STATISTICAL ANALYSIS PLAN

PROTOCOL: LAM-US-101

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

SPONSOR: CSPC Ouyi Pharmaceutical Co., Ltd., a subsidiary company within CSPC Pharmaceutical Group, Ltd (CSPC)
Conjupro Biotherapeutics Inc.
302 Carnegie Center Suite 100, Princeton, NJ 08540

PRODUCT : *Levamlodipine, the (S)amlodipine*

AUTHOR: James Zhou, Ph.D.
Contract Statistician
FHL Health LLC
6701 Democracy Blvd. Suite 300
Bethesda, MD 20817

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CRC REPRESENTATIVE DOCUMENT REVIEWED AND APPROVED BY:	
SIGNATURE:	DATE: 5 Sep 2018
NAME: Thomas J. Hochadel, Pharm.D.	
DEPARTMENT/TITLE: Chief Operating Officer	

STATISTICAL CRO REPRESENTATIVE DOCUMENT REVIEWED AND APPROVED BY:	
SIGNATURE:	DATE: 5 Sept 2018
NAME: James Zhou, Ph.D.	
DEPARTMENT/TITLE: Statistics/Contract Statistician FHL Health LLC	

SPONSOR COMPANY REPRESENTATIVE DOCUMENT REVIEWED AND APPROVED BY:	
SIGNATURE:	DATE: 05Sep2018
NAME: John Ilgenfritz	
DEPARTMENT/TITLE: Biostatistics /Consultant	

SPONSOR COMPANY REPRESENTATIVE DOCUMENT REVIEWED AND APPROVED BY:	
SIGNATURE:	DATE: 05 Sept 2018
NAME: Lan Lan	
DEPARTMENT/TITLE: Clinical Operations/Senior Project Manager	

TABLE OF CONTENTS

AMEMDMENT HISTORY

Not applicable

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
ATC	AnatomicalTherapeutic-Chemical
$AUC_{0\text{-}inf}$	Area under the analyte concentration-time curve from time 0 and extrapolated to infinite time, total exposure
BA	bioavailability
BMI	body mass index
BUN	Blood urea nitrogen
C_{max}	Maximum concentration
CRF	Case report form
CRU	Clinical research unit
CS	Clinically significant
CSPC Pharma	CSPC Pharmaceutical Co., Ltd.
CSR	Clinical Study Report
CV_B	between-subject coefficients of variation
CV_W	within-subject coefficients of variation
ECG	Electrocardiography
GGT	Gamma-glutamyl transferase
Hct	Hematocrit
Hgb	Hemoglobin
LDH	Lactic dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not clinically significant
PK	Pharmacokinetic(s)
QTcB	Bazett's QT correction
QTcF	Fridericia's QT correction
R	Reference product
RAND	Randomized Population
RBC	Red blood cell
SAE	Serious adverse event
SAF	Safety Population
SAP	statistical analysis plan
SCRN	Screened Population
SD	standard deviation
T	Test product
TEAE	Treatment-emergent AEs
TFLs	Tables, Figures, and Listings
WBC	White blood cell
WHO-DD	World Health Organization-Drug Dictionary

1 INTRODUCTION

This statistical analysis plan (SAP) describes the final statistical analysis for subject information and safety data to be done for the study entitled “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” (V2.0 21MAY2018). All planned PK analyses will be described in a separate PK analysis plan. Mock shells are also produced as a separate working document to facilitate programming of Tables, Figures, and Listings (TFLs) according to finalized SAP. The SAP is to be interpreted in conjunction with the protocol, and supersedes the statistical considerations identified in the protocol. If the final clinical study report contains changes to any planned statistical analyses, the justification for any such differences will be fully documented in the CSR.

1.1 Study Objectives

See protocol section 4.

1.2 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 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). 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. The same procedure will be performed at approximately same time points as noted for Period 1.

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. 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.

1.3 Sample Size Estimation

Based on an approximate CV_B of 20%, a CV_W is calculated to be 14% for C_{max} and 11% for $AUC_{0\text{-}inf}$, 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.

