Clinical Study Protocol

A Randomized, Open-label, Single-Dose, Two-Way Crossover Study to Assess the Relative Bioavailability of 5 mg of Levamlodipine Maleate Tablets versus 10 mg of Amlodipine Besylate Tablet (NORVASC® from Pfizer Inc.) in Healthy Subjects Followed by a Phase to Study Food Effect on the PK Profile of Levamlodipine

Short Title:	BA Study of Levamlodipine vs NORVASC®
IND Number:	124,947
Drug Name:	Levamlodipine，the (S)amlodipine
Study Phase:	Phase 1
Protocol Number:	LAM-US-101
Protocol Version:	Version 1.0 issued on February 23rd 2018
	Version 2.0 issued on May 21st 2018
Sponsor:	CSPC Ouyi Pharmaceutical Co., Ltd, a subsidiary company within CSPC Pharmaceutical Group, Ltd (CSPC)

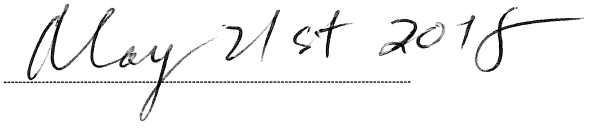
The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Main Changes Made to Version 1.0 to Generate Version 2.0

- eCRF has been changed to CRF, since paper CRFs will be used in this study.
- Wordings regarding urine samples for PK analysis have been deleted, since PK analysis will be done with plasma samples only.
- Wordings regarding blinding have been deleted, since this will be an open-label study.
- Wordings regarding barista cards have been deleted, since study drugs are packed in bottles.
- ECG for Day 2 in Table 5-3 has been deleted.
- Examples of acceptable contraceptive methods for females of childbearing potentials have been added.
- Few editorial changes have been made to further improve the quality of this protocol.

Signature of the sponsor's medically responsible person

The signatory agrees to the content of the final clinical study protocol as presented.

Date:  Signature: 

Signature of the Principal Investigator

By my signature, I confirm that my staff and I have carefully read and understand the protocol and agree to comply with the conduct and terms of the study specified herein and with any other study conduct procedures provided. I agree to review and comply with all relevant regulations and guidance principles. I understand that the trial will be conducted in compliance with the protocol/amendment(s), GCP and the applicable regulatory requirements including ethical standards as expressed in the Declaration of Helsinki.

I will not implement any protocol or amendment without agreement from CSPC. and prior submission to and written approval (where required) from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except when necessary to eliminate an immediate hazard to the patients or for administrative aspects of the study (where permitted by all applicable regulatory requirements).

I agree not to publish all or any part of the results of the study carried out under this protocol, without the prior written consent of CSPC.

Date: 05/21/2018 Signature: 

Table of Contents

1. PROTOCOL SYNOPSIS

Name of Sponsor/Company CSPC Ouyi Pharmaceutical Co., Ltd, a subsidiary company within CSPC Pharmaceutical Group, Ltd (CSPC)
Title of Study A Randomized, Open-label, Single-Dose, Two-Way Crossover Study to Assess the Relative Bioavailability of 5 mg of Levamlodipine Maleate Tablets versus 10 mg of Amlodipine Besylate Tablet (NORVASC® from Pfizer Inc.) in Healthy Subjects Followed by a Phase to Study Food Effect on the PK Profile of Levamlodipine
Phase of Development Phase 1
Investigational Product, Dosage and Mode of Administration Levamlodipine Maleate Tablet is a new investigational drug for the treatment of hypertension and Coronary Artery Disease (CAD) chronic stable angina. Levamlodipine is the pharmacologically active isomer in amlodipine, which presents in amlodipine as a 1:1 mixture with the (R)amlodipine. The to-be-marketed dosage strengths planned in the US are 1.25, 2.5 and 5 mg of levamlodipine maleate tablets with an anticipated dosage regimen of once daily.
Name of Active Ingredient Levamlodipine，the (S)amlodipine
Reference Therapy, Dosage and Mode of Administration Amlodipine Besylate Tablet (NORVASC® from Pfizer Inc.)
Study Center Collaborative Neuroscience Network, LLC (CNS) 2600 Redondo Avenue, Suite 500 Long Beach, CA 90806
Principal Investigator Mark Todd Leibowitz, MD
Objectives

The objectives of this study are (1) to assess the relative bioavailability (BA) of a single oral dose of either 5 mg of Levamlodipine Maleate Tablets from CSPC or 10 mg of Amlodipine Besylate Tablet (NORVASC®) from Pfizer Inc. under fasting condition in male and female healthy subjects; and (2) to evaluate food effect on the PK profile of Levamlodipine Maleate Tablets from CSPC.

Study Design

This study consists of 2 parts:

Part 1 will be a randomized, open-label, single-dose, two-way crossover study to assess the relative BA of levamlodipine maleate tablets from CSPC (Test) versus Amlodipine Besylate Tablet NORVASC® from Pfizer Inc. (Reference) after a single oral administration under fasted conditions in male and female healthy subjects. Approximately 32 healthy subjects will be enrolled in the US to obtain 27 completed subjects.

Eligible subject will be randomized to receive one of two treatment sequences (RT or TR; R=10 mg of NORVASC® and T=5 mg of levamlodipine maleate tablets) according to a randomization schedule prepared prior to the start of the study. All study drugs will be administered following an overnight fast for approximately 10 hours.

Eligible subjects will be admitted to the clinical research center (CRU) within 24 hours before baseline assessments in Period One and will stay at the CRU for 3 nights. A single dose of study drug should be taken orally with 240 ml (about 8 fluid ounces) of water at site after being fasted overnight, and meal will be allowed around 1 hour after dosing. Subjects should return to the CRU on Days 4 till 8 to provide PK samples and to receive study assessments. Serial blood samples will be obtained at defined time points for 7 days after dosing in each treatment for the measurement of plasma (S)amlodipine and (R)amlodipine concentrations.

After a wash-out period for at least 14-days since the last dosing, subjects will enter into Period Two to receive alternative reference or test drug. Thus, subjects who receive levamlodipine treatment in Period One will now receive NORVASC® treatment in Period Two, while subjects who receive NORVASC® treatment in Period One will now receive levamlodipine treatment in Period Two. The same procedure will be performed at approximately same time points as noted for Period One.

Part 2 will be a single-arm, open-label, single-dose phase to assess food effect on the PK profile of levamlodipine maleate tablets from CSPC. Subjects who have completed Part 1 will be rolled over to Part 2 after a wash-out period for at least 14-days since the last dosing. Subjects will receive a single oral administration of study drug under a high-fat / high-calorie meal that should derive approximately 150, 250 and 500-600 calories from protein, carbohydrate and fat, respectively.

Following an overnight fast for approximately 10 hours, subjects should start the

recommended meal 30 minutes prior to administration of study drug. Study subjects are to eat this meal in 30 minutes or less. The study drug should be administered with 240 mL (about 8 fluid ounces) of water immediately after the meal. No food should be allowed for at least 4 hours post-dose. Water can be allowed as desired except the one-hour period before and after drug administration. Subjects should receive standardized meals scheduled at approximately same time in each period of the study.

Subjects will be admitted to the CRU within 24 hours before drug administration and will stay at the CRU for 3 nights. Subjects should return to the CRU on Days 4 till 8 to provide PK samples and to receive study assessments. Serial blood samples will be obtained at defined time points for the measurement of plasma (S)amlodipine and (R)amlodipine concentrations.

Safety and tolerability will be monitored during the study.

Methodology

PK

A total of 23 blood samples will be collected at the following time points: within 30 min prior to dosing and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours after each dosing.

Each plasma sample prepared from blood PK sample will be divided into two equal parts, one as primary PK sample and one as back-up PK sample. Plasma concentrations of (S)amlodipine and (R)amlodipine will be measured with validated methods under GLP.

The plasma concentration time data for (S)amlodipine and (R)amlodipine will be analyzed using non-compartmental methods. Actual dosing and sampling times will be used for analyses. The primary PK parameters of interest are: C_{max}, t_{max}, t_{lag}, $t_{1/2}$, λ_z, MRT_{inf}, AUC_{last}, AUC_{inf}, AUC_{extrap}, Cl/F and V_d/f. Additional parameters may be estimated and reported, as appropriate.

Safety

Safety assessments will include the summaries of adverse events (AEs), vital signs, laboratory findings, 12-lead electrocardiography (ECG), and physical examination findings at various time points during the study.

Planned Subject Number

The planned total subject number for Part 1 is about 32 healthy volunteers in order to obtain 27 completed subjects. Subjects who have completed Part 1 will be rolled over to Part 2 to assess food effect on the PK profile of levamlodipine maleate tablets from CSPC.

Subject Selection Criteria

Inclusion Criteria

To participate in the study, subjects must meet all the following eligibility criteria at screening or admission:

1. Are capable of giving informed consent and complying with study procedures;
2. Are between the ages of 18 and 45 years old, inclusive;
3. Women of childbearing potential (WOCBP) must have a negative pregnancy test at Screening and be practicing a medically acceptable method of contraception with an annual failure rate of less than 1% during the study and 60 days after discontinuation of study treatment. Women are considered not childbearing potential if they are > 1 year postmenopausal or surgically sterile (ie, hysterectomy, bilateral oophorectomy, or bilateral salpingectomy tubal ligation). If serum βHCG is the standard of care, then this value can be used to determine eligibility
4. Considered healthy by the Principal Investigator, based on a detailed medical history, full physical examination, clinical laboratory tests, 12-lead ECG and vital signs;
5. Nonsmoker, defined as not having smoked or used any form of tobacco in more than 6 months before screening;
6. Body mass index (BMI) of 19 to 30 kg/m^2 inclusive and body weight not less than 50 kg;
7. Willing and able to adhere to study restrictions and to be confined at the clinical research center.

