PRODUCT: Lofexidine granules for reconstitution (oral)
PROTOCOL NUMBER / AMENDMENT: USWM-LX2-1001 / 4

SPONSOR:
USWM, LLC
4441 Springdale Rd.
Louisville, KY 40241
United States of America (USA)

TITLE:
A Study to Evaluate the Relative Bioavailability of a Test Formulation of Lofexidine Granules for Reconstitution and the Effect on Food on the Bioavailability of the Test Formula in Healthy Adult Subjects

DOCUMENT DATE: January 25, 2021
IND NUMBER: 47857
NCT NUMBER: NCT04188730

CONFIDENTIAL PROTOCOL

A study to evaluate the relative bioavailability of a test formulation of lofexidine granules for reconstitution and the effect of food on the bioavailability of the test formulation in healthy adult subjects

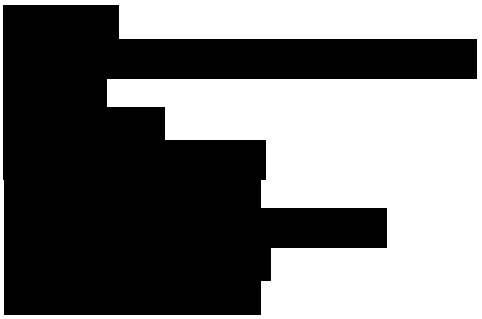
1.0 TITLE PAGE

DRUG PRODUCTS:	Lofexidine granules for reconstitution (oral), [redacted], final strength lofexidine 90 µg/mL LUCEMYRA® (lofexidine) tablets, EQ 0.18 mg base
DESIGN:	Open-Label, Single-Dose, Randomized, Three-Treatment, Three-Period, Four-Sequence, Crossover Study Evaluating Tablet (Fasted) versus Granules (Fasted) and the Effect of Food on the Granules (Fed versus Fasted)
POPULATION:	16 Healthy Adult Male and Female Subjects
SPONSOR:	USWM, LLC 4441 Springdale Rd. Louisville, KY 40241 United States of America (USA)
SPONSOR PROTOCOL NO.:	USWM-LX2-1001
[redacted]	[redacted]
ORIGINAL PROTOCOL DATE:	10/16/19
AMENDMENT 1 PROTOCOL DATE:	12/05/19
AMENDMENT 2 PROTOCOL DATE:	12/19/19
AMENDMENT 3 PROTOCOL DATE:	05 Oct 2020
AMENDMENT 4 PROTOCOL DATE:	25 Jan 2021
IND NO:	47857
CONTRACT RESEARCH ORGANIZATION:	[redacted]

CONFIDENTIAL PROTOCOL

A study to evaluate the relative bioavailability of a test formulation of lofexidine granules for reconstitution and the effect of food on the bioavailability of the test formulation in healthy adult subjects

SPONSOR REPRESENTATIVE:



Signature Date

This document is a confidential communication of [redacted]. *Receipt of this document constitutes an agreement by the recipient that no unpublished information contained herein will be disclosed without* [redacted] *written approval.*

Principal Investigator's Signature

I have received and read the Investigator's Brochure for lofexidine including the Package Insert. I agree to conduct Protocol No. USWM-LX2-1001 [redacted]) "A study to evaluate the relative bioavailability of a test formulation of lofexidine granules for reconstitution and the effect of food on the bioavailability of the test formulation in healthy adult subjects" in accordance with Good Clinical Practice (GCP), and all applicable regulations, including the Federal Food, Drug and Cosmetics Act., U.S. applicable Code of Federal Regulations (Title 21), and ICH Guidelines.

[redacted] Date

AMENDMENTS TO THE PROTOCOL

Amendments to the protocol after initial IRB approval are summarized below.

Amendment	Date	
4	25 Jan 2021	

The following update was made to the protocol dated 05 Oct 2020:

Throughout the protocol:

- At the request of the Sponsor, a third study period has been added to also evaluate the effect of food on the relative bioavailability of the test product. Updates to the study title, design, objectives, study conduct, study treatments, randomization, subject removal criteria, total blood volume collected during the study, pharmacokinetic and statistical analyses, and references have been made, as appropriate.
- At the request of the Sponsor, the volume of granules for reconstitution and dose volume administered to subjects has been removed from the protocol. A Pharmacy Manual will be provided by the Sponsor, which will include this information.

Section 1.0:

- Included IND number, for reference.

Section 5.3.3:

- For additional subject safety during the ongoing COVID-19 pandemic, "diabetes" and "respiratory conditions" have been added to Exclusion #3.

