studies for mavacamten are ongoing. New safety information could emerge from ongoing clinical studies, which would be reflected in the IB and DUSR.

2. Rationale for the Study and Administration

2.1 Rationale for the Study

The sponsor is developing mavacamten, a novel, small molecule, allosteric inhibitor of cardiac-specific and selective myosin, for the treatment of patients with symptomatic oHCM, a condition with significant unmet medical need. Currently, clinical studies in healthy subjects and patients with oHCM have been conducted in the United States, the European Union, the United Kingdom, Australia, and Japan. Future studies are expected to include study sites in China, so a Phase 1 clinical study is warranted to confirm the obtained tolerability and PK data of mavacamten in Chinese subjects. That study is commonly referred to as an ethno-bridging study.

Mavacamten is metabolized in part by CYP2C19, an enzyme with genetic polymorphism. The incidence of the PM phenotype for CYP2C19 ranges from around 2% in the Caucasian population to around 12% in the Asian population [24]. Limited data obtained thus far have indicated that the exposure to mavacamten may be increased by approximately 3-fold in subjects of CYP2C19 PM compared to subjects of CYP2C19 NM. The current study is designed to determine the exposure to mavacamten in healthy adult Chinese subjects with different genotypes of CYP2C19.

2.2 Rationale for Dose Selection

Previous study (MYK-461-011) had demonstrated that Japanese and Caucasian subjects with genotypes of CYP2C19 UM, RM or NM showed similar PK profiles after receiving a single 25 mg dose of mavacamten. The drug was well-tolerated in all subjects.

Meanwhile, the PK profile of a single dose of 15 mg mavacamten was assessed in subjects of CYP2C19 IM and CYP2C19 PM in studies MYK-461-011 and MYK-461-012.

To bridging these PK data, a PK study in healthy Chinese adults with CYP2C19 genotypes of UM, RM, NM, IM or PM will be implemented. Subjects with CYP2C19 genotypes of UM, NM, or RM will receive a single dose of 25 mg mavacamten (Cohort 2) as in MYK-461-011; subjects with CYP2C19 genotypes of IM or PM will receive a single dose of 15 mg mavacamten as in MYK-461-011 and MYK-461-012; in addition, subjects with CYP2C19 genotypes of UM, NM, or RM will also receive a single dose of 15 mg mavacamten, in order to evaluate the PK profiles of mavacamten in subjects with different genotypes (Cohort 1/3/4) at the same dose (15 mg).

3. Objectives

Primary:

To evaluate the PK of a single oral dose of mavacamten in healthy adult Chinese subjects with different CYP2C19 genotypes.

Secondary:

To evaluate the safety and tolerability of a single oral dose of mavacamten in healthy adult Chinese subjects with different CYP2C19 genotypes.

Exploratory:

To evaluate the population PK.

4. Overall Study Design

4.1 Study Design

This is an open-label, parallel-group, single-center Phase 1 clinical trial. Healthy adult Chinese subjects with different CYP2C19 genotypes (Cohort 1 and Cohort 2: CYP2C19 UM, RM, or NM; Cohort 3: CYP2C19 IM; Cohort 4: CYP2C19 PM) will be included and administered with a single oral dose of mavacamten to evaluate its PK profile. The doses administered include: 15 mg for cohort 1; 25 mg for Cohort 2; 15 mg for Cohort 3; 15 mg for Cohort 4. Blood samples will be collected from subjects at scheduled time points for PK testing. Series of safety assessments (including but not limited to AEs, laboratory tests, vital signs, and ECGs) will be performed during the whole study at specified time points.

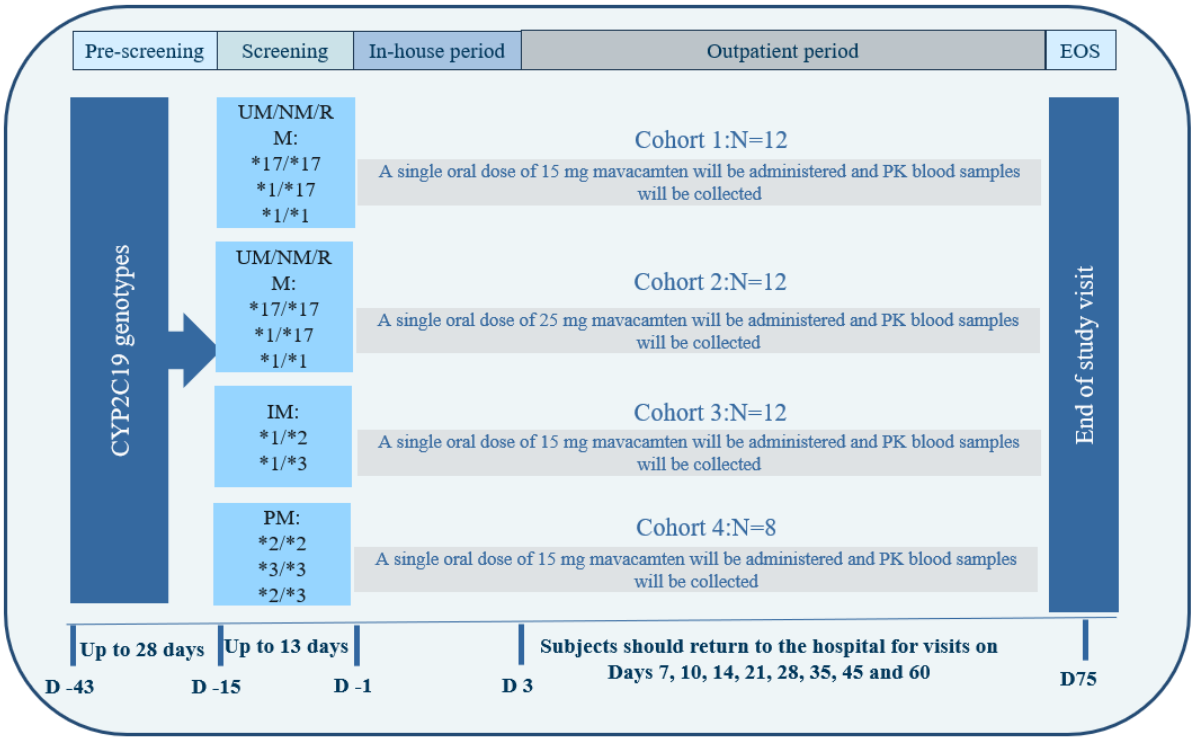

Figure: Overall Study Design

Abbreviations: CYP = Cytochrome P450; IM = intermediate metabolizer; NM = normal metabolizer; PM = poor metabolizer; RM = rapid metabolizer; UM = ultra- rapid metabolizer.