Exclusion Criteria

Subjects will be excluded from study entry if any of the following exclusion criteria are present at screening or admission:

1. Clinically significant history of gastrointestinal, cardiovascular, musculoskeletal, endocrine, hematologic, psychiatric, renal, hepatic, bronchopulmonary, neurologic, immunologic, lipid metabolism disorders, or drug hypersensitivity;
2. Subjects with a mean systolic blood pressure of three measurements >140 mmHg, or a mean diastolic blood pressure of three measurements >90 mmHg at screening. Blood pressure will be measured at sitting position;
3. Known or suspected malignancy;
4. Positive blood screen for human immunodeficiency virus (HIV), or hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV);
5. A history of seizure. However, a history of febrile seizure is allowed;
6. Positive pregnancy test result, or plan to become pregnant if female;
7. A hospital admission or major surgery within 30 days prior to screening;

8. Participation in any other investigational drug trial within 30 days prior to screening;
9. DSM-V substance use disorders within 6 months prior to screening;
10. A positive result for alcohol or drugs of abuse at screening or admission;
11. Tobacco use within 6 months prior to screening;
12. An unwillingness or inability to comply with food and beverage restrictions during study participation;
13. Donation or blood collection of more than 1 unit (approximate 450 mL) of blood (or blood products) or acute loss of blood during the 90 days prior to screening;
14. Use of prescription or over-the-counter (OTC) medications, and herbal medicines (including St John's Wort, herbal teas, garlic extracts) within 14 days prior to dosing;
15. A history of suicide attempt in the past 12 months and/or seen by the investigator as having a significant history of risk of suicide or homicide;
16. A history of intolerance or hypersensitivity to amlodipine or any excipients;
17. An unwillingness of male participants to use appropriate contraceptive measures if engaging in sex intercourse with a female partner of childbearing potential during the study and 60 days after discontinuation of study treatment. Sexual intercourse with pregnant or lactating women is prohibited.

Duration of Study

The total duration of the study for each completed subject is about 2 months, including about 44 days for Part 1 (up to 21 days for screening, 14 days for Period One before cross-over and 9 days for Period Two after cross-over) and about 14 days for Part 2 (5 days before dosing and 9 days after dosing).

Statistical Methods

PK

All the PK parameters and baseline subject characteristics will be summarized using descriptive statistics. The following PK parameters for plasma (S)amlodipine and (R)amlodipine concentrations will be compared between the study treatments by analysis of variance (ANOVA) including subject, treatment, and sequence effects in the model. Statistical significance will be tested at the 0.05 level (2-sided):

- AUC_{0-t} (Area under the concentration-time curve up to the time of the last quantifiable concentration)
- $AUC_{0-\infty}$ (Area under the concentration-time curve extrapolated to infinity)
- C_{max}
- t_{max}

- $t_{1/2}$

AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} will present estimates of extent and rate of absorption. t_{max} will be compared between treatments using the Wilcoxon-Singed Ranks test.

Relative bioavailability of Levamlodipine Maleate Tablets (T) and NORVASC® (R) will be determined based on AUC_{0-t}, AUC_{0-inf} and C_{max} of (S)amlodipine. The 90% confidence intervals (CIs) on the ratio of test to reference drugs will be calculated. Log-transformed PK parameters AUC_{0-t}, AUC_{0-inf} and C_{max} will be analyzed using ANOVA including terms for sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect. Bioequivalence limits will be 80–125%.

The PK parameters for plasma (S)amlodipine and (R)amlodipine concentrations will be compared within treatment of either Levamlodipine Maleate Tablets or NORVASC® to determine possible conversion of the 2 isomers in vivo.

Food effect will be evaluated based on AUC_{0-t}, AUC_{0-inf} and C_{max} of (S)amlodipine and will be determined by the changes of log-transformed PK parameters under fasting conditions and fed conditions.

Safety

Safety data will be summarized using descriptive statistics for all subjects who receive study drugs.

AEs will be coded using the MedDRA Dictionary, listed by subject and summarized frequency (number) for each treatment. Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary, and listed by reported term and Anatomical Therapeutic Class classification.

Any abnormal findings in physical examination and clinical laboratory tests will be summarized by treatment. Change from baseline will be calculated for clinical laboratory tests. For ECGs, the frequency (number) of clinically significant findings will be reported and summarized by treatment.

2. LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under curve
AUC_{inf}	Area under the analyte concentration-time curve from time 0 and extrapolated to infinite time, total exposure
AUC_{last}	Area under the analyte concentration time curve from time 0 to last quantifiable concentration
BMI	body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
C_{max}	Maximum concentration
Con med	Concomitant medication
CFR	Code of Federal Regulations
CI	Confidence interval
CRF	Case report form
CRO	Contract research organization
CRU	Clinical research unit
CSPC Pharma	CSPC Pharmaceutical Co., Ltd.
ECG	Electrocardiography
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl-transferase
Hct	Hematocrit
HCV	Hepatitis C virus
Hgb	Hemoglobin
HIV	Human immunodeficiency virus

Abbreviation	**Term**
IB	Investigational brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LC-MS/MS	Tandem mass spectrometric detection
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No observable adverse effect level
OTC	Over the Counter
PHI	Protected health information
PK	Pharmacokinetic(s)
R	Reference product
RBC	Red blood cell
SAE	Serious adverse event
SAD	Single ascending dose
SDV	Source document verification
$t_{½}$	Half life
T	Test product
TEAE	Treatment-emergent AEs
t_{max}	Time of maximum observed plasma concentration
WHO	World Health Organization

3. INTRODUCTION

Amlodipine is a third-generation calcium channel blocker that prevents calcium from entering myocardial cells and vascular smooth muscle cells, and thus has antihypertension effect. Amlodipine in the besylate salt form was developed by Pfizer Laboratories and was approved as NORVASC 2.5 mg, 5.0 mg, and 10.0 mg Tablets by the U.S. FDA for the treatment of hypertension in 1992 (NDA No. 019787). Generic equivalents of NORVASC have been marketed globally since 2007.

Amlodipine is a 1:1 racemic mixture of S-amlodipine (the levorotatory L-form) and R-amlodipine (the dextrorotatory D-form). S-amlodipine is the pharmacologically active moiety in racemic amlodipine. Clinically, S-amlodipine, at half the dose of amlodipine (2.5 mg vs. 5 mg, respectively), has been found to be equivalent to racemic amlodipine in efficacy, safety, and tolerability, with less edema, in patients with mild to moderate hypertension.

Levamlodipine maleate tablets 2.5 mg, a purified S-amlodipine tablet formulation, was approved for marketing in China in 2003 (Drug Code 86902770002300) for the treatment of hypertension and angina. Levamlodipine maleate tablets 2.5 mg are marketed under the trade name Xuanning® in China.

4. STUDY OBJECTIVES

The objectives of this study are (1) to assess the relative bioavailability (BA) of a single oral dose of either 5 mg of Levamlodipine Maleate Tablets from CSPC or 10 mg of Amlodipine Besylate Tablet (NORVASC®) from Pfizer Inc. under fasting condition in male and female healthy subjects; and (2) to evaluate food effect on PK profile of Levamlodipine Maleate Tablets.

5. INVESTIGATIONAL PLAN

5.1. Study Design

This study consists of 2 parts. **Part 1** will be a randomized, open-label, single-dose, two-way crossover study to assess the relative BA of 5 mg of levamlodipine maleate tablets from CSPC (Test Product) versus 10 mg of Amlodipine Besylate Tablet NORVASC® from Pfizer Inc. (Reference Product) after a single oral administration under fasted conditions in male and female healthy subjects. Approximately 32 healthy volunteers will be enrolled for Part 1 to obtain 27 completed subjects.

Part 2 will be a single-arm, open-label, single-dose phase to assess food effect on the PK profile of levamlodipine maleate tablets from CSPC. Subjects who have completed Part 1 will be rolled over to Part 2 after a wash-out period for at least 14-days since the last dosing. Subjects will

receive a single oral administration of 5 mg levamlodipine maleate tablets from CSPC under a high-fat/high-calorie meal that should derive approximately 150, 250 and 500-600 calories from protein, carbohydrate and fat, respectively.

5.2. Study Methods

The detailed timing and scheduling for **Part 1** are shown in Table 5-1, Table 5-2. Eligible subject will be randomized to receive one of two treatment sequences (RT or TR; R=10 mg of NORVASC® and T=5 mg of levamlodipine maleate tablets) according to a randomization schedule prepared prior to the start of the study. All study drugs will be administered following an overnight fast for approximately 10 hours.

Eligible subjects will be admitted to the clinical research center (CRU) within 24 hours before baseline assessments in Period 1 and will stay at the CRU for 3 nights. A single dose of study drug should be taken orally with 240 ml (about 8 fluid ounces) of water at site after being fasted overnight, and meal will be allowed around 1 hour after dosing. Subjects should return to the CRU on Days 4 till 8 to provide PK samples and to receive study assessments. Serial blood samples will be obtained at defined time points within 7 days after dosing in each treatment for the measurement of plasma (S)amlodipine and (R)amlodipine concentrations.

After a wash-out period for at least 14-days since the last dosing, subjects will enter into Period 2 to receive alternative reference or test drug. Thus, subjects who receive levamlodipine treatment in Period 1 will now receive NORVASC® treatment in Period Two, while subjects who receive NORVASC® treatment in Period One will now receive levamlodipine treatment in Period 2. The same procedure will be performed at approximately same time points as noted for Period 1.