Section 5.7:

- Updated and rearranged based in accordance with current [redacted] protocol template.

Section 7.0:

- Updated reference for the FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency.

Amendment	Date	
3	05 Oct 2020	

The following update was made to the protocol dated 12/19/19:

Section 1.0:

- Updated the Principal Investigator from [redacted] to [redacted] In addition, Sponsor Representative and Key Study Personnel has been updated to current information.
- [redacted].
- Updated List of Abbreviations.

Sections 1.0, 5.7.1 and 6.5.5:

- In accordance with Sponsor request, updated to reflect that [redacted] and not [redacted] will conduct pharmacokinetic and statistical analyses.

Sections 5.1 and 5.3.4:

- Included [redacted] standard language for study conduct during the ongoing COVID-19 pandemic.

Section 5.4.1 and Synopsis:

- Updated dosing procedures after discussions between [redacted] and Sponsor.

Section 5.5.1:

- Updated the MedDRA version to the current version utilized by [redacted].

Section 5.5.2.2

- Updated SAE contact information, at Sponsor request.

Section 7.0:

- Added references for FDA Guidances on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency and Compliance Policy for the Quantity of Bioavailability and Bioequivalence Samples Retained Under 21 CFR 320.38(c). These documents are cited within the protocol, where appropriate and subsequent references have been updated accordingly.

Appendix 8.2:

- In accordance with the Note to File generated on 17 Jan 2020, the taste questionnaire has been updated to remove "flavor" from the Taste Assessment evaluation.

Amendment	Date
2	12/19/19

The following update was made to the protocol dated 12/05/19:

Section 1.0:

- Updated the Principal Investigator from [redacted] to Carmelo [redacted]

Amendment	Date
1	12/05/19

Based on feedback on the protocol from NIDA for subject safety, the following updates were made to the protocol dated 10/16/19:

Sections 5.3.1.1 and 5.3.3:

- Screening blood pressure limit requirements were updated and an orthostatic blood pressure assessment/requirements at screening were added.

Sections 5.3.4 and 5.5.5:

- Added pre-dose blood pressure requirements for subject dosing eligibility as well as safety instructions for if a subject experiences clinically significant hypotension during the study.

KEY STUDY PERSONNEL

PRINCIPAL INVESTIGATOR: [redacted]

MEDICAL MONITOR: [redacted]

CLINICAL MANAGER: [redacted]

QUALITY ASSURANCE: [redacted]

SCIENTIFIC AFFAIRS: [redacted]

BIOANALYTICAL: [redacted]

STUDY FACILITIES

CLINICAL FACILITY: [redacted]

PHARMACOKINETICS/STATISTICS: [redacted]

INSTITUTIONAL REVIEW BOARD: [redacted]

BIOANALYTICAL LABORATORY: [redacted]

GENOTYPING FOR CLINICAL SAMPLES: [redacted]

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ANOVA	Analyses of Variance
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the time of last measurable concentration
BLQ	Below Limit of Quantitation
BMI	Body Mass Index
°C	Degrees Celsius
CDER	Center for Drug Evaluation and Research
C_{max}	Maximum observed plasma concentration
CL/F	Apparent total clearance of the drug from plasma
COVID-19	Coronavirus Disease of 2019
CNS	Central Nervous System
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
C_t	Last measurable plasma concentration
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EQ	Equivalent to
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GLM	General Linear Model
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	Intrauterine device
λ_z	Apparent first-order terminal rate constant
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
ng	Nanogram

Abbreviation	Definition
[redacted]IRB	[redacted] Institutional Review Board
OTC	Over-the-counter
PK	Pharmacokinetic
QA	Quality Assurance
RLD	Reference Listed Drug
RS	Reference Standard
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
$t_{½}$ or $T_{½}$	Apparent first-order terminal half-life
THC	Tetrahydrocannabinol
T_{max}	Time of maximum observed plasma concentration
USA	United States of America
V_Z/F	Apparent volume of distribution during the terminal phase