4.2 Study Periods

The overall study period for each subject is up to 16 weeks. The study periods are as follows:

- Pre-screening period: up to 28 days (Day -43 to Day -15);
- Screening period: up to 13 days (Day -14 to Day -2);
- In-house period: day -1 to Day 3;
- Outpatient period: Day 4 to Day 75.
- End of study visit: Day 75.

4.3 Study Procedures

4.3.1 Pre-screening Period (Day -43 to Day -15, up to 28 days)

Subjects who sign the pre-screening ICF will enter the pre-screening period to determine their CYP2C19 genotypes.

2 mL whole blood will be collected at each following time point for CYP2C19 genotypes analysis enter the pre-screening period (**See Table 2**). Refer to the relevant laboratory management manual for details of blood sample processing.

4.3.2 Screening Period (Day -14 to Day -2, up to 13 days)

After determining their genotypes, subjects who sign the main ICF will enter the screening period to receive screening examinations. Screening assessments can be repeated for one more time at the investigator's discretion within the screening window.

4.3.3 In-house Period (Day -1 to Day 3)

Eligible subjects will be divided into 4 parallel cohorts based on their CYP2C19 genotypes (Cohort 1 and Cohort 2: CYP2C19 UM, RM, or NM; Cohort 3: CYP2C19 IM; Cohort 4: CYP2C19 PM).

Subjects will be admitted to the CRU the day before dosing (Day-1) and receive a single oral dose of mavacamten (Cohort 1: 15 mg; Cohort 2: 25 mg; Cohort 3: 15 mg; Cohort 4: 15 mg) on Day 1. For subjects with CYP2C19 UM, RM, or NM, enrollment Cohort 1 first followed by Cohort 2, subjects can be enrolled to Cohort 3 and Cohort 4 in parallel. They will remain in the CRU until Day 3 (48 hours after administration of mavacamten) for PK and safety assessments.

4.3.4 Outpatient Period (Day 4 to Day 75)

Subjects who have finished the examinations on Day 3 will enter the outpatient period. Outpatient visits will occur on Days 7, 10, 14, 21, 28, 35, 45 and 60 to collect blood samples and perform safety assessments.

4.3.5 End of Study visit (Day 75)

End of study (EOS) Visit will occur on Day 75 to complete the final safety examination and obtain the last blood samples for PK assessment.

4.3.6 Unscheduled Visits

Subjects who have safety concerns should return to the CRU for unscheduled visit at the investigator's discretion. Unscheduled visits may be conducted for the collection of vital signs, ECGs, and/or the assessment of AEs. All information collected from unscheduled visits will be recorded in the eCRF and included in the clinical database.

4.3.7 Missed Visits

If a visit is missed, the visit and relevant assessments should be rescheduled as close as possible to the original date.

4.4 Behavioral Restrictions on Subjects

The following behavioral restrictions apply to the specified times throughout this clinical trial. If a subject does not comply with these restrictions or tests positive in any laboratory tests (e.g., drug, alcohol, pregnancy), he or she may be excluded or withdrawn from the study.

1) Subjects should not engage themselves in unaccustomed intensive exercises starting from 72 hours prior to the first dose to the EOS Visit;
2) Subjects will be required to abstain themselves from blood or plasma donation starting from the screening period to 3 months after the EOS Visit.
3) Subjects will have standardized meals during their stay in the CRU.
4) Subjects will be asked to abstain from alcohol starting from 48 hours before Day -1 to the EOS Visit.
5) Subjects will be asked to abstain from grapefruit or grapefruit juice, Seville oranges, and quinine (e.g., tonic water) starting from Day -1 to the EOS Visit;
6) During their stay in the CRU, subjects will be permitted to smoke up to 5 cigarettes per day.
7) Contraception requirements are described in **Section 9.2**.

5. Study Population

5.1 Study Population

Approximately 44 healthy adult Chinese subjects with different CYP2C19 genotypes will be enrolled in this clinical trial. This is a single-center study. Subjects will be divided into 4 cohorts.

- Cohorts 1 and 2: 12 healthy adult Chinese subjects to ensure that data will be obtained for at least 10 subjects; with their CYP2C19 genotypes being:
  - CYP2C19 UM: *17/*17 or
  - CYP2C19 RM: *1/*17 or
  - CYP2C19 NM: *1/*1;
- Cohort 3: 12 healthy adult Chinese subjects to ensure that data will be obtained for at least 10 subjects; with their CYP2C19 genotypes being:
  - CYP2C19 IM: *1/*2 or *1/*3;
- Cohort 4: 8 healthy adult Chinese subjects to ensure that data will be obtained for at least 6 subjects; with their CYP2C19 genotypes being:
  - CYP2C19 PM: *2/*2, *3/*3, or *2/*3.

5.2 Subject's Screening Number

All subjects who provide an informed consent will be assigned a screening number and a grouping number to distinguish them from one another as per the rules given below. The same screening number will be used from the time of informed consent to the EOS.

Pre-Screening No.: PXXX;

XXX: a serial number assigned to a subject who gives the informed consent at the study site.

Screening No.: SYYY

YYY: a serial number assigned to a subject enrolled into screening period.

Grouping No.: A/B/C/DZZZ

ZZZ: a serial number assigned to a subject enrolled into different groups (A: cohort 1; B: cohort 2; C: cohort 3; D: cohort 4), i.e., A005 as cohort 1 the fifth subject.

Replacement subjects will be assigned a subject number corresponding to the number of the subject he/she is replacing plus 100 (eg, Subject 105 replaces Subject 005)

5.3 Inclusion Criteria

Subjects can be enrolled in the study if they meet all of the following criteria:

1) Male or female between the ages of 18 and 60 (inclusive) at screening (one sex not less than 25% each cohort);
2) Subjects who are CYP2C19 UM (*17/*17), CYP2C19 RM (*1/*17), CYP2C19 NM (*1/*1), CYP2C19 IM (*1/*2 or *1/*3) or CYP2C19 PM (*2/*2, *3/*3, or *2/*3) as per central laboratory phenotype interpretation during the pre-screening period;

3) With a BMI between 18 kg/m^2 and 30 kg/m^2 (inclusive) at screening;

4) With a resting LVEF ≥ 55% by echocardiography at screening;

5) Healthy as determined by medical history, physical examination, vital signs, and laboratory test parameters (chemistry, hematology, coagulation and urinalysis), and 12-lead ECG at screening and on Day -1. Laboratory values outside the normal range are acceptable if such abnormalities are judged to be clinically insignificant. Screening assessments can be repeated for one more time at the investigator's discretion within the screening window;