The detailed timing and scheduling for **Part 2** are shown in Table 5-3. Following an overnight fast for approximately 10 hours, subjects will eat a high-fat/high-calorie. This meal should derive approximately 150, 250 and 500-600 calories from protein, carbohydrate and fat, respectively.

Subjects should start the recommended meal 30 minutes prior to administration of study drug, and finish this meal in 30 minutes or less. The study drug should be administered with 240 mL (about 8 fluid ounces) of water immediately after the meal. No food should be allowed for at least 4 hours post-dose. Water can be allowed as desired except the 1-hour period before and after drug administration.

Subjects will be admitted to the clinical research center (CRU) within 24 hours before drug administration and will stay at the CRU for 3 nights. Subjects should return to the CRU on Days 4 till 8 to provide PK samples and to receive study assessments. Serial blood samples will be obtained at defined time points for the measurement of plasma (S)amlodipine and (R)amlodipine concentrations.

Safety and tolerability will be monitored during the study.

Table 5-1. Schedule of Procedures for Part 1 - Period 1

	Screening	Clinical Research Unit (CRU)				Clinical Visits				
Day	**(Day -21 to -1)**	**Day 0 [1] (Baseline)**	**Day 1 (Dosing)**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**
Informed consent	X									
Medical history	X									
Physical examination [2]	X									X
Vital signs [3]	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X[4]								X
Clinical safety tests	X[5]	X								X
Drug/alcohol test	X	X								X
Pregnancy test [6]	X	X								
Admission to CRU		X								
Randomization			X							
Dose administration			X							
PK blood samples [7]			X	X	X	X	X	X	X	X
AE & ConMed		X	X	X	X	X	X	X	X	X
Discharge from CRU					X					

[1] Baseline.

[2] Including body weight and height at screen only.

[3] Complete vital sign measurements at screening visit, Day 0 and 0, 24, 96 and 168 hours after dosing. Blood pressure and heart rate only at other time points. Three measurements of blood pressure at screening visit and a single measurement at other time points.

[4] Three ECG tests with 3 min interval in between on Day 0. The means of the three ECG tests will be used as baselines.

[5] HIV, hepatitis B & C screen test at screening visit only.

[6] Serum test at screening and urine test on Day 0 for females of childbearing potential only.

[7] Pharmacokinetic blood samples will be collected at the following time points: Pre-dose (within 30 min prior) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours after dosing (acceptable windows: ± 2 min for 0 to 2-hr post dose period and ± 5 min thereafter)

AE = adverse event; ConMed = concomitant medications; CRU = clinical research unit; ECG = electrocardiogram; PK =pharmacokinetics.

Table 5-2. Schedule of Procedures for Part 1 - Period 2

	Wash-out	Clinical Research Unit (CRU)				Clinical Visits				
Day	**At least 14 days since the last dosing**	**Day 0 (Admission)**	**Day 1 (Dosing)**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**
Admission to CRU		X								
Cross-over of treatment		X								
Physical examination		X								X
Vital signs [1]		X	X	X	X	X	X	X	X	X
12-lead ECG		X								X
Clinical safety tests		X								X
Drug/alcohol test		X								X
Pregnancy test [2]		X								X
Dose administration			X							
PK blood samples [3]			X	X	X	X	X	X	X	X
AE & ConMed		X	X	X	X	X	X	X	X	X
Discharge from CRU					X					

[1] Complete vital sign measurements at 0, 24, 96 and 168 hours after dosing. Blood pressure and heart rate only at other time points. Three measurements of blood pressure at screening visit and a single measurement at other time points.

[2] Urine test for females of childbearing potential only.

[3] Pharmacokinetic blood samples will be collected at the following time points: Pre-dose (within 30 min prior) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours after dosing (acceptable windows: ± 2 min for 0 to 2-hr post dose period and ± 5 min thereafter)

AE = adverse event; ConMed = concomitant medications; CRU = clinical research unit; ECG = electrocardiogram; PK =pharmacokinetics.

Table 5-3. Schedule of Procedures for Part 2 (Food Effect)

	Wash-out	Clinical Research Unit (CRU)				Clinical Visits				
Day	**At least 14 days since the last dosing**	**Day 0 (Admission)**	**Day 1 (Dosing)**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8** [5]
Admission to CRU		X								
Physical examination		X								X
Vital signs [1]		X	X	X	X	X	X	X	X	X
12-lead ECG		X								X
Clinical safety tests		X								X
Drug/alcohol test		X								X
Pregnancy test [2]		X								X
High-fat/calorie meal [3]			X							
Dose administration			X							
PK blood samples [4]			X	X	X	X	X	X	X	X
AE & ConMed		X	X	X	X	X	X	X	X	X
Discharge from CRU					X					

[1] Complete vital sign measurements on Day 0 and 0, 24, 96 and 168 hours after dosing. Blood pressure and heart rate only at other time points.

[2] Urine test for females of childbearing potential only.

[3] The meal should be started 30 minutes prior to administration of study drug, and finished in 30 minutes or less

[4] Pharmacokinetic blood samples will be collected at the following time points: Pre-dose (within 30 min prior) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours after dosing (acceptable windows: ± 2 min for 0 to 2-hr post dose period and ± 5 min thereafter)

[5] End-of the study or early termination.

AE = adverse event; Con Med = concomitant medications; CRU = clinical research unit; ECG = electrocardiogram; PK =pharmacokinetics.

5.3. Number of Subjects

The planned total subject number is about 32 healthy volunteers for Part 1 in order to obtain 27 completed subjects. Subjects who have completed Part 1 will be rolled over to Part 2 to assess food effect on the PK profile of levamlodipine maleate tablets.

5.4. Treatment Assignment

Subjects receive the study treatments in Part 1 and Part 2 according to the following scheme

<table>
<tr><td rowspan="3">Part 1
(BE under fasted conditions)</td><td>Treatment A (Test Product)</td><td>A single dose of one 5 mg levamlodipine maleate tablet under fasted conditions (manufactured by CSPC Ouyi Pharmaceutical Co., Ltd., Hebei, China)</td></tr>
<tr><td>Treatment B (Reference Product)</td><td>A single oral dose of one 10 mg NORVASC® (amlodipine besylate) tablet under fasting conditions (manufactured by Pfizer Inc., New York, NY)</td></tr>
<tr><td colspan="2">The randomly assigned treatment sequences will be:
Sequence 1 (AB): Treatment A in Period 1; Treatment B in Period 2
Sequence 2 (BA): Treatment B in Period 1; Treatment A in Period 2</td></tr>
<tr><td>Part 2
(Food effect)</td><td>Test Product under fed condition</td><td>A single dose of one 5 mg levamlodipine maleate tablet under fed conditions (manufactured by CSPC Ouyi Pharmaceutical Co., Ltd., Hebei, China)
Subjects should take a high-fat / high-calorie meal approximately 30 minutes prior to administration of the test product.</td></tr>
</table>

5.5. Criteria for Study Termination

The Principal Investigator has the right to terminate the study in the interest of subject safety and welfare in consultation with CSPC Pharma. CSPC Pharma reserves the right to terminate or amend the study at any time for administrative reasons or if continuation of the protocol would present a potential safety risk to the subjects.

6. SELECTION AND WITHDRAWAL OF SUBJECTS

6.1. Subject Inclusion Criteria

To participate in the study, subjects must meet all the following eligibility criteria at screening or admission:

1. Are capable of giving informed consent and complying with study procedures;

2. Are between the ages of 18 and 45 years old, inclusive;
3. Women of childbearing potential (WOCBP) must have a negative pregnancy test at Screening and be practicing a medically acceptable method of contraception with an annual failure rate of less than 1% during the study and 60 days after discontinuation of study treatment. Women are considered not childbearing potential if they are > 1 year postmenopausal or surgically sterile (ie, hysterectomy, bilateral oophorectomy, or bilateral salpingectomy tubal ligation). If serum βHCG is the standard of care, then this value can be used to determine eligibility
4. Considered healthy by the Principal Investigator, based on a detailed medical history, full physical examination, clinical laboratory tests, 12-lead ECG and vital signs;
5. Nonsmoker, defined as not having smoked or used any form of tobacco in more than 6 months before screening;
6. Body mass index (BMI) of 19 to 30 kg/m^2 inclusive and body weight not less than 50 kg;
7. Willing and able to adhere to study restrictions and to be confined at the clinical research center.

6.2. Subject Exclusion Criteria

Subjects will be excluded from study entry if any of the following exclusion criteria are present at screening or admission:

1. Clinically significant history of gastrointestinal, cardiovascular, musculoskeletal, endocrine, hematologic, psychiatric, renal, hepatic, bronchopulmonary, neurologic, immunologic, lipid metabolism disorders, or drug hypersensitivity;
2. Subjects with a mean systolic blood pressure of three measurements >140 mmHg, or a mean diastolic blood pressure of three measurements >90 mmHg at screening. Blood pressure will be measured at sitting position.
3. Known or suspected malignancy;
4. Positive blood screen for human immunodeficiency virus (HIV), or hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV);
5. A history of seizure. However, a history of febrile seizure is allowed;
6. Positive pregnancy test result, or plan to become pregnant if female;
7. A hospital admission or major surgery within 30 days prior to screening;
8. Participation in any other investigational drug trial within 30 days prior to screening;
9. DSM-V substance use disorder within 6 months prior to screening;
10. A positive result for alcohol or drugs of abuse at screening or admission;
11. Tobacco use within 6 months prior to screening;
12. An unwillingness or inability to comply with food and beverage restrictions during study participation;
13. Donation or blood collection of more than 1 unit (approximate 450 mL) of blood (or blood products) or acute loss of blood during the 90 days prior to screening;
14. Use of prescription or over-the-counter (OTC) medications, and herbal medicines (including St John's Wort, herbal teas, garlic extracts) within 14 days prior to dosing;

15. A history of suicide attempt in the past 12 months and/or seen by the investigator as having a significant history of risk of suicide or homicide;
16. A history of intolerance or hypersensitivity to amlodipine or any excipients;
17. An unwillingness of male participants to use appropriate contraceptive measures if engaging in sex intercourse with a female partner of childbearing potential during the study and 60 days after discontinuation of study treatment. Sexual intercourse with pregnant or lactating women is prohibited。

6.3. Prior and Concomitant Medication and Substance

Illicit drug use and abuse of alcohol is prohibited prior to or during the study.