STUDY SYNOPSIS

Drug Products:	Lofexidine granules for reconstitution (oral), [redacted], final strength lofexidine 90 µg/mL LUCEMYRA® (lofexidine) tablets, EQ 0.18 mg base
Study Phase:	Comparative Bioavailability, Phase I Study
Agency of Submission:	United States (U.S.) Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER)
Study Objectives:	The primary objectives of this study are to evaluate the relative bioavailability of a test formulation of lofexidine granules for reconstitution (oral), final concentration 90 µg/mL ([redacted]) compared to the Orange Book RS/RLD product, LUCEMYRA tablets, EQ 0.18 mg base (US WorldMeds, LLC) under fasted conditions and to evaluate the effect of food on the relative bioavailability of lofexidine granules for reconstitution (oral) when administered under fed compared to fasted conditions, following a single 0.36 mg dose to healthy adult male and female subjects. The secondary objective is to assess the safety and tolerability of a single 0.36 mg oral dose of lofexidine granules for reconstitution formulation when administered to healthy subjects under fasted and fed conditions.
Study Design:	Open-label, single-dose, randomized, three-treatment, three-period, four-sequence, crossover study evaluating tablet (fasted) versus granules (fasted) and the effect of food on the granules (fed versus fasted).
Subject Population:	The subject population will include 16 healthy, non-tobacco-, non-nicotine-using adult male and female subjects who satisfy all entry criteria.
Study Treatments:	**Treatment A**: Lofexidine oral solution (90 µg/mL) reconstituted from Lofexidine Granules for Reconstitution (Oral)(Manufactured by [redacted]) – 0.36 mg total dose Administered following an overnight fast of at least 10 hours. **Treatment B**: 2 × LUCEMYRA Tablets, EQ 0.18 mg base (US WorldMeds, LLC) – 0.36 mg total dose Administered following an overnight fast of at least 10 hours. **Treatment C:** Lofexidine oral solution (90 µg/mL) reconstituted

	from Lofexidine Granules for Reconstitution (Oral)(Manufactured by [redacted]) – 0.36 mg total dose Administered 30 minutes after the start of an FDA-recommended standardized high-fat, high-calorie breakfast preceded by an overnight fast of at least 10 hours. The volume of lofexidine granules for reconstitution and dose volume to be administered to subjects (Treatments A and C) will be included in the Pharmacy Manual, to be provided by the Sponsor prior to study start.
Treatment Administration:	Eligible subjects will receive a 0.36 mg oral dose of the test (Treatment A and C) or reference (Treatment B) treatment according to a three-treatment, four-sequence randomization schedule under direct observation. **Treatments A and C** Treatment A will be administered following an overnight fast of at least 10 hours. Treatment C will be administered at 30 minutes after the start of an FDA-recommended standardized high-fat, high-calorie breakfast preceded by an overnight fast of at least 10 hours. Lofexidine will be supplied as granules for reconstitution (oral), [redacted]. The granules will be reconstituted no more than 2 hours prior to dosing according to the instructions outlined in Section 5.4.1. [redacted] [redacted] Following this, the subjects will be provided with a volume of room temperature

	distilled water to drink such that the total volume of the oral suspension administered, the volume of rinse, and the water provided after the dose equals 240 mL (i.e., volume of dose + volume of rinse + volume of additional water = 240 mL). Immediately after, a mouth check will be performed to confirm that the oral solution, mouth rinse and additional water have been swallowed. **Treatment B** Subjects will be administered one dose of 2 × 0.18 mg LUCEMYRA tablets following an overnight fast of at least 10 hours. The dose will be administered with 240 mL of room temperature distilled water. Subjects will be instructed to swallow the two tablets whole without chewing or biting. Any subject who bites or chews the tablets will be discontinued from the study. Immediately after dosing a mouth check will be performed to confirm that the tablets were swallowed whole without chewing or biting. The volume of lofexidine granules for reconstitution will be administered to subjects in accordance to the instructions included in the Pharmacy Manual, to be provided by the Sponsor prior to study start. Additionally, dose preparation and administration procedures will be generated by [redacted] Pharmacy department and approved by the Sponsor before initial dosing in Period I.
Taste Assessment for Treatments A or C:	Within 10 minutes after completion of the dosing procedure for the subject's first dose of lofexidine granules (Treatment A or C), each subject will be required to complete a Taste Assessment Questionnaire (see Appendix 8.2). The taste assessment will be completed once by each subject, after the subject's first dose of lofexidine granules, whether administered in the fed or fasted state.
Plasma Sample Collection:	Blood samples will be collected pre-dose (0-hour, within 45 minutes prior to dosing and before breakfast, if applicable [relative to the dosing minute]) and at 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 7.0, 10.0, 16.0, 24.0, 30.0, 36.0, 48.0 and 54.0 hours post-dose; 17 samples/period in 6 mL K_2EDTA vacutainers. The total maximum volume of blood collected for pharmacokinetic sampling may be up to 306 mL. [redacted] The total volume of blood collected during this study is anticipated to be