6) Female subjects shall not be pregnant or breastfeeding and, if sexually active with male partner(s), must adopt one of the following highly effective contraceptive methods from the Screening Visit through 5 months after administration of the IMP:

   - Estrogen and progesterone containing hormonal contraception associated with inhibition of ovulation or progesterone only hormonal contraception associated with inhibition of ovulation by oral, implantable, or injectable routes of administration;
   - IUD;
   - IUS;
   - Bilateral tubal ligation;
   - Females who have been surgically sterilized for more than 6 months or postmenopausal for more than 1 year. Permanent sterilization includes documented hysterectomy, bilateral oophorectomy, bilateral salpingectomy, and/or bilateral tubal ligation for at least 6 months prior to screening. Females are considered as postmenopausal if they have had amenorrhea for at least 1 year or more following cessation of all exogenous hormonal treatments and their follicle stimulating hormone levels are in the postmenopausal range;

7) Male partners of female subjects must also adopt a contraceptive method (e.g., barrier, condom or vasectomy) from screening to 5 months after administration of the investigational drug.

8) Able to understand and comply with the study procedures, understand the risks involved in this study, and provide written informed consent according to local and institutional guidelines before the screening procedure.

5.4 Exclusion Criteria

Subjects must not be enrolled in the study if they meet any one of the following criteria:

1) History of clinically significant arrhythmia, LV systolic dysfunction, or coronary artery disease, or QTc >450 ms at screening and on Day;

2) History of any type of malignant tumors, other than in situ cervical cancer or surgically excised non melanomatous skin cancers, within 5 years of the screening visit;

3) Positive serologic tests at screening for infections with HIV antibody, HCV antibody, or HBV surface antigen at screening;

4) Vital sign meet any of the following criteria: a) ear temperature was greater than 37.5 ℃; b) heart rate was greater than 100 beats / min or less than 50 beats / min; c) systolic blood pressure was greater than 139 mmHg or less than 90 mmHg; d) diastolic blood pressure was greater than 90 mmHg or less than 50 mmHg at screening and on Day -1;

5) Subjects who have taken prescription medications within 28 days prior to screening or 5 times of $T_{1/2}$ (if known), whichever is longer; or those who have taken over-the-counter medications (including herbal medications and nutritional supplements) within 14 days prior to screening or 5 times of $T_{1/2}$ (if known), whichever is longer (acetaminophen up to 1.5 g per day is allowed);

6) History or evidence of any other clinically significant abnormalities, conditions, or diseases (with the exception of those outlined above) that, in the opinion of the investigator, would pose a risk to the safety of the subject or interfere with study evaluation, procedures, or its completion;

7) Any condition or treatment for a condition that might interfere with the conduct of the trial or might, in the opinion of the investigator, put the subject at risk, including but not limited to, alcoholism, drug dependence or abuse, and psychiatric conditions, if he/she participates in this study;

8) Positive test for alcohol or drug abuse at screening and on Day -1;

9) Use of tobacco exceeding 10 cigarettes per day or nicotine-containing products of equivalent amount within 28 days prior to screening;

10) Hypersensitivity to mavacamten or any of the components of its formulation (Inactive ingredients are silicon dioxide, mannitol, hypromellose, croscarmellose sodium, and magnesium stearate (non-bovine). The capsule contains gelatin, titanium dioxide, black iron oxide, red iron oxide, and yellow iron oxide);

11) Prior exposure to mavacamten;

12) Prior exposure to the investigational drug (or current use of an investigational device) within 30 days prior to screening, or at least 5 times of $T_{1/2}$ (if known), whichever is longer;

13) Unable to comply with the study restrictions/requirements, including the number of required visits to the clinical site;

14) Had donated over or lost 400 mL blood in 60 days or plasma in the last 2 weeks prior to the screening visit;

15) Known infection of COVID-19 (i.e., positive for polymerase chain reaction) within 6 months prior to screening.

16) Unsuitable to participate in the study as judged by the investigator;

5.5 Withdrawal & Replacement of Subjects and Termination of Clinical Trial

5.5.1 Withdrawal of Subjects from Clinical Trial

Subjects are free to revoke their informed consent and withdraw from the study at any time and for any reason. If a subject chooses to withdraw from the study, the investigator will attempt to obtain the assessments listed for the EOS Visit (see **Table 1**).

The investigator or sponsor may withdraw a study subject from the study for any of the following reasons, including but not limited to the following:

- Noncompliance with study procedures/restrictions;
- The sponsor terminates the clinical trial;
- At discretion of the investigator

In all cases, the reason(s) for study withdrawal will be recorded in the source document and in the appropriate eCRF.

5.5.2 Subject Replacement

Subjects who withdraw or discontinue the clinical study due to other reasons other than AEs may be replaced at the discretion of the investigator, and should be discussed with sponsor before replacement if possible.

5.5.3 Discontinuation of the Clinical Study

The sponsor retains the right to terminate the study. Specific circumstances that may lead to discontinuation of the study include, but are not limited to:

- Request by Ethics Commission (EC), Center for Drug Evaluation (CDE) or the National Health Commission of the Peoples' Republic of China to discontinue the study;
- Unsatisfactory subject enrollment;
- The incidence or severity of AEs in this or other studies indicating potential health hazard caused by the study dosing.

6. Investigational Drug

6.1 Basic Information of Mavacamten

Table 4 Investigational Drug

Name of Study Drug	Mavacamten
Dosage Form	Capsules
Strength	10 mg and 15 mg
Dosage	Single dose of 15 mg or 25 mg
Route of Administration	Oral
Investigational Medicinal Product (IMP)	Mavacamten
Supplier	Sponsor
Packaging and Labeling	Refer to Section 6.2

Abbreviations: IMP = investigational medicinal product;

6.2 Preparation, Handling, Storage, and Accountability

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

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

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

- **Formulation, Packaging, and Labeling**

Mavacamten capsules is blue opaque capsules printed with a yellow band on the body and black band on the cap. Each capsule contains white or off-white powder. Mavacamten capsules are supplied in 2 strengths: 10 mg and 15 mg.

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

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

6.3 Dose Regimen

Subjects receive a single dose of mavacamten on Day 1;

Cohort 1: 15 mg (15 mg capsule × 1);

Cohort 2: 25 mg (10 mg capsule × 1 and 15 mg capsule × 1);

Cohort 3: 15 mg (15 mg capsule × 1);

Cohort 4: 15 mg (15 mg capsule × 1).

6.4 Administration

All subjects will receive mavacamten in an open-label manner.

The IMP for this clinical study is mavacamten. Study medication throughout this protocol refers to IMP as well as any other protocol-required medications (note that for this protocol, there are no other required study medications).