1.4 Randomization

In Part 1, subjects will be assigned in a ratio of 1:1 to receive one of two treatment sequences (RT or TR; R=10 mg of NORVASC® and T=5 mg of levamlodipine maleate tablets). Each sequence will have 16 subjects randomized for a total of 32 patients. {The text presented in this section had been edited from that in Section 8.1 of the protocol. See Section 8 of this SAP for further details}

1.5 Study Data

The study data to be analyzed include all clinical data captured by the case report form (CRF), including safety lab data. The CRF database will be locked for the final analyses.

2 GENERAL ANALYSIS DEFINITIONS

All analysis dataset preparations and statistical analyses will be performed using SAS® version 9.4 or higher. No imputation will be performed for missing data unless stated otherwise. Listings for CSR Appendix 16.2 will include all the subject data points being collected or derived for analyses. Data listings will be provided for all subjects up to the point of withdrawal.

2.1 Study Parts and Treatment Sequences/Groups

For analyses per randomized, the two randomized treatment sequences will be labelled as “Levamlodipine, Then NORVASC” and “NORVASC, Then Levamlodipine”. For analysis per treated, the two actual treatment groups will be labelled as Levamlodipine and NORVASC. The two study parts will be labelled as “Study Part 1” and “Study Part 2”.

2.2 Statistical Hypothesis Tests

No statistical hypothesis tests will be performed for the analyses described in this SAP. The bioequivalence data does have associated hypothesis testing which is detailed in a separate analysis plan for PK analyses.

2.3 Study Periods, Visit, and Day

The overall study consists of initial screening and three treatment periods, separated by two wash-out periods between treatment periods. Each treatment period includes a 3-day visit admitted in the CRU, followed by 5 daily visits. A reference date refers to the start date of the study drug administration for each treatment period. All efficacy and safety assessments at all visits will be assigned a day relative to this date within each treatment period. The relative day will be defined as: visit date – reference date + 1 for visits on or after the reference date, and visit date – reference date for visits before the reference date. Consequently there is no 'Day 0' defined.

In general, the baseline is defined as the last assessment before the intake of the first study medication during each treatment period unless specifically stated otherwise. All scheduled assessments after first administration of study drug will be used. Repeat/unscheduled assessments will not be used in descriptive statistics or any per-time point analysis, but will be shown in listings as applicable. Pre-dose unscheduled assessments will be taken into account for baseline determination and post first dose unscheduled assessments will be taken into account for worst-case determination as applicable.

2.4 Analysis Populations

2.4.1 Screened Population

All subjects who were screened and signed the informed consent are included in the Screened Population (SCRN).

2.4.2 Randomized Population

All randomized subjects are included in the Randomized Population (RAND).

2.4.3 Safety Population

All safety endpoints will be evaluated on the Safety Population (SAF), consisting of all subjects who received at least one dose of study drug and will be analyzed by the treatment group as treated.

2.4.4 Pharmacokinetic Population

The Pharmacokinetic Population is documented in a separate analysis plan for PK analyses. It is not applicable to the analyses described in this statistical analysis plan.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when subjects are assigned to analysis populations prior to final database lock.

A summary table of number (%) of patients in each analysis population/set will be provided (Table 14.1.1).

2.5 Definition of Subgroups

No subgroup analyses are planned.

2.6 Descriptive Summaries

Summary statistics and statistical analyses will generally only be performed for subjects included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used. All tabulated summaries will include two Study Parts and Treatment Sequences/Groups. For endpoints that are continuous in nature: number of observations, mean, median, minimum and maximum, and standard deviation (SD) values will be presented as descriptive summary. For endpoints that are categorical in nature: frequency counts and percentages will be presented as descriptive summary.

The number of decimal places to display for calculated data will be determined by the original scale of the data. Means and medians will be reported with one (1) additional decimal place. Standard deviation will be reported with two (2) additional decimal places. Minimum and maximum will be reported with the same number of significant digits as the method of capture.