	approximately 352.5 mL for male subjects and approximately 367.5 mL for female subjects.
Bioanalytical:	Concentrations of lofexidine in plasma will be measured by [redacted] using a fully validated analytical method.
Safety monitoring:	Safety will be assessed by qualified study staff by evaluating the following: reported adverse events, clinical laboratory test results, vital sign measurements, ECG findings, Columbia-Suicide Severity Rating Scale (C-SSRS) assessments, physical examination (including height and body weight measurements at screening) and concomitant medication usage.
Confinement:	Subjects will enter the clinical facility on Day -1 at least 10.5 hours before dosing and will remain confined until at least 54 hours after dosing in each study period.
Returns:	None
Washout Period:	The interval between doses will be at least 7 days.
Study Duration:	Approximately 45 days from the start of screening to the last clinical event.
Pharmacokinetic Parameters:	AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, λ_z $T_{½}$, CL/F and Vd/F
Statistical Analyses:	Confidence intervals (90%) on the geometric mean ratios (obtained from logarithmic transformed data) for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for the comparison of Treatment A to Treatment B (to compare the test formulation and reference product under fasted conditions) and the comparison of Treatment C to Treatment A (to compare the granules for reconstitution [test formulation] under fed and fasted conditions) will be constructed to test two-one-sided hypotheses at the $\alpha = 0.05$ level of significance. Descriptive statistics (n, mean, SD, % coefficient of variation (%CV), minimum, median, maximum) will be reported for lofexidine concentrations at each time point by treatment. Descriptive statistics (n, mean, SD, % coefficient of variation (%CV), geometric mean, minimum, median, maximum) will be reported for all PK parameters. A description of all of the statistical analyses will be provided in the Statistical Analysis Plan (SAP).

2.0 TABLE OF CONTENTS

3.0 INTRODUCTION

[redacted]

LUCEMYRA is well absorbed and pharmacokinetics are approximately dose-proportional

4.0 STUDY OBJECTIVES

The primary objectives of this study are to evaluate the relative bioavailability of a test formulation of lofexidine granules for reconstitution (oral), final concentration 90 µg/mL (compared to the Orange Book RS/RLD product, LUCEMYRA tablets, EQ 0.18 mg base (US WorldMeds, LLC) under fasted conditions and to evaluate the effect of food on the relative bioavailability of lofexidine granules for reconstitution (oral) when administered under fed compared to fasted conditions, to healthy adult male and female subjects.

The secondary objective is to assess the safety and tolerability of a single 0.36 mg oral dose of lofexidine granules for reconstitution formulation when administered to healthy subjects under fasted and fed conditions.

5.0 INVESTIGATIONAL PLAN

5.1 Study Design and Plan Description

This is an open-label, single-dose, randomized, three-treatment, three-period, four-sequence, crossover study comparing equal doses of the test formulation and reference product under fasted conditions and comparing the bioavailability of the granules for reconstitution [test formulation] under fed and fasted conditions. In two of the study periods, a single 0.36 mg dose of lofexidine will be administered to subjects following an overnight fast of at least 10 hours. In a third study period, a single 0.36 mg dose of lofexidine will be administered 30 minutes after the start of an FDA-recommended standardized high-fat, high-calorie breakfast preceded by an overnight fast of at least 10 hours. The subjects will receive either lofexidine granules for reconstitution (oral)† (Treatment A or C) or two (2) LUCEMYRA tablets, EQ 0.18 mg base (Treatment B). The subjects will receive the test formulation in two of the study periods and the reference product in a third study period according to a four-sequence randomization schedule. Serial blood samples will be collected at pre-dose and at specified time points over 54 hours after dosing in each study period. Subjects will be confined at the clinical facility from at least 10.5 hours before dosing

until after the 54-hour blood sample collection in each study period. The interval between doses will be at least 7 days.

† The volume of lofexidine granules for reconstitution to be administered to subjects will be included in the Pharmacy Manual, to be provided by the Sponsor prior to study start.

The plasma concentrations of lofexidine will be measured by fully validated analytical procedures. Statistical analysis using an average bioavailability approach will be performed to estimate the bioavailability of the test formulation relative to the reference product under fasted conditions. The bioavailability of the granules for reconstitution [test formulation] under fasted and fed conditions will also be compared.

If study conduct is disrupted as a result of the COVID-19 pandemic, contingency measures implemented to manage study conduct will be discussed within the final report.

5.2 Selection of Study Design

The study was designed based on the known pharmacokinetics of LUCEMYRA tablets and generally accepted standards for the conduct of bioavailability studies under fasted and fed conditions.[1-7]

To minimize any possibility of a carry-over effect, a washout period of at least 7 days was selected for this study.