Mavacamten will be administered at the CRU by a trained, qualified staff member. Subjects will receive a single dose of mavacamten on Day 1.

Subjects should take mavacamten with approximately 240 mL of water. Subjects should fast overnight (for at least 8 hours) before taking mavacamten and should not eat any food until 3 hours after taking mavacamten. Water will be allowed except for 1 hour before and after dosing.

6.5 Dosing Compliance

Mavacamten will be administered by a trained, qualified CRU staff member on Day 1.

6.6 Prior and Concomitant Therapy

6.6.1 Prior Therapy

At the time of signing the main ICF, subjects will be asked about their medication history over the previous 28 days, including prescription and nonprescription medications, herbal medications, vitamins, and minerals.

If a subject has not taken any prescription medication within 28 days or 5 times of half-life (if known), whichever is longer, of screening or any over-the-counter medication (including herbal preparations and nutritional supplements, but excluding acetaminophen up to 1.5 g per day) within 14 days or 5 times of half-life (if known), whichever is longer, of screening, the individual may proceed to the screening assessment.

6.6.2 Concomitant Medications

All concomitant medications, whether prescription or over-the-counter, vitamin and/or mineral supplements, herbs, and medications taken for an AE or study procedure (e.g., biopsy). should be documented in the medical notes and entered into eCRF, including start/stop dates, route, and indication.

6.6.3 Prohibited Medications

All prescription medication is prohibited from 28 days before screening through the EOS Visit, and all over-the-counter medication (including herbal preparations and nutritional supplements, but not including up to 1.5 g acetaminophen daily) is prohibited from 14 days before screening through the EOS Visit.

7. Study Assessments

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

The study procedures to be performed during the study are described below. Additional details are provided in Table 1 of this document. When several assessments are to be conducted at the same time point, the preferred order of assessments is ECG, vital signs, sample collection for PK and laboratory assessments. The order of assessments may vary slightly at specific time points to facilitate the most contemporaneous performance of the required assessments. Unscheduled or additional safety assessments may be performed if necessary, in the opinion of the investigator.

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

7.1 PK Assessments

PK Blood Sampling Schedule

3mL whole blood will be collected at each following time point for PK analysis.

Blood samples will be obtained to determine mavacamten concentrations at pre-dose (within 60 min before dosing), 10 min, 20 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 8 h, 12 h, 24 h, and 48 hours after dosing of mavacamten. Additional blood samples will be collected at Days 7, 10, 14, 21, 28, 35, 45, 60 and 75 (**See Table 2**).

PK Blood Sample Processing

Refer to the relevant laboratory management manual for details of blood sample processing.

7.2 Safety Assessments

Safety will be assessed throughout the study (**Table 1**). Safety assessments include physical examinations, vital signs, ECGs, observed and subject-reported AEs, and safety laboratory results.

Any abnormal findings judged by the investigator to be clinically significant will be recorded as an AE (See **Section 8.1**).

Physical Examination

Physical examinations will be conducted at screening Day-1, Day 3 and at the EOS Visit. A complete physical examination will be conducted at screening and the EOS Visit. An abbreviated physical examination will be conducted on Days -1 and 3 (**Table 1**).

A complete physical examination includes assessments of general appearance, skin, head and neck, mouth, lymph nodes, thyroid, abdomen, and musculoskeletal, cardiovascular, neurological, and respiratory systems. Brief physical examination included cardiovascular and respiratory examinations.

Height (cm) and body weight (kg) will be measured at screening, and BMI (kg/m^2) will be calculated. Body weight (kg) will be measured at EOS.

Vital Signs

Vital signs will be assessed at each study visit and include temperature, HR, respiratory rate, and systolic and diastolic BP in a supine position after 5 minutes of rest (**Table 1**). While the

subject is in the CRU, vital signs will be taken upon rising in the morning. On Day 1, vital signs should be collected within 3 h before IMP dosing.

12-lead ECG

Twelve-lead ECG evaluations will be performed after 10 minutes of rest in the supine position at screening, Day -1, Day 1 (pre-dose, within 3 h before dosing, and at 2 h±30 min post-dose), Day 3, Day 28, Day 60 and the EOS Visit (**Table 1**). Parameters to be evaluated include, but are not limited to: HR, rhythm, PR interval, QRS interval, QT interval, P wave, QRS complex, T wave morphology, ST segment displacement, etc.

The investigator will judge the overall interpretation as normal or abnormal with clinical significance or abnormal with no clinical significance. The investigator will review the ECG with any other clinical findings, subject's medical history, and laboratory data to determine the clinical significance of the findings.

The investigator may add extra 12-lead ECG safety assessments if there are any clinically significant abnormal findings or if the investigator considers it is required for any other safety reason. These assessments should be recorded as an unscheduled assessment.

Other Safety Assessments

Refer to Section 8.1 for information on AE assessment and Section 6.6.2 for concomitant therapy assessments.

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

8. Assessment, Recording and Reporting of Adverse Events

8.1 Definitions

8.1.1 Adverse Events

An AE is any untoward medical occurrence in a subject after receiving the investigational product and does not necessarily have a clear causal relationship with the investigational drug. An AE can therefore be any unfavorable and unintended sign (e.g., tachycardia, enlarged liver, clinically significant or abnormal laboratory result), subject-reported symptom (e.g., nausea, chest pain), or evidence of any disease activity temporally associated with the use of a study medication, whether or not related to the use of the study medication.

In clinical studies, an AE can include an undesirable medical event occurring at any time after the subject has signed pre-screening ICF and main ICF, even if no study drug has been administered before the occurrence of the AE. For this study, only blood sampling study procedure related AEs (e.g., blood sampling) will be collected during pre-screening and screening period.

An AE or SAE may also result from procedures specified in the protocol.

For sponsor to collect more information about clinically significant laboratory results or diagnostic tests (e.g., hematology, ECG), at a min, the following abnormalities should be captured in the AE eCRF:

- Any test result that meets the definition of a SAE;
- Any clinically significant test abnormality (e.g., >3 × deviation from the upper or lower limit of the analyzing laboratory reference range, or as otherwise specified in the protocol);
- Any test abnormality that requires the subject to receive specific corrective therapy, close observation, more frequent follow-up assessment, or further diagnostic investigation.

The following additional points should be considered for AEs:

- **Preplanned medical surgeries or procedures**
  - Preplanned surgeries or procedures that were scheduled prior to signing of ICF are not considered as AEs.
- **Hospitalization for preplanned surgeries or procedures**
- **Overdose**
  - Cases of overdose with any medication without manifested side effects are not considered AEs.