3 PLANNED INTERIM ANALYSIS

No interim analyses are planned.

4 SUBJECT INFORMATION

In general, all subject-level parameters will be summarized for the Randomized Population based on randomized treatment sequence group, unless stated otherwise.

4.1 Disposition Information

Summaries will be provided for the following disposition information: Number of subjects screened, screening failures, randomized, completed Part 1, and completed or discontinued study with the reasons of discontinuation. The reasons of discontinuations include following categories:

- Adverse Event
- Subject Requested Withdrawal
- Investigator Decision
- Sponsor Decision
- Subject Lost to Follow-up
- Subject Died
- Pregnancy
- Other

The randomized treatment sequence group will be shown for Randomized Population (Table 14.1.2).

4.2 Protocol Deviations

All reported major protocol deviations and determined exclusions from any analysis population(s) will be documented and included in the CSR.

4.3 Demographics and Baseline Characteristics

Descriptive statistics or frequency tabulation will be provided for the following parameters.

4.3.1 Demographic Parameters

Descriptive statistics or frequency tabulation will be provided for following parameters (Table 14.1.3.1):

- Age (years): continuous and categorized as 18-40 years and 41-45 years
- Sex (Male, Female)
- Race (White, Black or African American, Others – for all other race categories captured on CRF)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Weight at baseline (kg)
- Height at baseline (cm)
- Body Mass Index (BMI) at baseline = Weight at baseline (kg) / [Height at baseline (m)]^2 (rounded to 1 decimal. Although available in the raw data, BMI will be recalculated from last weight and height measurement before start of treatment)

4.3.2 Tobacco and Alcohol Use

Descriptive statistics or frequency tabulation will be provided for the following parameters related to tobacco or alcohol use (Table 14.1.3.2):

- Smoking status (Never Smoked, Current Smoker, Ex-Smoker)
- Used tobacco in past 6 months (Yes, No)
- Had alcohol in past 6 months (Yes, No)
- Average number of drinks per week

4.4 Medical History

All reported medical history will be coded by Medical Dictionary for Regulatory Activities (MedDRA, version 20.0), and summarized by MedDRA system organ class and preferred term, in order of descending overall frequency for the Randomized Population (Table 14.1.4).

4.5 Prior and Concomitant Medications

All reported medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD, version September 2018) and summarized separated for each of following two categories:

1) Prior medication: medication received during the 4 weeks (30 days) prior to Screening but is no longer taking, collected on the CRF page “Prior Medication” at screening.
2) Concomitant medication: medication received during the study, collected on the CRF page “Concomitant Medication”.

Prior medications will be included in the subject data listing (Listing 16.2.5.1). A frequency tabulation for concomitant medications will be shown by WHO-DD ATC class level 4 and preferred term for the Safety Population (Table 14.1.5).

4.6 Extent of Exposure

Frequency tabulation will be provided for the number and percentage of subjects exposed within each treatment period for the Safety Population (Table 14.1.6).

5 SAFETY

All safety analyses will be done on the Safety Population.

There are three treatment phases to be allocated to all safety assessments, namely Treatment Phases 1, 2, and 3. The Treatment Phase 1 starts at the datetime of first study drug dosing and ends before the datetime of second study drug dosing or early termination of study, whichever earlier. The Treatment Phase 2 starts at the datetime of second study drug dosing and ends before the datetime of third study drug dosing or early termination of study, whichever earlier. The Treatment Phase 3 starts at the datetime of third study drug dosing and ends at the end of study.

All safety parameters will be summarized based on the actual treatment group within each study part based on the Safety Population. In other words, data associated with the same treatment group throughout the Study Part 1 (Treatment Phases 1 and 2) will be combined for summary by the actual treatment.

5.1 Adverse Events

5.1.1 Coding of Adverse Events

The verbatim terms of adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 20.0). Events are summarized by system organ class and preferred.