5.3 Selection of Study Population

The subject population will include 16 healthy, non-tobacco-, non-nicotine-using adult male and female subjects who satisfy all entry criteria.

5.3.1 Screening

5.3.1.1 Health Assessments

The following health assessments will be performed within 28 days before initial study dosing (unless otherwise specified):

1. Medical and social history, sitting/supine vital sign assessment (temperature, respiration rate, pulse, and blood pressure) and orthostatic blood pressure assessment (within 3 minutes of standing from a sitting/supine position), physical examination (including height and weight), and 12 lead ECG (conducted in triplicate).
2. Clinical laboratory tests, including electrolytes (12.5 mL blood collection and urine sample) – see Appendix 8.1.1.
3. Follicle stimulating hormone (FSH) test, if applicable – see Appendix 8.1.6.
4. HIV, Hepatitis B surface antigen and Hepatitis C antibody screen (17 mL blood collection) – see Appendix 8.1.1.

5. Urine drug panel – see Appendix 8.1.3.
6. Serum pregnancy test; females only (5 mL blood collection) – see Appendix 8.1.5.

5.3.1.2 Demographics

The name, birth date, sex, race, ethnicity, body weight, and height will be recorded for each subject.

5.3.2 Inclusion Criteria

1. Males and females, 18-50 years of age, inclusive, with a Body Mass Index (BMI) of 20.0-35.0 kg/m², inclusive. BMI will be calculated using [redacted] Standard Operating Procedures (BMI [kg/m^2] = 703 × weight (lbs) / [height (in)] ^{2}).
2. Female subjects must meet **at least** one of the following criterion:
   - Agree to abstain from sexual intercourse from screening and throughout the duration of the study.
   - Have used and agree to continue to use a reliable method of contraception (e.g., condom with spermicide, IUD, hormonal contraceptives) for at least 30 days before initial dosing and throughout the duration of the study.
   - Surgically sterile (bilateral oophorectomy or hysterectomy, bilateral tubal ligation or Essure® device placement at least 3 months prior to initial dosing).
   - At least 1 year postmenopausal and have a documented FSH level ≥ 40 mIU/mL at screening.
3. Good health as determined by lack of clinically significant abnormalities in health assessments performed at screening.
4. Signed and dated informed consent form, which meets all criteria of current FDA regulations.

5.3.3 Exclusion Criteria

1. Females who are pregnant, lactating, or likely to become pregnant during the study.
2. History of allergy or sensitivity to lofexidine or any component of the study drug or history of any drug hypersensitivity or intolerance which, in the opinion of the Investigator, would compromise the safety of the subject or the study.
3. Significant history or current evidence of chronic infectious disease, system disorders, or organ dysfunction, especially cardiovascular disorders (e.g., severe coronary insufficiency, recent myocardial infarction [within 1 year before initial dosing], cerebrovascular disease),

respiratory disorders, congenital long QT syndrome, diabetes, hepatic or renal disorders (e.g., chronic renal failure).

4. Pulse < 50 bpm or symptomatic bradycardia, as determined by the Investigator.
5. Clinically significant history of hypotension, as determined by the Investigator, or has a sitting/supine systolic blood pressure < 90 mmHg and/or diastolic blood pressure < 60 mmHg, **or** hypertension, as determined by the Investigator, or has sitting/supine systolic blood pressure > 190 mmHg and/or diastolic > 95 mmHg; determined at screening.
6. Experiences reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg within 3 minutes of standing from a resting (sitting or supine) position; determined at screening.
7. 12-lead ECG, conducted in triplicate, considered by the Investigator to be clinically significant (e.g., second or third degree heart block, uncontrolled arrhythmia) or has a QTcF (Fridericia's correction) interval > 440 msec in 2 of the 3 ECGs performed; determined at screening.
8. Clinically significant history or presence of any gastrointestinal disease or history of malabsorption within the last year, as determined by the Investigator.
9. History of any psychiatric disorders occurring within the last two years that required the subject to be hospitalized or treated with medication.
10. Subject has history of suicidality based on responses provided on the Columbia-Suicide Severity Rating Scale (C-SSRS), or is at risk for self-harm or harm to others based on clinical interview, at the discretion of the Investigator.
11. Ingestion of grapefruit-containing food or beverages (e.g., Fresca®) within 7 days before dosing.
12. Ingestion of alcohol- or caffeine/xanthine-containing food or beverages (e.g., chocolate, coffee, tea, cola) or energy drinks (e.g., Red Bull, 5-Hour Energy®, Monster Energy®) within 72 hours before dosing.
13. Use of any over-the-counter (OTC) medication, nutritional or dietary supplements, or vitamins within 7 days before dosing.
14. Use of any prescription drugs (except hormonal contraceptives) within 14 days before dosing.
15. Use of pharmacologic agents known to significantly induce or inhibit drug-metabolizing enzymes (especially drugs that induce or inhibit CYP2D6 such as bupropion, fluoxetine, metoclopramide, paroxetine, quinidine or glutethimide) within 30 days before initial dosing.