Subjects may not use tobacco containing products within 6 months prior to screening and at any time during the study.

The use of prescription medications or OTC products, including herbal product (e.g., St John's Wort, herbal teas, garlic extracts) is prohibited within 14 days prior to dosing.

After the subjects are enrolled and during the entire study period, subjects must adhere to the following prohibitions:

- Consumption of alcohol is not permitted within 48 hours prior to dosing and during the study
- Consumption of caffeine containing food or beverages is not permitted within 24 hours prior to dosing
- Use of acetaminophen at < 3g/day is permitted until 24 hours prior to dosing
- No administration of any prescription drugs, unless necessary for the treatment of an AE in the opinion of the Investigator.

All prescription medications and OTC products, including herbal products, taken in the 30 days prior to dosing or during the study period will be documented in the subject's source documentation and the case report form (CRF).

6.4. Subject Withdraw Criteria

Subjects will be informed that they have the right to withdraw from the study at any time for any reason without prejudice to their medical care. The Investigator also has the right to withdraw subjects from the study if it is in the best interest of the subject, or if the subject experiences an adverse event that warrants premature withdrawal.

Subjects may be withdrawn from the study if they:

- Have entered the study in violation of the protocol
- Use or require the use of prohibited concomitant medication(s)
- Are non-compliant with study procedures
- Experience an AE that warrants premature withdrawal

All treated subjects, should be followed according to the Schedule of Procedures. All subjects, even those who have discontinued prematurely, should have all evaluations for the End-of-Study visit performed, if possible. All procedures should be documented in the subject source documents and CRF. For all subjects who withdraw prematurely, the Investigator will indicate one of the following reasons for withdrawal on the CRF:

- Adverse event
- Death
- Protocol violation
- Lost to follow-up
- Subject's decision
- Other (reason to be specified by the Investigator)

In case of subjects' discontinuation from the study due to an AE, such subjects will be closely monitored until the resolution or stabilization of the AE. The Investigator should document the reason for discontinuation in the source documentation and CRF.

In the event that a subject withdraws participation from the study early, early withdrawal should be documented by the Investigator (or designee) in the appropriate CRF pages and source documents when confirmed.

7. STUDY PROCEDURES

The following sections describe in detail all study procedures. The schedule of procedures is presented in Table 5-1，Table 5-2，Table 5-3.

7.1. Part 1- Period One

7.1.1. Screening (Day -21 to -1)

Subjects will report to the CRU for a screening visit between Day -21 and Day -1 prior to the dosing. The following information and procedures will be performed and documented as part of the screening assessments:

- Prior to the performance of any study-related activities or evaluations, the subject must be thoroughly informed about all aspects of the study, including scheduled visits and activities. Each subject will sign the study-specific consent form prior to any screening procedures. A signed copy of the informed consent form (ICF) will be given to each consenting subject and another signed copy will be retained in the subject's study records.
- Medical history, including review of prior and ongoing medications taken in previous 30 days
- Physical examination including height and weight measurements. BMI will be calculated

- Vital sign measurements including blood pressure (three measurements), heart rate, respiratory rate and temperature. Subjects should be resting for at least 5 minutes prior to measurement. Vital signs will be measured in sitting position.
- A single 12-lead ECG (subject should be resting for at least 5 min prior to recording). ECG will be recorded in supine position
- Overnight fasting blood sample collection for safety tests as defined in Appendix A. HIV, and hepatitis B and C evaluations will be done at screening visit only
- Drug/alcohol test
- Serum pregnancy test at screening for females of childbearing potential.

Compliance with inclusion criteria and exclusion criteria will be verified against information collected and documented in the source documents and the CRF. Laboratory results obtained at screening will be used to verify eligibility.

Examples of contraception methods for participant or partner may include vasectomized partner (at least 6 months prior to dosing); intrauterine device; condom with spermicidal gel, foam, cream, film, or suppository; diaphragm with spermicidal gel, foam, cream, film, or suppository; or cervical cap with spermicidal gel, foam, cream, film, or suppository. A female of non-childbearing potential must have had at least 12 continuous months of natural (spontaneous) amenorrhea, follicle-stimulating hormone level > 40 mIU/mL at Screening, or have had surgical bilateral oophorectomy or hysterectomy > 6 weeks prior to Screening.

Once all inclusion criteria are met, exclusion criteria ruled out, and laboratory measurements obtained, eligible subjects will be scheduled for the admission (Day 0) visit within 21 days of screening.

7.1.2. Baseline (Day 0)

Subjects will be admitted to the CRU on Day 0 and remain sequestered at the CRU until the collection of the PK sample of 48 hours after dosing.

On arrival at the clinical research unit, all subjects will undergo the following assessments:

- Vital signs including blood pressure, heart rate, respiratory rate and temperature
- Three 12-lead ECGs will be recorded with 3-min interval at this visit. The means of the three ECGs will be used as the baselines.
- Overnight fasting blood sample collection for safety tests
- Drug/alcohol test
- Urine pregnancy test for females of childbearing potential
- Admission to the CRU for eligible subjects
- Assessment of AEs and concomitant medications

Enrolled patients will be fasted from 10 pm the day prior to dosing until approximately 4 hours after administration the next day (dosing day). Water intake will be permitted until 6 am of the dosing day.

7.1.3. Dosing (Day 1)

The following assessments and procedures will be performed and documented at this visit:

- Vital signs. Prior to dosing, blood pressure, heart rate, respiratory rate and temperature will be measured. For all other time points, only blood pressure and heart rate will be measured
- Randomization to treatment
- Administration of study drug. Dose will be administered orally with 240 mL of room temperature water in an upright position under fasting conditions at approximately 8 am. Subjects should not drink water and need to maintain an upright position for 2 hours after the administration of the study drug. Lunch will be served at approximately 4 hours after the administration and dinner as the standard meal at approximately 10 hours post dose. If needed, evening snack can be provided. Time of administration will be documented for both study drug and meals.
- Pharmacokinetic blood samples will be collected at the following time points:
  Pre-dose (within 30 min prior) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours after dosing (acceptable windows: ± 2 min for 0 to 2-hr post dose period and ± 5 min thereafter)
- Assessment of AEs and concomitant medications.

All doses of study drug will be administered orally under fasting conditions at approximately 8 am on the day of dosing. Subjects will be closely supervised and within sight of study personnel within 8 hours after dosing. Actual times for dosing, each assessment and meals (start times for meals on the day of dosing) must be recorded. Any deviations from the protocol-specified administration schedule will also be documented.

7.1.4. Days 2 through 7

The following assessments and procedures will be performed and documented.

- Daily vital sign measurements
- Pharmacokinetic blood sample collections (acceptable windows: ± 5 min). See PK timepoints in section 7.1.3 and footnote of Table 5-1
- Assessment of AEs and concomitant medications daily
- Discharge from CRU on Day 3 after the 48-hour after dosing PK sample is obtained. Subjects will be remined to return to CRU at defined time to provide PK sample and to receive study assessments

7.1.5. Day 8

The following assessments and procedures will be performed and documented.

- Physical examination
- Vital sign measurements

- A single 12-lead ECG
- Overnight fasting blood sample collection for safety tests
- Drug and alcohol test
- Pharmacokinetic blood sample collections (acceptable windows: ± 5 min). See PK timepoints in section 7.1.3 and footnote of Table 5-1
- Assessment of AEs and concomitant medications daily

7.2. Part 1- Period Two

After a wash-out period for at least 14-day since the last dosing, subjects will be evaluated for their eligibility for Period Two. Eligible subjects will crossover to the alternative reference or test drug. Thus, subjects who receive levamlodipine treatment in Period One will now receive NORVASC® treatment in Period Two, while subjects who receive NORVASC® treatment in Period One will now receive levamlodipine treatment in Period Two. The same procedure will be performed at the same time points as noted for Period One.

7.2.1. Admission (Day 0)

The following assessments and procedures will be performed and documented:

- Admission to CRU
- Cross-over to treatment
- Physical examination
- Vital signs
- A single 12-lead ECG record
- Overnight fasting blood sample collection for safety tests
- Drug/alcohol test
- Urine pregnant test for females of childbearing potential
- Assessment of AEs and concomitant medications.

7.2.2. Dosing (Day 1)

The following assessments and procedures will be performed and documented:

- Vital signs. Prior to dosing, blood pressure, heart rate, respiratory rate and temperature will be measured. For all other time points, only blood pressure and heart rate will be measured
- Administration of study drug. Dose will be administered orally with 240 mL of room temperature water in an upright position under fasting conditions at approximately 8 am. Subjects should not drink water and need to maintain an upright position for 2 hours after the administration of the study drug. Lunch will be served at approximately 4 hours after the administration and dinner as the standard meal at approximately 10 hours post dose. If needed, evening snack can be provided. Time of administration will be documented for both study drug and meals.
- Pharmacokinetic blood samples will be collected at the following time points:

Pre-dose (within 30 min prior) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours after dosing (acceptable windows: ± 2 min for 0 to 2-hr post dose period and ± 5 min thereafter)

- Assessment of AEs and concomitant medications.