5.1.2 Treatment-Emergent AE

Pre-treatment AEs are defined as AEs that were reported or worsened after signing the ICF up to the start of first study drug dosing. Treatment-emergent AEs (TEAE) are defined as AEs that were reported or worsened on or after the start of study drug dosing and before the start of subsequent drug dose (Treatment Periods 1 and 2) or up to and including the end of the follow-up phase (Treatment Period 3).

5.1.3 Phase Allocation of TEAE

Adverse events are allocated to phases based on their start date and time. If the start date and time of an event falls between (or on) the start and stop date and time of a phase, the TEAE is attributed to that phase (treatment-emergent principle).

Rule: phase start datetime ≤ TEAE start datetime ≤ phase stop datetime.

In case of partial AE start dates and or times, the events are allocated to the phases using the available partial information on start and end datetime; no imputation will be done. If, for instance, for the AE start date only month and year are available, these data are compared to the month and year information of the phases. This rule may lead to multiplication of the event as a consequence of its assignment to multiple phases. In case of a completely missing AE start date, the event is allocated to the first treatment phase, except if the end date of the AE falls before the start of this treatment phase. In case of any other missing scenarios, the phase allocation of AE will be determined by manual data review prior to database lock.

5.1.4 Variables Attributed to Adverse Events:

- AE term (verbatim and MedDRA preferred term and system organ class)
- Start datetime, End datetime, and duration of AE
- Frequency (Single Episode, Intermittent, Continuous)
- Serious AE (Yes/No), if yes classification will be listed
- Severity (Mild, Moderate, Severe)
- Relation to study treatment (Not related, Possibly Related, Probably Related)
- Action taken with study treatment (No Action Taken, Non-Drug Therapy , Medication Given, Discontinued, Other)
- Outcome of AE (Recovered/Resolved, Resolved/Resolved with Sequelae, Recovering/Resolving, Not Recovered/Not Resolved, Fatal, Unknown)

5.1.5 Analysis Methods

There will be no formal statistical testing unless indicated otherwise.
A summary will be provided for the following TEAEs for each treatment within each study part (Part 1 and 2) (Table 14.3.1.1):

- any AE
- any AE at least possibly related to study medication
- any serious AE
- any AE leading to early withdrawal
- any AE leading to death

The adverse events will be shown by MedDRA system organ class and preferred term, in order of descending overall frequency. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized for each treatment within each study part. Incidence tabulations will be provided for overall summary (Table 14.3.1.2), summary by highest severity (Table 14.3.1.3), and summary by relatedness (Table 14.3.1.4).

5.2 Clinical Laboratory Evaluations

Numeric measurements of hematology, blood chemistry and urinalysis will be evaluated. Following parameters will be reported:

Hematology

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

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

Urinalysis

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

Actual values of numerical lab results and changes from baseline will be summarized at Day 8 for each treatment within each study part (Table 14.3.2.1.1-

14.3.2.1.3). Shift tables from the baseline to Day 8 will be presented (Table 14.3.2.2.1-14.3.2.2.3). Categorical lab results will be included in the subject data listing (Listing 16.2.8).

5.3 Vital Signs

Summary statistics will be presented for the actual values and change from baseline values (as appropriate) at each collected time point for all vital signs measured at sitting position: Oral Temperature (Celsius), Heart Rate (bpm), Systolic Blood Pressure (mmHg), Diastolic Blood Pressure (mmHg), Respiratory Rate (breaths/min). Changes from baseline for blood pressures and heart rate will include Days 1, 2, 3, 4, 5, 6, 7, and 8, and changes from baseline for oral temperature and respiratory rate will include Days 1, 2, 5, and 8 for each treatment within each study part (Table 14.3.3).

5.4 Electrocardiogram

P-R interval (msec), QT interval (msec), QRS duration (msec), Ventricular heart rate (beats/min), QTcB intervals (msec) using Bazett's correction formula, and QTcF intervals (msec) using Fridericia's correction formula will be collected on CRF. The mean values of triplicate ECG assessments prior to dosing will be used as the baseline. Actual values and changes from baseline will be summarized at each scheduled timepoint (Day 8) for each treatment within each study part (Table 14.3.4.1). In addition, frequency tabulation of the overall ECG results (Normal, Abnormal NCS, and Abnormal CS) will be summarized (Table 14.3.4.2).