16. Use of benzodiazepines, other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, barbiturates, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids) or methadone within 14 days before initial dosing.
17. Receipt of any drug as part of a research study within 30 days before initial dosing.
18. Drug or alcohol addiction requiring treatment in the 12 months before initial dosing.
19. History of excessive alcohol consumption (on average more than 14 units of alcohol/week) during the past 12 months.
20. Donation or significant loss of whole blood (480 mL or more) within 30 days or plasma within 14 days before initial dosing.
21. Positive test results for HIV, Hepatitis B surface antigen, or Hepatitis C antibody.
22. Positive test results for drugs of abuse (benzodiazepines, cocaine, cannabinoids/THC, opiates and at screening only: amphetamines, barbiturates, methadone and phencyclidine).
23. Positive test results for alcohol at check-in.
24. If female, has a positive pregnancy test.
25. Use of tobacco or nicotine-containing products within 30 days before initial dosing.

Subjects who fail to meet eligibility criteria at Screening may be eligible to rescreen, at the Investigator's discretion, during the 28-day screening period.

Violations of the above restrictions may result in the Investigator excluding the subject from entering the study, or discontinuing the subject's ongoing participation. Individual exceptions to the above restrictions, that the Investigator does not believe will affect subject safety or the integrity of the study data, may be allowed if approved by Sponsor's Representative.

5.3.4 Removal of Subjects from the Study

Subjects will be informed that they are free to withdraw from the study at any time and for any reason or, if necessary, the Investigator or Sponsor may withdraw a subject from the study to protect the health of a subject. A subject may also be withdrawn for not complying with study procedures. The final report will include reasons for withdrawals, adverse events and any necessary medical treatment.

The Period I pre-dose safety ECG will be collected in triplicate and must show QTcF findings that remain ≤ 440 msec on two of the three recordings for the subject to be eligible to receive study drug in Period I. If two of the three QTcF intervals exceed 440 msec, the subject will not be eligible to receive the study

drug in Period I and will be discontinued from further participation in the study.

The Periods II and III check-in and pre-dose safety ECGs will be collected in triplicate and must show QTcF findings that are ≤ 440 msec on two of the three recordings for the subject to be eligible to receive study drug in the respective study period. If two of the three QTcF intervals exceed 440 msec, the subject will not be eligible to receive the study drug in the respective study period. The subject may participate in subsequent periods of the study, as applicable, at the discretion of the Investigator.

Any subject with a QTcF interval exceeding 500 msec at any safety ECG reading (as applicable, see Section 5.5.5), will be discontinued from the study.

The subject must have a pre-dose systolic blood pressure ≥ 90 mmHg to be eligible for dosing in the respective study period. If the subject's pre-dose systolic blood pressure is < 90 mmHg, the assessment must be repeated 2 additional times, 10 minutes apart. If two of the three systolic blood pressure measurements are < 90 mmHg, the subject will not be eligible to receive the study drug in the respective study period. The subject may participate in subsequent periods of the study, as applicable, at the discretion of the Investigator.

Subjects who experience a serious AE due to hypotension or bradycardia in a specific study period will not be eligible to participate in subsequent periods of the study. In such a case, observations and sample collections should be completed for the subject following dosing in the respective study period and the subject will then be discontinued from the study (i.e., will not receive the dose in subsequent periods of the study).

Any subject who experiences emesis within 10 hours of dosing (based on two times the anticipated maximum T_{max} of about 5 hours for lofexidine) will be discontinued from the specific study period.[5] The subject may participate in subsequent periods of the study, as applicable, at the discretion of the Investigator.

In addition, in accordance with the FDA Guidance on the Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency, study discontinuations due to COVID-19 will be documented in the subject's eCRF and summarized in the final report.[8]

Subjects who are discontinued or withdraw from study participation should remain in the clinical facility until such time as the Investigator considers it safe for the subject to be discharged. Subjects who are discontinued or withdraw from the study will not be replaced.

5.4 Treatments

5.4.1 Treatment Administration

Eligible subjects will receive a 0.36 mg oral dose of the test formulation (Treatment A or C) or reference product (Treatment B) according to a three-treatment, four-sequence randomization schedule under direct observation.