All doses of study drug will be administered orally under fasting conditions at approximately 8 am on the day of dosing. Subjects will be closely supervised and within sight of study personnel within 8 hours after dosing. Actual times for dosing, each assessment and meals (start times for meals on the day of dosing) must be recorded. Any deviations from the protocol-specified administration schedule will also be documented.

7.2.3. Days 2 through 7

The following assessments and procedures will be performed and documented.

- Daily vital sign measurements
- Pharmacokinetic blood sample collections (acceptable windows: ± 5 min). See PK timepoints in section 7.2.2 and footnote of Table 5-2
- Assessment of AEs and concomitant medication daily
- Discharge from CRU on Day 3 after the 48-hour after dosing PK sample is obtained. Subjects will be remined to return to CRU at defined time to provide PK sample and to receive study assessments

7.2.4. Day 8

The following assessments and procedures will be performed and documented.

- Physical examination
- Vital sign measurements
- A single 12-lead ECG
- Overnight fasting blood sample collection for safety tests
- Drug/alcohol test
- Urine pregnancy test for females of childbearing potential
- Pharmacokinetic blood sample collections (acceptable windows: ± 5 min). See PK timepoints in section 7.2.2 and footnote of Table 5-2
- Assessment of AEs and concomitant medication daily
- Discharge from the CRU

7.3. Part 2 (Food Effect)

7.3.1. Admission (Day 0)

Subjects who have completed Part 1 will be rolled over to Part 2 after a wash-out period for at least 14-days since the last dosing to assess food effect on the PK profile of levamlodipine maleate tablets from CSPC. Eligible subjects will be admitted to the CRU on Day 0 and remain sequestered at the CRU until the collection of the 48-hour PK sample after dosing.

On arrival at the clinical research unit, all subjects will undergo the following assessments:

- Physical examination
- Vital signs including blood pressure, heart rate, respiratory rate and temperature
- A single 12-lead ECG
- Overnight fasting blood sample collection for safety tests
- Drug/alcohol test
- Urine pregnancy test for females of childbearing potential
- Admission to the CRU
- Assessment of AEs and concomitant medications

Enrolled patients will be fasted from 10 pm the day prior to dosing until approximately 4 hours after administration the next day (dosing day). Water intake will be permitted until 6 am of the dosing day.

7.3.2. Dosing (Day 1)

The following assessments and procedures will be performed and documented at this visit:

- Vital signs. Prior to dosing, blood pressure, heart rate, respiratory rate and temperature will be measured. For all other time points, only blood pressure and heart rate will be measured
- High-fat/high-calorie meal. Following an overnight fast of at least 10 hours, subjects should start the recommended meal 30 minutes prior to administration of the drug product. Study subjects should eat the a high-fat / high-calorie meal in 30 minutes or less. This meal should derive approximately 150, 250 and 500-600 calories from protein, carbohydrate and fat, respectively. Subjects should receive standardized meals scheduled at the same time in each period of the study.
- Administration of study drug. Dose will be administered orally with 240 mL of room temperature water in an upright position under using meal conditions at approximately 8 am. No food should be allowed for at least 4 hours post-dose. Water can be allowed as desired except for one hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.
- Pharmacokinetic blood samples will be collected at the following time points:
  Pre-dose (within 30 min prior) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours after dosing (acceptable windows: ± 2 min for 0 to 2-hr post dose period and ± 5 min thereafter)
- Assessment of AEs and concomitant medications.

Subjects will be supervised and within sight of study personnel within 8 hours after dosing. Actual times for dosing, each assessment and meals (start times for meals on the day of dosing) must be recorded. Any deviations from the protocol-specified administration schedule will also be documented.

7.3.3. Days 2 through 7

The following assessments and procedures will be performed and documented.

- Daily vital sign measurements
- Pharmacokinetic blood sample collections (acceptable windows: ± 5 min). See PK timepoints in section 7.3.2 and footnote of Table 5-3
- Assessment of AEs and concomitant medications daily
- Discharge from CRU on Day 3 after the 48-hour after dosing PK sample is obtained. Subjects will be remined to return to CRU at defined time to provide PK sample and to receive study assessments

7.3.4. Day 8

The following assessments and procedures will be performed and documented.

- Physical examination
- Vital sign measurements
- A single 12-lead ECG
- Overnight fasting blood sample collection for safety tests
- Drug/alcohol test
- Urine pregnant test for females of childbearing potential
- Pharmacokinetic blood sample collections (acceptable windows: ± 5 min). See PK timepoints in section 7.3.2 and footnote of Table 5-3
- Assessment of AEs and concomitant medications daily

7.4. Early Withdrawal Visit

In the event that a subject discontinues study participation at any time prior to the final End-of-Study visit, if possible, the subject should complete all follow-up assessments, as described for Day 8. The reason for discontinuation must be fully documented in the subject's source documentation and in the CRF.

8. TREATMENT OF SUBJECTS

8.1. Methods of Assigning Subjects in Part 1

Subject treatment assignment will be based on a generated randomization scheme with a ratio of 1:1 (test: reference). Each treatment group will have 16 subjects randomized to receive either test drug or reference drug.

8.2 Methods of Assigning Subjects in Part 2

All subjects who have completed Part 1 will be rolled over to Part 2 after a wash-out period for at least 14 days since the last dosing to assess food effect on the PK profile of levamlodipine maleate tablets. Subjects will receive a single oral administration of study drug under a high-fat /

high-calorie meal. This meal should derive approximately 150, 250 and 500-600 calories from protein, carbohydrate and fat, respectively.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug Packaging and Labeling

Test and reference drugs will be packaged in bottles and labeled according to applicable regulatory requirements. The label for study drugs will include at least the following information:

- Name and address of sponsor
- Protocol number of other identifier to reference the study
- Storage conditions

The clinical site pharmacist or designee will prepare the study drug according to the randomization scheme, maintain the drug packaging and labeling log.

9.2. Study Drug Storage and Accountability

All investigational drug supplies will be stored in a secure, locked area, under the responsibility of the Investigator or other authorized individual.

The Investigator or designee must maintain accurate records of the receipt of all study drug, including date received, lot number, expiration date if applicable, amount received, condition of the package and the disposition of all study drug.

Current dispensing records will also be maintained including the date and amount of study drug dispensed and the identity of the subject receiving the study drug.

9.3. Study Drug Handling and Disposal

All unused study drug and supplies must be returned to CSPC Pharma or disposed according to sponsor's instruction after the study is completed and the drug accountability log is reconciled.

10. PHARMACOKINETICS ASSESSMENTS

Plasma concentrations of (S)amlodipine and (R)amlodipine will be measured with validated methods under GLP.

Guidelines for preparing, labeling, storing and shipping plasma samples for bioanalytical analyses will be provided in a separate manual.

10.1. Blood Sample Collection

A total of 23 blood samples will be collected at the following time points: within 30 min prior to dosing and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours after each dosing.

Contents of tube will be mixed thoroughly with gentle inversion (a minimum of 8 times) to mix the anti-coagulant. Total volume of blood collected for determination of study drug concentration will be approximately 100 mL (16 × 6mL) for each subject.

10.2. Sample Storage and Shipping

All blood samples will be stored on ice or at 4°C for no more than 30 minutes until plasma is harvested. Blood samples will be centrifuged in a refrigerated centrifuge (approximately 4°C) at ~2000 g for 10 minutes. The harvested plasma will be split into two approximately equal aliquots and stored in 2 mL or appropriate size cryovial tubes. The plasma samples will be frozen within approximately 60 minutes of harvesting and stored at –70°C or –80°C pending shipment for drug analysis.

10.3. Specimen Labeling

Labels will be affixed to the cryovial and polypropylene tubes in a manner that will prevent the label from being detached or smeared after being wet or freezing. The tube labels will follow the instruction to be provided in the PK Lab Manual.

The site will provide a sample inventory page, listing the information above for each sample. The sample inventory page will also include the treatment and study part/period for each series of tubes.

10.4. Sample Shipping Instructions

All plasma samples will be kept frozen and shipped on dry ice by the same day or overnight courier to the designated laboratory.

Plasma samples will be sent to the designated laboratory in two separate shipments. The first shipment of samples (the primary aliquot of each sample) will be shipped based on the schedule specified in the PK Lab Manual. The second aliquot of each sample will be shipped after notification from the designated laboratory.

10.5. Bioanalytical Methodology

Plasma samples will be analyzed by the designated bioanalytical lab using validated methods of liquid chromatographic separation with tandem mass spectrometric detection (LC-MS/MS) for concentrations of (S)amlodipine and (R)amlodipine.

10.6. PK Parameters

The plasma concentration time data for (S)amlodipine and (R)amlodipine will be analyzed using non-compartmental methods. Actual dosing and sampling times will be used for analyses. The

primary PK parameters of interest are: C_{max}, t_{max}, t_{lag}, $t_{1/2}$, λ_z, MRT_{inf}, AUC_{last}, AUC_{inf}, AUC_{extrap}, Cl/F and V_d/f. Additional parameters may be estimated and reported, as appropriate.

11. ASSESSMENT OF SAFETY

For specific timing of assessments, please see Table 5-1, Table 5-2, Table 5-3 for Schedule of Procedures.

11.1.1. Medical History

Demographic characteristics (age, sex, race and ethnicity) will be collected at screening visit. Medical history will be reviewed and collected at screening visit.