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

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

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that led to the procedure is the AE;
- Situations in which an untoward medical occurrence did not occur (admission to a hospital due to medical insurance and/or convenience);

8.1.2 Serious Adverse Events (SAEs)

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

- Results in death;
- Is immediately life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires subject hospitalization or prolongation of existing hospitalization;
- Resulting in persistent or significant disability or incapability or substantial disruption of the ability to conduct normal life functions;
- Results in a congenital abnormality or birth defect.

Is an important medical event that may not result in death, be life-threatening, or require hospitalization, but may be considered a SAE when, based upon appropriate medical judgment, it may require medical or surgical intervention to prevent one of the outcomes listed above.

8.2 Collection and Reporting of AEs

8.2.1 Collection Time

AEs will be assessed from the time the subject signs pre-screening ICF through the end of the study. However, only study procedure related AEs (e.g., blood sampling) will be collected during the pre-screening and screening period.

8.2.2 Description

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

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

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

8.2.3 Start Date/Time and Stop Date/Time

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

8.2.4 Relationship to Study Drug

The investigator should assess causality to be "related" or "unrelated" by answering the question "Is there a reasonable possibility that the AE may have been caused by the IMP/study medication?".

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

- Dechallenge: Did the event abate after study medication was reduced or interrupted?

- Rechallenge: Did the event reappear after study medication was reintroduced?
- Whether there is a reasonable temporal relationship between the AE and administration (or procedure);
- Confounding risk factors;
- Amount and duration of study drug exposure;
- Concomitant medications.

8.2.5 Intensity

The following criteria will be used for evaluation of AE intensity:

Mild; asymptomatic or mild; clinical or diagnostic observations only; intervention not indicated.

Moderate; minimal, local, or non-invasive treatment indication, age-related instrumental activities of daily living limited*.

Severe: medically significant but not immediately life-threatening; leading to hospitalization or prolongation of hospitalization; disabling; personal activities of daily living are limited**.

Life-threatening, urgent treatment indicated.

Death related to AEs.

*Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care activities of daily living refer to bathing, dressing and undressing, eating, washing, taking medicine, etc., and not bedridden.

8.2.6 Seriousness

Record SAEs or indicate them to be non-serious according to the criteria described in **Section 8.1.2**.

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

Severity is a variable for intensity assessment (**Section 8.2.5**), whereas seriousness is defined by the criteria under **Section 8.1.2.**。

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

8.2.7 Outcomes

Record the outcome of the AEs based on the options provided in the eCRF. The outcome of a SAE should be recorded in the SAE form.

8.3 Reporting and Assessment of SAE

All SAEs occurring after the administration (defined as the period from the first administration of study drug to the EOS regardless of causality) will be reported by the investigator or designee to the sponsor/designee within 24 hours of knowledge of the event or sequelae. Deaths and SAEs occurring after the end of the study and considered related to study medication or study procedure must also be reported. SAE reporting instructions are provided in the related manual.

8.4 Reporting of Adverse Events of Special Interest

Symptomatic overdose, outcomes of a pregnancy, and LVEF≤30% as determined by local site are considered as Adverse Events of Special Interests (AESIs).

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

8.5 Reporting of Drug-induced Liver Injury

To facilitate appropriate monitoring for signals of drug-induced liver injury (DILI), cases of concurrent aspartate/alanine (AST/ALT) and total bilirubin (TBL) elevation according to the criteria specified (3 × upper limit of normal [ULN] for AST/ALT and 2 × ULN for TBL in participants with no underlying liver disease and eligibility criteria requiring normal liver function at baseline) require to be reported to sponsor as an SAE within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded).

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

8.6 Follow-up of AEs and SAEs

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

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

The sponsor retains the right to request additional information from any subject who also has an AE/SAE at the end of the study, if judged necessary.

8.7 Reporting and Follow-up of Pregnancy

Pregnancies occurring at any time between study drug administration and up to 5 months after study drug administration must be reported for female subjects or female partners of male subjects. The investigator is responsible for informing the sponsor within 24 hours of knowledge of the pregnancy even if no AE has occurred per the reporting guidelines. The subject will be asked to provide information on the outcome of the pregnancy through 6 months after birth or details of premature termination. Spontaneous miscarriage and congenital abnormalities will be reported as SAEs. Consent to report information regarding pregnancy

and pregnancy outcomes should be obtained from the partner of the male subject.

Pregnancy of a subject or partner of a male subject should be entered in the Pregnancy Notification CRF. Pregnancy follow-up should be documented on a follow-up form and be reported to the sponsor or designee within 24 hours.

Any SAE experienced by a subject during pregnancy must be reported using a SAE form within 24 hours.

8.8 Safety Reporting to Investigators, Institutional Review Boards, Independent Ethics Committees, and Regulatory Authorities

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical study. The sponsor will conduct safety reports to regulatory authorities, the institutional review boards (IRBs)/independent ethics committees (IECs) and investigators in compliance with country-specific regulatory requirements.

Suspicious and Unexpected Serious Adverse Reactions (SUSARs) are SAEs that qualify for mandatory expedited reporting to regulatory authorities when the SAE is suspected to be caused by the study drug and is considered unexpected (i.e., not defined as expected in the current IB, clinical study protocol). In this case, the sponsor/designee will report to the relevant regulatory authority and forward a formal notification describing the SUSAR to investigators, according to regulatory requirements. Each investigator must then notify his/her IRB/IEC of the SUSAR as required by local regulatory authorities and in accordance with their IRB/IEC policy.

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

9. Risks and Precautions

9.1 General Risks

Based on nonclinical data and the available clinical data, four important risks have been described: heart failure due to systolic dysfunction defined as symptomatic LVEF < 50%, teratogenicity, QT prolongation, increased risk of heart failure due to interaction with CYP2C19 and potent CYP3A4 inhibitors. Please refer to **Section 1.3** for details of relevant risks. Corresponding risk control measures have been developed by the sponsor for these risks, including collection and assessment of AEs, setting of corresponding subject eligibility criteria and dose interruption/discontinuation criteria, close monitoring of subjects' indicators during the study, etc. Details can be found in the corresponding sections.

9.2 Pregnancy

9.2.1 Avoidance of Pregnancy

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

9.2.2 Acceptable Methods of Contraception

Highly effective methods of birth control are defined as those that result in a low failure rate (< 1% per year) when used consistently and correctly. From the time of screening through 5 months after the last dose of study drug, female subjects should practice true abstinence or use effective means of contraception as follows:

- Estrogen and progesterone containing hormonal contraception associated with inhibition of ovulation or progesterone only hormonal contraception associated with inhibition of ovulation by oral, implantable, or injectable routes of administration;
- Intrauterine device (IUD);
- Intrauterine system (IUS);
- Bilateral tubal ligation;
- Females have been surgically sterilized for more than 6 months or postmenopausal for more than 1 year. Permanent sterilization is defined in **Section 9.2.1**.