Treatments A and C

Treatment A will be administered following an overnight fast of at least 10 hours. Treatment C will be administered at 30 minutes after the start of an FDA-recommended standardized high-fat, high-calorie breakfast preceded by an overnight fast of at least 10 hours.

Lofexidine will be supplied as granules for reconstitution (oral), [redacted]. The granules will be reconstituted no more than 2 hours prior to dosing according to the instructions that follow:

The volume of lofexidine granules for reconstitution will be administered to subjects in accordance to the instructions included in the Pharmacy Manual, to be provided by the Sponsor prior to study start. Additionally, dose preparation and administration procedures will be generated by [redacted] Pharmacy department and approved by the Sponsor before initial dosing in Period I.

[redacted]

[redacted] Following this, the subjects will be provided with a volume of room temperature distilled water to drink such that the total volume of the oral suspension administered, the volume of rinse, and the water provided after the dose equals 240 mL (i.e., volume of dose + volume of rinse + volume of additional water = 240 mL). Immediately after, a mouth check will be performed to confirm that the oral solution, mouth rinse and additional water have been swallowed.

Within 10 minutes after completion of the dosing procedure for the subject's first dose of lofexidine granules (Treatment A or C), each subject will be required to complete a Taste Assessment Questionnaire (see Appendix 8.2). The taste assessment will be completed once by each subject, after the subject's first dose of lofexidine granules, whether administered in the fed or fasted state.

Treatment B

Subjects will be administered one dose of 2 × 0.18 mg LUCEMYRA tablets following an overnight fast of at least 10 hours. The dose will be administered with 240 mL of room temperature distilled water. Subjects will be instructed to swallow the two tablets whole without chewing or biting. Any subject who bites or chews the tablets will be discontinued from the study. Immediately after dosing a mouth check will be performed to confirm that the tablets were swallowed whole without chewing or biting.

5.4.2 Identity of Investigational Products

The following products will be used in this study:

Test: Lofexidine Granules for Reconstitution (Oral), [redacted], final strength lofexidine 90 µg/mL (Manufactured by [redacted])

Reference: LUCEMYRA Tablets, EQ 0.18 mg base (US WorldMeds, LLC)

The following treatments will be used in this study:

Treatment A: Lofexidine oral solution (90 µg/mL) reconstituted from Lofexidine Granules for Reconstitution (Oral) (Manufactured by [redacted]) – 0.36 mg total dose

Administered following an overnight fast of at least 10 hours.

Treatment B: 2 × LUCEMYRA Tablets, EQ 0.18 mg base (US WorldMeds, LLC) – 0.36 mg total dose

Administered following an overnight fast of at least 10 hours.

Treatment C: Lofexidine oral solution (90 µg/mL) reconstituted from Lofexidine Granules for Reconstitution (Oral) (Manufactured by [redacted]) – 0.36 mg total dose

Administered 30 minutes after the start of an FDA-recommended standardized high-fat, high-calorie breakfast preceded by an overnight fast of at least 10 hours.

The volume of lofexidine granules for reconstitution to be administered to subjects (Treatments A and C) will be included in the Pharmacy Manual, to be provided by the Sponsor prior to study start.

The same lot of each product will be used during the entire study.

As applicable, the Sponsor should notify [redacted] before shipment of study drug to the clinic. Drug should be shipped to the attention of the Pharmacy at the following address:

Attn: Pharmacy
[redacted]

5.4.3 Method of Assigning Subjects to Treatment Groups

Treatments will be administered according to a three-treatment, three-period, four-sequence design as outlined below. The randomization will be generated in blocks of four with each sequence occurring once in each block.

Sequence	Period I	Period II	Period III
1 (N=4)	Treatment B	Treatment A	Treatment C
2 (N=4)	Treatment B	Treatment C	Treatment A
3 (N=4)	Treatment A	Treatment C	Treatment B
4 (N=4)	Treatment C	Treatment A	Treatment B

Treatment A = Lofexidine granules – fasted conditions
Treatment B = LUCEMYRA tablets – fasted conditions
Treatment C = Lofexidine granules – fed conditions

The randomization schedule will be generated by the Biostatistics Department at [redacted] before the first dosing period using SAS®, Version 9.4 or higher.

5.4.4 Study Conduct

Confinement: Subjects will enter the clinical facility on Day -1 at least 10.5 hours before dosing and will remain confined until at least 54 hours after dosing in each study period.

Returns: None

Washout: The interval between doses will be at least 7 days.