11.1.2. Vital Signs

Vital signs, including blood pressure, pulse rate, respiratory rate, and oral temperature, will be measured at the screening and other visits. Subjects should be resting for at least 5 minutes prior to measurement. Vital signs will be measured in sitting position.

Vital signs may be repeated for clinically significant abnormal vital signs at the discretion of the Investigator.

11.1.3. Physical Examination

Physical examinations will be performed by qualified personnel at the screening and few other visits. At the screening visit, height (centimeters) and weight (kilograms) will be measured and BMI will be calculated. All abnormal findings will be documented in the source documentation and the CRF.

11.1.4. Electrocardiogram

Standard resting 12-lead ECGs will be performed at multiple visits. All ECGs will be performed after the subject has rested for at least 5 minutes.

At baseline, three ECGs will be recorded with approximately 3-min interval. The means of the three ECGs will be used as baselines.

Multiple parameters such as HR, PR, RR, QRS, QT and QTcB or QTcF will be measured.

Post-dose ECGs must be evaluated for safety by the Investigator or his/her designee. The final conduction intervals entered into the CRF will be those generated by the ECG machine, unless deemed significantly inaccurate by the review performed by the Investigator or designee. In these cases, the over-read intervals will be documented in the CRF. The Investigator will also record an overall assessment of the ECG. Clinically significant abnormal ECGs may be repeated at the discretion of the Investigator.

11.1.5. Clinical Laboratory Assessments

Hematology, blood chemistry, and urinalysis evaluations will be performed at screening and few other visits. The list of clinical laboratory assessments is included in Appendix A. Subjects should be fasted overnight prior to blood sample collection for safety tests.

The total volume of blood collected for safety laboratory assessments will be approximately 70 mL.

The results of clinical laboratory tests conducted at the screening visit must be assessed by the Investigator to determine each subject's eligibility for participation in the study. The Investigator should signify review of the laboratory reports by signing and dating the report. If subjects' values are out of range and the Investigator deems the out of range value is clinically significant, the Investigator must discuss and agree upon individual cases with CSPC Pharma's Medical Monitor prior to enrollment.

Any significant abnormalities should be fully investigated. Whenever possible, the etiology of the abnormal findings will be documented on the CRF. Laboratory results with clinically significant abnormal values may be repeated for verification. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result or to monitor the course of an AE should be obtained when clinically indicated. In particular, if a clinically significant abnormal result is observed that is not resolved by the final study visit, repeat tests will be performed if possible and resolution or stability of the abnormality will be recorded in the source documentation.

Any clinically significant laboratory abnormalities that are either serious (e.g., require medical intervention or result hospital admission) or unexpected will be promptly reported to the CSPC Pharma's representative. Any additional relevant laboratory results obtained by the Investigator during the course of this study will be reported to CSPC Pharma.

Virus serology (HIV, and hepatitis B and C) will be assessed at the screening visit only, and must be negative to qualify enrollment.

Drug and alcohol tests will be conducted at the screening visit and on Day -1. Results must be negative to qualify enrollment prior to dosing.

Serum pregnancy test will be performed at screening visit, and urine pregnancy test on Day -1 for female subjects only.

11.2. Adverse Events

Adverse events will be recorded beginning immediately after the ICF is signed. Subjects will be instructed to report AEs during the study and staff will query subjects regarding AEs throughout the study. The Investigator (and/or designee) must document all AEs reported by the subject from the time subjects give consent through completion of the End-of-Treatment visit. Any subject who is withdrawn from the study due to an AE shall be followed until the event has

resolved or stabilized, and the Investigator will document available follow-up information on the subject's source documentation and CRF.

11.2.1. Definitions of Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product. An AE is any symptom, sign, illness, or experience that develops or worsens in severity during the course of the study. Adverse events reported after consent but before the first dose of study drug are still to be documented by the Investigator but will be considered non-treatment-emergent AEs. Adverse events will be considered treatment emergent if the onset date is after the first dose of study drug.

The severity of each AE will be graded by the Investigator according to the following criteria:

- Mild: awareness of sign or symptom, but easily tolerated
- Moderate: discomfort sufficient to cause interference with normal activities
- Severe: incapacitating, with inability to perform normal activities

Inter-current illnesses or injuries should be regarded as AEs. Abnormal results of laboratory tests or diagnostic procedures are considered to be AEs if the abnormality:

- Is associated with clinical signs or symptoms
- Is considered by the Investigator to be of clinical significance
- Results in study withdrawal
- Fulfills any of the criteria for an SAE, as described in this section
- Requires intervention or further evaluation to determine the etiology of the abnormality and/or assess the risk to the subject
- Requires treatment

An SAE is any untoward medical occurrence at any dose that:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a medically important event that may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above

The term "life threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. Death is an outcome of an event. The event that resulted in death should be recorded and reported on the SAE form and documented in the CRF.

The Investigator must assess the relationship between the AE and the study drug by using the following definitions:

- Probably related: The AE follows a reasonable temporal sequence from administration of the medication; OR the AE follows a known pattern of or response to the study drug; OR an alternative explanation (e.g., concomitant disease, environmental factors, and/or concomitant medication) is less likely than attribution to the study drug; OR the AE diminishes or disappears upon cessation or reduction of dose of medication; OR the AE reappears upon re-administration of the medication.
- Possibly related: The AE follows a reasonable temporal sequence from administration of the medication; OR an alternative explanation (e.g., concomitant disease, environmental factors, and/or concomitant medication) is inconclusive, thus the causal relationship cannot be excluded; OR the AE diminishes or disappears upon cessation or reduction of dose of medication.
- Not related: The AE does not follow a reasonable temporal sequence from administration of the medication; OR the AE does not follow a known pattern of or response to the study drug; OR the AE can be attributed to another factor (e.g., concomitant disease, environmental factors, and/or concomitant medication).

11.2.2. Adverse Events of Special Interest

The following adverse events of special interest that are considered to be associated with the levamlodipine maleate tablets will be collected:

Common adverse reactions:

- Autonomic nerves system: flushing
- Body as a Whole: Fatigue
- Cardiovascular, general: edema
- Central and peripheral nervous system: Headache, Dizziness
- The gastrointestinal tract: abdominal pain, nausea Heart rate/rhythm: palpitations Psychological: sleepiness
- In clinical trials found no clinical laboratory abnormalities associated with this product.

Rare adverse reactions in post-marketing experience:

- Autonomic nerves system: dry mouth, perspiration
- Body as a Whole: weakness, back pain, body discomfort, pain, weight increase/decrease
- Cardiovascular, general: hypotension, syncope
- Central and peripheral nervous system: high muscle tension, hypesthesia/paresthesia, peripheral neuropathy, tremor
- Endocrine: hyperplasia of mammary glands
- The gastrointestinal tract: constipation: dyspepsia (including gastritis), gingival hyperplasia, pancreatitis, vomiting

- Metabolic/nutritional: hyperglycemia Musculoskeletal: arthralgia, muscle cramps pain, muscle pain
- Platelet/bleeding and clotting: purpura, thrombocytopenic purpura
- Psychological: impotence, insomnia, mood changes
- Respiratory system: cough, dyspnea
- Dermatologic: baldness, epichrosis
- Special feeling: taste disorder, tinnitus
- Urinary system: frequent micturition
- blood vessels (extracardiac) : vasculitis
- Vision: visual disturbance
- White blood cells/reticuloendothelial system: leucopenia

There have been rare reports of anaphylaxis caused by amlodipine, including pruritus, rash, vasogenic edema and erythema multiforme.

11.2.3. Recording Adverse Events

All AEs (regardless of seriousness or relationship to study drug) including those from the time of consent to the End-of-Treatment visit are to be recorded in the subject's source documents and on the corresponding page(s) in the CRF. Whenever possible, symptoms, signs, and laboratory abnormalities should be grouped as a single syndrome or diagnosis. The Investigator should specify the date of onset, intensity, action taken with respect to study drug, corrective treatment/therapy given, outcome and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the study drug, according to the definitions noted in Section 11.2.1. All medications administered to treat an AE must be recorded in the subject's source documentation and documented in the CRF.

11.2.4. Reporting of Serious Adverse Events

Reporting of SAEs will be conducted in accordance with the appropriate regulatory guidelines. All SAEs that occur from the time of consent to the End-of-Study visit must be reported, whether or not the event is considered associated with the study drug. The Investigator must complete the SAE Reporting Form and submit it by fax with other relevant source documentation to CSPC Pharma within 24 hours of awareness of the event.

The Investigator must also provide with urgent priority (upon receipt of a request) other relevant documentation (e.g., copies of diagnostic test results, hospital discharge summary, and/or autopsy report) and send this information by fax to CSPC Pharma.

All SAEs must be recorded in the subject's source documentation and documented in the CRF. Medications administered in association with the SAE must be documented in the CRF and in the subject's source documentation. The Investigator must also promptly notify the Institutional Review Board (IRB) /Independent Ethics Committee (IEC) of SAEs, including any follow-up information, in accordance with local institutional policy and applicable regulatory requirements.

Regulatory authorities will be notified of any AE associated with the use of the study drug that is both serious and unexpected, in accordance with the appropriate local regulatory guidelines. Notification of the event will be made by written, expedited safety report.

11.2.5. Adverse Event Follow-up

The Investigator should take all appropriate measures to ensure the safety of the subjects, including referral to a specialist if indicated. The Investigator should follow up on the outcome of any AE until the event has resolved or stabilized.

This implies that follow-up may continue after the subject discontinues from the study and that additional information may be requested.

Any SAE brought to the attention of the Investigator within 30 days after cessation of study drug and considered by him/her to be caused by the study drug with a reasonable possibility, should be reported through the SAE reporting process.