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

9.2.3 Pregnancy Reporting and Follow-up

Pregnancies occurring at any time between study drug administration and up to 5 months after study drug administration must be reported for female subjects and female partners of male subjects. The investigator is responsible for informing the sponsor within 24 hours of knowledge of the pregnancy even if no AE has occurred per the reporting guidelines. The subject will be asked to provide information on the outcome of the pregnancy from the delivery through 6 months after birth or details of premature termination. Spontaneous miscarriage and congenital abnormalities will be reported as SAEs.

10. Statistical Methods

10.1 10.1 Sample Size

No formal hypothesis testing will be conducted. The number of subjects in each cohort is expected to provide sufficient data to allow the assessment of the safety, tolerability and PK profile of mavacamten in Chinese subjects. Hence approximately 8-12 subjects will be enrolled in Phase I to obtain adequate PK and safety data based on China regulatory consideration.

Four cohorts are expected to enroll approximately 44 healthy adult subjects.

- Cohorts 1: 12 subjects (CYP2C19 UM/RM/NM) to ensure that PK data will be obtained for at least 10 subjects;
- Cohorts 2: 12 subjects (CYP2C19 UM/RM/NM) to ensure that PK data will be obtained for at least 10 subjects;
- Cohort 3: 12 subjects (CYP2C19 IM) to ensure that PK data will be obtained for at least 10 subjects;
- Cohort 4: 8 subjects (CYP2C19 PM) to ensure that PK data will be obtained for at least 6 subjects.

10.2 Study Endpoints

10.2.1 Pharmacokinetic Endpoints

- Area under curve $AUC_{(0\text{-last})}$, $AUC_{(0\text{-inf})}$;
- Maximum concentration (C_{max});
- Time to maximum concentration (T_{max});
- Elimination half-life ($T_{1/2}$);
- Apparent volume of distribution (V_d/F);
- Apparent clearance (CL/F).

10.2.2 Safety Endpoints

- Vital signs;
- Physical examination findings;
- ECG parameters;
- Laboratory data, including blood chemistry, hematology, coagulation, and urinalysis;
- AE.

10.2.3 Exploratory Endpoint

- Population PK model may be assessed to investigate ethnic differences on key PK parameters including clearance and volume of distribution.

10.3 Statistical Analysis

Before database lock, a final statistical analysis plan (SAP) for clinical data and PK analysis will be prepared that will contain full details of all planned analyses. An outline of the intended methodology is presented below.

10.3.1 Statistical Analysis Datasets

Two analysis populations are defined in this study.

Pharmacokinetics Set (PKS): The pharmacokinetic (PK) analysis set consists of all subjects exposed to mavacamten with at least one study drug concentration value. The PKS will be used for PK analysis.

Safety Analysis Set (SAS): All subjects exposed to mavacamten, regardless of the doses administered, will be included in the SAS. The SAS is used for safety analysis.

10.3.2 General Principles

Measurement data will be statistically described using the number of subjects, mean, standard deviation, median, min and max. Categorical variables will be summarized using counts and percentages.

Pharmacokinetics parameters will be calculated using standard non-compartmental model of WinNonlin (version 8.2 or higher). Other statistical analyses will be performed using SAS (version 9.4 or higher) software.

10.3.3 Subject Disposition

The number and percentage of subjects who completed and discontinued the study, including reasons for early discontinuation, will be presented by cohort and all subjects.

10.3.4 Demographic and Baseline Characteristics

Demographic characteristics, baseline characteristics, medical history, and CYP2C19 genotype will be summarized descriptively by cohort and all subjects.

10.3.5 Efficacy Analysis

Not applicable.

10.3.6 Pharmacokinetic Analysis

All PK analyses will be conducted in the pharmacokinetics set. The plasma concentration-time data of mavacamten for individual subject will be listed and displayed graphically in the linear and semi-log scales. The plasma concentration-time data for each cohort will be summarized descriptively in tabular and the mean concentration-time curve will be plotted on the linear and semi-log scales by cohort. The PK parameter data will be listed and summarized descriptively in tabular format by cohort. Statistics include the number of subjects, arithmetic mean, GM, SD, and CV, min, median, and max.

- **Effect of different CYP2C19 genotypes (UM/RM/NM vs IM vs PM)**

To examine the exposure to mavacamten for subjects with the UM/RM/NM vs IM vs PM genotype, analysis of variance (ANOVA) model will be constructed using log-transformed $AUC_{(0\text{-last})}$, $AUC_{(0\text{-inf})}$ and C_{max}. The $AUC_{(0\text{-last})}$, $AUC_{(0\text{-inf})}$ and C_{max} will be compared between the cohort 1 and cohort 2 (CYP2C19 UM/RM/NM), cohort 3 (CYP2C19 IM), and cohort 4 (CYP2C19 PM). The reference group will be cohort 1 and test groups will be cohort 2 to cohort

4 and the GM ratios of each parameter between all cohorts and the corresponding 2-sided 90% confidence intervals will be calculated.

Further details are presented in the SAP.

10.3.7 Ethnic Impact

The established PopPK will be included in this trial for subsequent ethnic sensitivity analysis and will be reported separately. This analysis will be performed after and within the approval of the relevant regulatory authorities.

10.3.8 Safety Analysis

All safety analyses will be performed based on the Safety Set.

The safety analysis period is defined as the time between study drug administration and the EOS Visit. Any AE that occurs before study drug administration or after the EOS will not be included in the safety analyses. Safety analyses will be based on descriptive statistics of AEs across cohorts and review of individual subject data such as AEs, safety laboratory data, vital signs, physical examination results, and ECG parameters.

10.3.8.1 Adverse Events

AEs will be mapped to system organ classes and preferred terms using the MedDRA. AEs will be monitored throughout the study to determine their severity and their potential relationship to the investigational drug. An AE that occurs on or after the first dose of study drug, or an AE that occurs prior to the first dose of study drug, worsens in severity at or after the first dose of study drug, will be considered a post dose-emergent AE.

The incidence of AEs will be summarized by cohort and all subjects and by system organ class, preferred term, severity, and relationship to study drug. Severe and life-threatening AEs, SAEs, and AEs leading to study withdrawal, if any, will also be presented in data listings.