5.5 Physical Examinations

Physical examination data will be included in the subject data listing (Listing 16.2.11).

5.6 Drug, Alcohol, and Pregnancy Screen

Drug, alcohol, and pregnancy screen data will be included in the subject data listing (Listing 16.2.12).

6 EXPLORATORY

If adequate data are available, an analysis will be performed for PK profile (e.g., Tmax) in conjunction with time to occurrence of adverse events. A separate analysis plan will be prepared for such exploratory analysis.

7 CHANGES FROM PROTOCOL

The randomization section of this SAP (Section 1.4) has been revised from what was stated in the protocol section 8.1. Section 8.1 of the protocol stated "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." The revisions made in the SAP Section 1.4 reflect the cross-over design and is consistent with all other

parts of the protocol as well the separate randomization specifications document created for the study.

8 REFERENCES

None

9 TABLES, LISTINGS, AND FIGURES FOR CSR APPENDEX 14

Following tables are to be included in the post-text Appendix 14 of CSR, and may be modified with Sponsor's approval.

Number	Title	Population
T14.1.1	Analysis Populations	RAND
T14.1.2	Subject Disposition	RAND
T14.1.3.1	Demographics	RAND
T14.1.3.2	Tobacco and Alcohol Use	RAND
T14.1.4	Medical History by MedDRA System Organ Class and Preferred Term	RAND
T14.1.5	Concomitant Medication	SAF
T14.1.6	Treatment Exposure	SAF
T14.3.1.1	Summary of Treatment-Emergent Adverse Events	SAF
T14.3.1.2	Frequency of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	SAF
T14.3.1.3	Frequency of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term and by Highest Severity	SAF
T14.3.1.4	Frequency of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term and by Relatedness	SAF
T14.3.2.1.1	Changes in hematology measurements	SAF
T14.3.2.1.2	Changes in serum chemistry measurements	SAF
T14.3.2.1.3	Changes in urinalysis measurements	SAF
T14.3.2.2.1	Shift Table in hematology measurements	SAF
T14.3.2.2.2	Shift Table in serum chemistry measurements	SAF
T14.3.2.2.3	Shift Table in urinalysis measurements	SAF
T14.3.3	Changes from baseline in vital sign measurements	SAF
T14.3.4.1	Changes from baseline in Electrocardiogram measurements	SAF
T14.3.4.2	Frequency of overall Electrocardiogram results	SAF

10 LISTINGS FOR CSR APPENDEX 16.2

Number	Title	Population
L16.2.1.1	Screen Failures	SCRN
L16.2.1.2	Analysis Populations	RAND
L16.2.1.3	Subject Disposition	RAND
L16.2.1.4	Study Periods and Visits	RAND

Number	Title	Population
L16.2.2.1	Inclusion Criterion Not Met or Exclusion Criteria Met	RAND
L16.2.2.2	Randomization	RAND
L16.2.3.1	Demographics and Baseline Characteristics	RAND
L16.2.3.2	Tobacco and Alcohol Use	RAND
L16.2.4	Medical History	RAND
L16.2.5.1	Prior Medications	RAND
L16.2.5.2	Concomitant Medications	SAF
L16.2.6.1	Extent of Exposure	SAF
L16.2.6.2	Admission to and Discharge from CRU	SAF
L16.2.6.3	Meal Pre-Study Drug Administration, and Lunch and Dinner Post Study Drug Administration	SAF
L16.2.7	Treatment Emergent Adverse Events	SAF
L16.2.8	Clinical Laboratory Results	SAF
L16.2.9	Vital Signs	SAF
L16.2.10.1	Electrocardiogram Test Results	SAF
L16.2.10.2	Electrocardiogram Results – Clinical Significance	SAF
L16.2.11	Physical Examinations	SAF
L16.2.12	Drug, Alcohol, and Pregnancy Screen Results	SAF

11 ATTACHMENTS

None