12. STATISTICAL METHODOLOGY

12.1. Sample Size Determination

Based on an approximate CV_B of 20%, a CV_W is calculated to be 14% for C_{max} and 11% for $AUC_{0-\infty}$, respectively. Thus, an N value of approximately 18 completed subjects for AUC (%CV rounded off to 10%), an N value (interpolated) of approximately 27 completed subjects would be required for the proposed bioequivalence study. With an estimated drop-out rate of 20% in this cross-over study, approximately 32 subjects will be enrolled.

12.2. Analysis Population

The Safety Population will be defined as all subjects who receive at least one dose of study drug. The Pharmacokinetic Population will be defined as all subjects who receive active drug, have no major protocol violations, and have sufficient pharmacokinetic data to obtain reliable estimates of the key pharmacokinetic variables.

12.3. Pharmacokinetics

Pharmacokinetic parameters described in Section 10 will be calculated using standard non-compartmental methods and validated software. Individual and mean (SD) concentration time profiles will be presented graphically. All pharmacokinetic parameters will be summarized by treatment (dose group), using descriptive statistics (e.g., n, arithmetic mean, SD, geometric mean, median, and coefficient of variation).

Additional details regarding the pharmacokinetic analyses will be presented in the Statistical Analysis Plan.

Food effect will be evaluated based on AUC_{0-t}, AUC_{0-inf} and C_{max} of (S)amlodipine and will be determined by the changes of log-transformed PK parameters under fasting conditions and fed conditions.

12.4. Demographic Characteristics

Demographic characteristics will be summarized for the subjects enrolled in the study using descriptive statistics.

An attempt will be made to enroll similar numbers of men and women in each dose group.

12.5. Exposure to Study Drug

Each subject's exposure to study drug will be summarized using descriptive statistics, i.e., the number of subjects exposed to each dose.

12.6. Concomitant Medications

Concomitant medications will be coded using the World Health Organization (WHO) Enhanced dictionary.

12.7. Safety Analyses

Safety evaluations will be based on the incidence, intensity, and relatedness of AEs and changes in subjects' physical examination findings, ECGs, vital signs, clinical laboratory results. Safety variables will be tabulated and presented for all subjects in the Safety Population. Data will be summarized by treatment. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) for preferred term and system organ class, listed by subject. Treatment-emergent AEs (TEAEs) will be summarized by treatment, where treatment-emergent is defined as any event not present prior to the initiation of the treatments or any event already present that worsens in either intensity or frequency following exposure to the treatments. All AEs will be summarized by relationship to study drug and by intensity.

Deaths, SAEs, and AEs resulting in study discontinuation will be tabulated and detailed in narratives.

If adequate data are available, an analysis will be performed for PK profile (e.g., T_{max}) in conjunction with time to occurrence of adverse events.

Change from baseline, defined as time of admission to the CRU (Day 0), in clinical laboratory parameters, 12 lead ECGs, and vital sign parameters will be summarized by treatment and study period.

Additional safety analyses may be defined in the Statistical Analysis Plan.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

At regular intervals during the study, the site will be contacted through monitoring visits, letters, and telephone calls by a representative to review study progress, Investigator and subject compliance with study protocol requirements, and any emergent problems. During monitoring visits, the following points will be reviewed in accordance with all applicable regulatory requirements and SOPs: original medical records and other source documents, the Investigator site file, screening logs, subject informed consent, subject recruitment and follow-up, SAE documentation and reporting, documentation and reporting of endpoints, study drug allocation, subject compliance with the study drug regimen, study drug accountability, concomitant therapy use, and quality of data. In addition, other required regulatory documents will be reviewed, including but not limited to: IRB/IEC composition and correspondence, laboratory certification(s), delegation of authority, and Investigator and study personnel curricula vitae.

13.2. Sponsor's Responsibility

CSPC Pharma or its designee is responsible for the following:

1. Selecting qualified Investigators
2. Providing Investigators with the information they need to properly conduct an investigation
3. Ensuring proper monitoring of the investigation
4. Ensuring that the applicable regulatory authorities, and all participating Investigators are properly informed of significant new information regarding AEs or risks associated with the medication being studied

As the sponsor, CSPC Pharma has delegated some responsibilities to a Contract Research Organization (CRO).

13.3. Audits and Inspections

CSPC Pharma's Quality Assurance Unit (or representative) may conduct audits at the study site(s). Audits will include, but are not limited to: drug supply, presence of required documents, the informed consent process, laboratory specimen processing, and comparison of CRFs with source documents. The Investigator agrees to cooperate with audits conducted at a reasonable time and in a reasonable manner.

Regulatory authorities worldwide may also audit the Investigator during or after the study. The Investigator should contact CSPC Pharma immediately if this occurs, and must fully cooperate with the audits conducted at a reasonable time in a reasonable manner.

The Investigator is required to make all study documentation promptly available for inspection, review or audit at the study site upon request by sponsor, its representatives, or any appropriate regulatory agencies.

14. QUALITY CONTROL AND QUALITY ASSURANCE

A quality control and quality assurance plan, addressing aspects of the trial that may affect data integrity or the protection of human subjects, may be instituted for this study. All audit findings will be summarized and placed on file with appropriate documentation of response/resolution.

15. ETHICS

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and the Investigator abide by Good Clinical Practice (GCP), including but not limited to Title 21 Code of Federal Regulations (CFR) Parts 50, 56, and 312 and the International Conference on Harmonisation (ICH) guidelines and directives. Compliance with these regulations also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki, Tokyo 2004 and applicable local regulatory requirements and law.

Copies of these materials are available from CSPC Pharma and the CRO designee by request. The purpose of these regulations, legal obligations and guidance is to define the standards and principles for the proper conduct of clinical trials that have been developed by the medical, scientific, and regulatory communities. They are not intended to impede or restrict clinical research.

The ethical standards defined within GCP are intended to ensure that:

1. Human subjects are provided with an adequate understanding of the possible risks of their participation in the study, and that they have a free choice to participate or not.
2. The study is conducted with diligence and in conformance with the protocol in such a way as to protect subject safety and ensure the integrity of the findings.
3. The potential benefits of the research justify the risks.

The Investigator is responsible for protecting the rights, safety, and welfare of subjects under his/her care, and for the control of the medications under investigation.

The Principal Investigator will ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study drug, and their study related duties and functions. The Investigator will maintain a list of sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties. Individuals ineligible to conduct or work on clinical studies, including those ineligible as a result of debarment under the Generic Drug Enforcement Act of 1992, will not be allowed to conductor work on studies sponsored by CSPC Pharma. The Investigator is required to immediately disclose to CSPC Pharma in writing, if any person involved in the conduct of the study is debarred pursuant to a hearing by US FDA under this anti-fraud law, or if any proceeding for debarment is pending, or is (to the best of the Investigator’s knowledge) threatened.

The rest of this section of the protocol describes in more detail the specific GCP-defined responsibilities the Investigator assumes by agreeing to participate in this study.

15.1. Ethics Review

The Investigator (or designee) must submit this study protocol, the CSPC Pharma approved ICF, patient information sheets (PISs), subject recruitment materials, and other appropriated documents to the appropriate IRB or IEC, and following review of the submitted materials is required to forward to CSPC Pharma (or designee) a copy of the written and dated approval/favorable opinion signed by the Chairman, along with a list of the IRB/IEC composition.

The approval/favorable opinion should clearly state the trial (study number, protocol title, and version number), the documents reviewed (Protocol, ICF, IB, etc) and the date of the review. The study will not commence at the study site until CSPC Pharma has received a copy of this written and dated approval/favorable opinion.

During the trial, any amendment to the protocol and the ICF (as appropriate) should be submitted to the IRB/IEC. The IRB/IEC should also be informed of any event likely to affect the safety of subjects or the continued conduct of the trial, in particular any change in safety. Additionally, all updates to the IB will be sent to the IRB/IEC. A progress report will be sent to the IRB/IEC and the protocol will be reviewed annually (e.g., re-approved) or more frequently, as required by IRB/IEC or local regulations.

The Investigator will notify the IRB/IEC of the conclusion of the clinical study within 1 month of completion or termination of the study. The final report sent to the IRB/IEC will also be sent to CSPC Pharma, along with the completed CRFs and all necessary regulatory documents, thereby fulfilling the Investigator's regulatory responsibility.

The Investigator will maintain a copy of all correspondence with the IRB/IEC, including copies of approved documents. The Investigator will also maintain a copy of the IRB/IEC membership list, including members' occupation and qualifications (or a statement confirming compliance with GCP requirements for committee composition). An IRB or IEC General Assurance Number may be accepted in lieu of a membership roster.

15.2. Ethical Conduct of the Study

This study will be conducted in accordance with GCP as delineated by Title 21 CFR Parts 50,56, and 312, and the ICH guidelines and directives. Participating Investigators, including members of the Committees and National Coordinators, will receive compensation for their time but will receive no financial profit from their activities related to the trial.

Before the first subject is enrolled in the study, all ethical, regulatory, and legal requirements must be met.

An Investigator participating in this study is required to maintain complete and accurate study documentation in compliance with current GCP standards and all applicable local regulations related to the conduct of a clinical study.

15.3. Written Informed Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative, as applicable, in accordance with local practice and regulations. Written informed consent must be obtained from all subjects participating in a clinical study conducted by CSPC Pharma.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject. The subject must be given sufficient time to consider whether to participate in the study.

A copy of the ICF, signed and dated by the subject, must be given to the subject. Confirmation of a subject's informed consent must also be documented in the subject's source documentation prior to any testing under this protocol, including screening tests and assessments.