10.3.8.2 Other Safety Analyses

Safety laboratory tests (hematology, blood chemistry, coagulation, and urinalysis), vital signs, physical examinations, and ECG results will be summarized by visit time point using descriptive statistics based on the Safety Analysis Set. For safety laboratory data and vital signs, results at each visit and changes from baseline will be described. Subjects with laboratory and/or vital signs results outside the reference range will be listed. Abnormal physical and ECG findings will be listed. Concomitant medications, if any, will be summarized.

10.3.9 PopPK Analysis

PopPK analysis will be conducted with the data from current study LB2001-101 and other mavacamten studies. All analysis will be based on the actual sampling times recorded in the study. Additional details of the PopPK model development and analysis will be provided in a separate PopPK DAP and results of the PopPK analysis will be reported separately from the clinical study report (CSR).

Note: PopPK analysis will be performed only after approval by relevant regulatory authorities and within the approved scope.

11. Data Collection and Management

11.1 Data Confidentiality

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

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

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

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

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

11.2 Study Site Monitoring

Before study initiation, the sponsor (or designated Contract Research Organization [CRO]) will review the protocol and eCRFs with the investigators and their staff at a study site initiation meeting or at an investigator's meeting. During the study, the field monitor will visit the study site regularly to check the completeness of subject records, the accuracy of entries in the eCRFs, the adherence to the protocol and to the Good clinical practice (GCP), the progress of enrollment, and to ensure that study drug is being stored, dispensed, and counted appropriately according to specifications. Key study personnel must be available to assist the field monitor during these visits.

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

The investigator must give the field monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Full verification for the presence of ICF, adherence to the inclusion/exclusion criteria and documentation of SAEs is required in the sponsor's monitoring standards. Additional checks of the consistency of the source data with the eCRFs need to be performed according to the study specific monitoring plan.

11.3 Data Collection

The designated site staff will enter the data required by the protocol into the eCRFs. The eCRFs have been built using fully validated secure web-enabled software. The investigator and site staff will not be given access to the electronic data capture (EDC) system until they have been trained.

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

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

11.4 Database Management and Quality Control

The sponsor (or designated CRO) will review the data entered into eCRFs by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the study site via the EDC system. Designated site staff are required to respond promptly to queries and to make any necessary changes to the data if needed.

Prior medications, concomitant treatments, and post-treatment anti-cancer medications entered into the database will be coded using the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the MedDRA terminology.

PK data will be processed centrally and the results will be sent electronically to the sponsor.

The occurrence of any protocol deviations will be recorded. Once the data has been verified to be complete and accurate, the database will be declared locked and made available for data analysis. Appropriate sponsor authorization is required prior to making any database changes to locked data.

After database lock, the investigator will receive a copy of his/her subjects' data for archiving at the study site.

11.5 Study Documentation, Record Keeping and Retention of Documents

Each participating study site will maintain appropriate medical and research records for this trial, in compliance with the International Conference on Harmonization (ICH) E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in sponsored study, each study site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

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

12. Study Compliance and Ethical Considerations

12.1 Regulatory and Ethical Compliance

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

12.2 Informed Consent

The ICFs used for the study must comply with the Declaration of Helsinki, ICH GCP guidelines, and any other local regulations. The investigator must explain the medical aspects of the study including the nature of the study and the treatment in such a manner that the potential subject is aware of potential benefits and risks. Potential subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Subjects, or an impartial witness, must give informed consent in writing.

Prior to participation in any study-related procedures, subjects must sign and date an EC approved written ICF in a language the subject can understand. The informed consent process must be conducted, documented in the source document (including the date), and the form must be signed before the subject undergoes any study specific procedures.

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

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

12.3 Ethics Committee

The term EC used in this document refers to an IRB or IEC or equivalent. The EC must review and, if appropriate, approve the following documents, as applicable:

- Study protocol and amendment(s);
- Study ICF(s) and amendment(s);
- Subject recruitment procedures/documents (e.g., advertisements);
- Written information to be provided to subjects;
- IB and available safety information (Note: ECs do not approve IBs but are responsible for acknowledging receipt);
- Information about payments and compensation available to subjects.

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

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

- All SAEs (as described in **Section 8.2**);
- Any new information that may affect adversely the safety of the subjects or the conduct of the trial;
- Protocol deviations;
- A synopsis of the study report upon study completion.

Documentation of subsequent reviews and approved by EC of the study must also be forwarded to the sponsor if any.

12.4 Confidentiality of Study Documents and Subject Records

The investigator must ensure pseudonymous of the subjects by replacing names with the study-specific subject identification number; subjects must not be identified by names in any documents submitted to the sponsor. The names of study subjects and all other confidential information are subject to medical confidentiality and the provisions of the General Data Protection Regulation (GDPR) and other applicable regulations or laws. Subject data may only be passed on in pseudonymous form beyond the study site.

Signed ICFs and subject identification log kept at the study site to enable subject identification must be kept strictly confidential.

13. Management Procedures

13.1 Sponsor's Responsibilities

The sponsor reserves the right to terminate the study at any time. The sponsor and the investigators will assure that adequate consideration is given to the protection of the subjects' interests. Specific circumstances that may precipitate such termination are:

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

The sponsor will purchase clinical trial insurance in accordance with the laws of the country/region in which the study is conducted and provide insurance certificates to participating clinical sites upon request.

13.1.1 Subject Data Confidentiality

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

The sponsor ensures that the personal data are:

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

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

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

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

13.1.2 Investigator Training

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

13.1.3 Ongoing Communication of Safety Information During the Study

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

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

13.1.4 Study Monitoring

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

13.1.5 Study Auditing and Inspecting

The sponsor may audit the study conduct, compliance with the protocol, and accuracy of the data in clinical site.

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

13.2 Investigator's Responsibilities

13.2.1 Screening Log

The investigator must keep a record that lists all subjects who signed an ICF and the reason for non-inclusion if the potential subject does not ultimately enroll.

13.2.2 Mavacamten Accountability

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

13.2.3 Reporting and Recording of Study Data

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

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

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

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

13.2.4 Source Data and Documents

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

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

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

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

13.2.5 Subject Identity Information

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

13.2.6 Record Retention

The sponsor will inform the investigator in writing when it is acceptable to dispose of any study records. To enable evaluation and/or audits from regulatory authorities or the sponsor, the investigator should agree to keep records, including the identity of all subjects (i.e., subject identification code list and all source documents), all original signed ICFs, copies of all eCRFs, original laboratory reports, detailed records of study medication disposition, and all essential documents for the conduct of a clinical study. To comply with international regulations, the records should be retained by the investigator for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing application in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. However, the investigator may need to retain these documents for a longer period if required by the local regulatory requirements or by an agreement with sponsor.

13.2.7 Protocol Deviations

Unless there is a safety concern, no protocol deviations from the study protocol or waiver of compliance with the study protocol will be allowed. In the event of a safety concern, the investigator or designee must document and explain the reason for any deviation from the approved protocol. The investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to subject without prior EC approval. Immediately after the implemented deviation or change, the investigator must report and explain the reasons for the protocol deviation to the sponsor and EC as per EC's requirement. The medical monitor will review the protocol deviation and notify the study monitor of the response.

13.2.8 Blood Sample Collection/Storage

Blood samples collected as per the requirements described above will be stored at -70±10 °C and shipped to a central laboratory for drug concentration analysis as part of protocol procedures. Please refer to the relevant laboratory management manual for details of blood sample processing.

13.3 Protocol Amendments and Study Administrative Instructions

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

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

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

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

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

13.4 Study Management

- **Use of computerized systems**

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

- EDC system to capture protocol-required subject data: clinical sites will enter data from source documents into eCRFs for each study visit using a web-based interface. Study monitors and data management personnel will use this system to review data and generate queries and reports as needed.

Information in the above systems will be provided to the investigator, clinical site personnel, and other personnel as appropriate. Measures will be taken to ensure data security and accuracy; including, but not limited to, user training, granting of user accounts and privileges to trained and authorized personnel in a role-based manner, username/password/electronic signature requirements enforcement, programmed and manual edit checks as outlined in data validation specifications, computer generated audit trails, centralized data management, and routine study monitoring.

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

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

- **Study records**

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

visit logs, laboratory reference ranges and laboratory certification or quality control procedures, and laboratory director's curriculum vitae.

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

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

14. Publication Policy

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

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

15. References

[1] Frey N, Luedde M, and Katus HA. Mechanisms of disease: hypertrophic cardiomyopathy. Nat Rev Cardiol. 2011:9: 91-100.

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

[3] Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA Guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2011;58: e212-60.

[4] Maron MS. Clinical utility of cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Cardiovasc Magn Reson 2012, 1: 13.

[5] Alfares AA, Kelly MA, McDermott G, Funke BH, Lebo MS, Baxter SB, Shen J, et al. Results of clinical genetic testing of 2,912 probands with hypertrophic cardiomyopathy: expanded panels offer limited additional sensitivity, Genet Med. 2015;17: 880-8.

[6] Chuan P, Sivaramakrishnan S, Ashely EA, Spudich JA. Cell-intrinsic functional effects of the α-cardiac myosin Arg-403-Gln mutation in familial hypertrophic cardiomyopathy. Biophys J. 2012;102: 2782-90.

[7] Sommese RF, Sung J, Nag S, et al. Molecular consequences of the R453C hypertrophic cardiomyopathy mutation on human beta-cardiac myosin motor function. Proc Natl Acad Sci USA. 2013; 110:12607-12.

[8] Sung J, Choe E, Elting M, et al. Single molecule studies of recombinant human α- and β-cardiac myosin to elucidate molecular mechanism of familial hypertrophic and dilated cardiomyopathies. Biophysical J. 2012;102: 613a-4a.

[9] Maron, MS, Rowin EJ, Olivotto I, Casey SA, Arretini A, Tomberli B, et al. Contemporary Natural History and Management of Nonobstructive Hypertrophic Cardiomyopathy, J Am Coll Cardiol. 2016;67: 1399-409.

[10] Husser DL, Ueberham J, Jacob D, Heuer S, Riedel-Heller J, Walker G, et al. Prevalence of clinically apparent hypertrophic cardiomyopathy in Germany-An analysis of over 5 million patients. PLoS One. 2018:13: e0196612.

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

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

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

[14] Maron MS, Olivotto I, Zenovich AG, Link MS, Pandian NG, Kuvin JT, et al., Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract

obstruction. Circulation. 2006; 114:2232-2239.

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

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

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

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

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

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

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

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

[23] Kim LK, Swaminathan RV, Looser P, Minutello RM, Wong SC, Bergman G, et al. Hospital Volume Outcomes After Septal Myectomy and Alcohol Septal Ablation for Treatment of Obstructive Hypertrophic Cardiomyopathy: US Nationwide Inpatient Database, 2003-2011. JAMA Cardiol. 2016;1: 324-32.

[24] Yelena I, James A, Jianan Z, et al. CYP2C19 Allele Frequencies in Over 2.2 Million Direct-to-Consumer Genetics Research Subjects and the Potential Implication for Prescriptions in a Large Health System, Clin Transl Sci. 2020;13, 1298-306.

Appendix 1 Laboratory Tests

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

Hematology	Coagulation function	Blood chemistry	Urinalysis[a]
• White blood cell count including differential • Red blood cell count • Hemoglobin • Haematocrit • Platelet count	• PT • INR • APTT • TT • FIB	• Sodium • Potassium • Chloride • Calcium • Magnesium • Urea nitrogen • Creatinine • Uric acid • ALP • ALT • AST • Total bilirubin • Direct bilirubin • Total protein • Albumin • CK • Glucose	• Specific gravity urine • Urine pH • Protein urine • Urine glucose • Urine leukocyte esterase • Urine ketone body • Red blood cells urine • White blood cells urine

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CK = creatine kinase; FIB = fibrinogen; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; INR = international normalized ratio; PT = prothrombin time; TT = thrombin time.

[a]Urine microscopy and dipstick will be performed.

Safety laboratory assessments (hematology, blood chemistry, coagulation test, urinalysis) has no need to be repeated on Day -1 if latest results are within 7 days. Details are provided in **Table 1**.

The following non-safety laboratory parameters will be measured at screening:

- Hepatitis virus test (HBV and HCV): HBV antigen, HCV antibody;
- HIV test: HIV antibody;
- FSH (post-menopausal females only);
- Pregnancy test (β-hCG) (all women of childbearing potential);
- Alcohol or drug abuse test.

Sponsor's Signature Page

Authorization of the Sponsor

This protocol (An Open-Label, Parallel-Group, Single-Center Phase 1 Clinical Study to Evaluate the Pharmacokinetics of a Single Oral Dose of Mavacamten in Healthy Adult Chinese Subjects) has been reviewed and approved by representatives of Shanghai LianBio Development Co., Ltd.

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

Investigator's Signature Page

I have read and understood the contents of the clinical protocol (An Open-Label, Parallel-Group, Single-Center Phase 1 Clinical Trial to Evaluate the Pharmacokinetics of a Single Oral Dose of Mavacamten in Healthy Adult Chinese Subjects).

I have reviewed this protocol and agree to implement this protocol in compliance with the ethical principles deriving from the Declaration of Helsinki, GCP of ICH, and the requirements of any regulatory authority and/or IRB/IEC.

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

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

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