Each consent form should contain an authorization allowing the Principal Investigator(s) and CSPC Pharma to use and disclose patient health information (PHI) in compliance with local law.

The original signed consent form will be retained with the study records.

16. DATA HANDLING AND RECORD KEEPING

16.1. Data Collection

All data obtained for analysis in the clinical study described in this protocol will be documented in the CRF. Data reported in the CRFs should be consistent with and substantiated by the subject's medical record and original source documents. Any discrepancies must be explained. Unless explicitly allowed in the CRF instructions, blank data fields are not acceptable. If a field is blank because the item was not done, the field will be marked "Not Done". If the item is unknown, the field will be marked "Unknown".

Prior to the start of the study, the Principal Investigator will complete a Delegation of Authority form (Site Signature and Delegation Log), showing the signatures and handwritten initials of all individuals and the delegation of responsibilities, such as identifying those individuals who are authorized to make or change entries on CRFs.

16.2. Case Report Form Completion

Data within the CRF will be monitored by the Clinical Research Associate according to the Monitoring Plan. Queries will be generated based on discrepancies found while monitoring. Site personnel will review and respond to these queries appropriately. Additionally, the CRO and

CSPC Pharma may periodically perform aggregate data reviews, which could result in queries being generated for site personnel resolution. The final, completed CRF for each subject must be signed and dated by the Principal Investigator to signify that the Principal Investigator has reviewed the CRF and certifies it to be complete and accurate.

16.3. Database Management, Data Clarification, and Quality Assurance

A designated CRO will be responsible for data management. Data Management will develop a Data Management Plan (DMP) document and provide it to CSPC Pharma for approval. The DMP document will define all activities in the data collection and cleaning process. The detailed DMP will be based on the protocol, work scope, contract, analysis plans, data-flows, CRFs, data cleaning procedures, other supporting documents, and data management standards and practices.

The programmed data validations will be run to check for database completeness and consistency, and queries will be generated upon data entry or via review by a Clinical Data Manager after entry. The site will respond to the data queries in a timely manner.

Concurrent medications entered into the database will be coded using a WHO Anatomical Therapeutic Chemical dictionary. Coexistent diseases and AEs will be coded using MedDRA.

Quality control procedures will be conducted prior to database lock according to the designated CRO SOPs.

When the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time will only be made by joint written agreement between CSPC Pharma, the Trial Statistician, the Data Manager, and the Quality Assurance Auditor according to designated CRO SOPs.

16.4. Inspection of Records/Source Documents

According to the ICH guidelines for GCP, the sponsor or designee must verify data entered in the CRF against the source documents, except for the pre-identified source data directly documented in the CRF (if applicable). The ICF will include a statement by which the subject allows the sponsor’s duly authorized personnel, the IRB/IEC, and the regulatory authorities to have direct access to source data that supports the data in the CRF (e.g., subject’s medical file, appointment books, and original laboratory records). These personnel, bound by professional secrecy, must keep confidential all personal medical information.

The objective of source document verification (SDV) is to comply with GCP and international regulatory requirements and to reduce the risks of fraud. Source document verification means ensuring that the source documents are an accurate and verifiable reflection of the subject’s participation in the study and that all relevant information that is recorded in the source document is accurately entered into the CRF.

Where source documents serve as the basis for deriving data for the trial, SDV should ensure that these documents are correctly labeled and filed and that the data derived from them are correct.

All source documents pertaining to this study will be maintained by the Investigator and made available for inspection by authorized persons. If electronic progress notes and other electronic source documents are not Title 21 CFR Part 11 compliant, they are not considered a valid source for this study. If electronic records are printed, they should been marked as certified, all progress notes must be dated and signed by the Principal Investigator or sub-Investigator at the time of the visit. CSPC Pharma reserves the right to terminate the study for refusal of the Investigator to supply original source documentation for this clinical study.

The Investigator will note in a source independent from the CRF the following information:

1. Information to confirm that the subject exists (e.g., initials, date of birth, sex)
2. Confirmation that the subject satisfies the inclusion/exclusion criteria
3. Confirmation that the subject is taking part in the clinical trial
4. Confirmation of the informed consent process
5. Visit dates and documentation of protocol assessments and procedures
6. Information concerning all AEs
7. Details of concomitant and investigational medications

Source document verification is not a substitute for clinical trial monitoring, the purpose of which is to ensure that the protocol has been followed correctly, the CRF has been fully and accurately completed, SDV has been carried out, and the study timelines and enrollment goals and requirements have been met.

16.5. Retention of Records

The Investigator must maintain all study documentation as confidential, and take measures to prevent accidental or premature destruction of these documents.

The Investigator must retain the study documents at least 2 years after the last approval of a marketing application/new drug application for the indication investigated or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product (e.g., the Investigational New Drug application is withdrawn). These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with CSPC Pharma.

The Investigator must notify CSPC Pharma prior to destroying any study essential documents.

If the Investigator can no longer ensure archiving, he/she shall inform CSPC Pharma. The relevant records shall be transferred to a mutually agreed upon designee.

17. CONFIDENTIALITY

All information disclosed or provided by CSPC Pharma (or designee) or produced during the trial including, but not limited to, the protocol, the CRFs, the IB, and the results obtained during the course of the trial (if applicable), are confidential. The Investigator or any person under

his/her authority agrees to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of CSPC Pharma.

However, submission of this protocol and any other necessary documentation to the IRB/IEC is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from CSPC Pharma. However, authorized regulatory officials and sponsor personnel (or designee) will be allowed full access to inspect and copy the records. The copied and inspected records will remain at the site and will not be transmitted or removed from the site.

All study drugs, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by CSPC Pharma and responsible ethics committee(s) or regulatory authorities.

Subjects will be identified only by unique subject numbers in CRFs. Their full names may, however, be made known to a regulatory agency or other authorized officials in the event of inspections. Documents containing the full name or other personally identifiable information of the subject are to remain at the site. This information will not be transferred to CSPC Pharma nor be contained in regulatory filings. In the event of inspections by authorized agencies, this subject identification may be disclosed.

17.1. Subject Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., PHI authorization in North America).

The subject will not be identified by name in the CRF or in any study reports and these reports will be used for research purposes only. CSPC Pharma, its partner(s) and designee(s), and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject’s personal medical data confidential.

CSPC Pharma will protect individual subject information to the fullest extent possible during this trial. At no time will a subject become identified in any publication or presentation.

However, the subject may have to become identified in the event of a regulatory authority auditor inspection in order to verify the accuracy of the data. Access to subject information is at the discretion of CSPC Pharma and cannot occur prior to database lock or other specified events as determined solely by the discretion of CSPC Pharma.

18. STUDY PROTOCOL AMENDMENTS

The Investigator will not make any changes to this protocol without prior written consent from CSPC Pharma and subsequent approval by the IRB/IEC. Any permanent change to the protocol, whether it is an overall change or a change for specific study center(s), must be handled as a protocol amendment. Any amendment to the protocol that appears necessary as the study progresses will be fully discussed by the Investigator(s) and CSPC Pharma. If agreement is reached regarding the need for an amendment, it will be written by CSPC Pharma. The written amendment must be submitted to the chairman of the IRB/IEC identified with this responsibility. Except for administrative amendments, Investigators must await IRB/IEC approval of protocol amendments before implementing the change(s).

Administrative amendments are defined as having no effect on the safety of the research subjects, scope of the investigation, or quality of the trial. However, a protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately, and the IRB/IEC notified within 5 days. CSPC Pharma will ensure submission of any protocol amendments to the appropriate regulatory agencies.

When, in the judgment of the chairman of the local IRB/IEC, the Investigators, and/or CSPC Pharma, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, the Investigator will obtain repeat informed consent from subjects enrolled in the study before expecting continued participation.

19. PUBLICATION

All information concerning the product as well as any information such as clinical indications for the study drugs, their formula, their formulation, methods of manufacture and other scientific data relating to it, that have been provided by CSPC Pharma or designee, and are unpublished, are confidential and must remain the sole property of CSPC Pharma.

The Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from CSPC Pharma is obtained. CSPC Pharma has full ownership of the CRFs completed as part of the study.

By signing the study protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by CSPC Pharma. If necessary, the authorities will be notified of the Investigator’s name, address, qualifications, and extent of involvement.

CSPC Pharma or designee will prepare a final report on the study. The Investigator may not publish or present any information on this study without first presenting the information to CSPC Pharma for review.

APPENDIX A. LABORATORY ASSESSMENTS

Hematology

Hemoglobin (Hgb)
Hematocrit (Hct)
Platelet count
Red blood cell (RBC) count
White blood cell (WBC) count with differential

Alcohol test

Urine Drug Screen

Amphetamines
Barbiturates
Cannabinoids
Cocaine metabolites
Opiates
Benzodiazepines
Methamphetamine

Clinical Chemistry

Blood urea nitrogen (BUN)
Creatinine
Total bilirubin
Alkaline phosphatase
Aspartate transaminase (AST)
Alanine transaminase (ALT)
Gamma-glutamyl transferase (GGT)
Lactic dehydrogenase (LDH)
Glucose
Albumin
Total protein
Bicarbonate
Phosphate
Sodium
Potassium
Chloride
Calcium
Total cholesterol
Urate

Serology Screen

Human immunodeficiency virus (HIV)
Hepatitis B surface antigen (HBsAg)
Hepatitis C virus (HCV)

Other

Pregnancy test

Urinalysis

pH
Specific gravity
Protein
Glucose
Ketones
Bilirubin
Blood
Nitrites
Leukocytes
Urobilinogen
Microscopic urine analysis