Fasting: During the fasted periods of the study (Treatments A and B) all subjects will fast (except water) for at least 10 hours before dosing. During the fed period of the study (Treatment C) all subjects will fast (except water) for at least 10 hours prior to receiving a standardized high-fat, high-calorie breakfast.

After dosing, subjects will fast until at least 4 hours post-dose.

Meals: A meal will be served on the evening of Day -1 and consumed at least 10 hours before dosing or receiving a standardized high-fat, high-calorie breakfast (as applicable for each study period). During confinement, the subjects should consume only the food and beverages provided.

In the fed period of the study (Treatment C), subjects should start a FDA-recommended standardized high-fat, high-calorie breakfast 30 minutes prior to dosing and should consume this meal within the 30 minutes before dosing.

A standard meal will be provided at 4 hours after dosing in each study period. Meals after 4 hours will be scheduled at appropriate times by the clinic. For all subjects, during confinement, the same meal plan will be used in each period of the study. When meals and blood sample collections coincide, samples will be collected before meals are served.

Fluids: Fluids will be restricted from four (4) hours before dosing until eight (8) hours after dosing, with the exception of 240 mL water administered with the dose, scheduled water administrations and milk given with breakfast (fed study period only). At -4, -3, -2 and -1 hours (± 15 minutes) before dosing all subjects will be required to drink 300 mL of room temperature water and at 2, 4, 6 and 8 hours (± 15 minutes) after dosing, all subjects will be required to drink 240 mL of room temperature water. Water will be encouraged *ad lib* at all other times. No fluids other than water and those served with meals will be permitted.

Ambulatory: For safety purposes, subjects will be confined to bed for the first 8 hours post-dose and should remain sitting upright or supine during this time, except as required for study procedures. Subjects will be escorted by site staff when out of bed for the first 8 hours post-dose. If a subject is experiencing an Adverse Event or other medical conditions that prevents the subject from remaining sitting upright for safety reasons, the subject may be allowed to lie down, at the discretion of the Investigator. No strenuous activity will be permitted during confinement.

Tobacco: The use of tobacco or nicotine-containing products is prohibited from 30 days before initial dosing and throughout the duration of the study.

5.5 Safety Evaluation

An Investigator will be present at the clinical facility for dosing and available by cell phone throughout the study.

5.5.1 Adverse Events (AEs)

Adverse events (AEs) will be assessed and recorded daily after each dosing, as needed by study staff during clinic confinement, and end of study (or upon early termination, if applicable). If an AE requires medical attention, it will be reported to a study Investigator immediately. A study Investigator, or qualified designee, must meet with the subject, if possible, to assess all medical and psychiatric AEs reported by the subject, as well as those recorded by other study staff.

AEs will be collected through both solicited and unsolicited means and subsequently coded in tabular form using the MedDRA Version 23.0 or higher adverse event dictionary. The subjects will be encouraged to report signs, symptoms, and any changes in health to the clinic staff.

Adverse events will be assessed by asking the subject, "How have you been feeling since I saw you last?" After current AEs are assessed, the study Investigator must review with the subject and assess any AEs unresolved from the previous day. After each daily AE assessment, the Investigator (or designee) will record in the subject's source document and AE eCRF, according to the procedures described in Section 5.5.1.3, the type of AE and whether serious or non-serious, severity of each AE, and the relationship to the study drug. These categories are asking for the Investigator's best judgment of the severity and relatedness of each AE.

Any study subject with a related AE will be followed by the Investigator until the event is resolved to the satisfaction of the Principal Investigator and Sponsor's Medical Monitor. If the AE is unrelated, the subject will not be discharged until medically stable, and then will be referred, at the subject's sole expense, for ongoing care and/or treatment, which may include psychological and lifestyle counseling, support groups, or pharmacological and medical treatment.

5.5.1.1 Definitions

Adverse Event

Per 21 Code of Federal Regulations (CFR) 312.32, an AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, such an occurrence is considered an AE if it occurs after the Investigational Medicinal Product (IMP) has been administered. An AE includes any noxious, pathologic, or unintended change in anatomic, physiologic, or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes.

[redacted]. Study events occurring after signing informed consent but prior to IMP administration are to be documented in the subject's medical history source and eCRF.

Serious Adverse Event

Per 21CFR.312.32, an SAE is an AE occurring after administration of the IMP at any dose, comparator or placebo, that fulfils one or more of the following:

1. Results in death during the period of protocol-defined surveillance
2. Is life-threatening *(NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject, in the view of the Investigator, was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)*
3. Requires inpatient hospitalization or prolongation of existing hospitalization
4. Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
5. Results in a congenital anomaly/birth defect
6. Is an important medical event

Hospitalization: Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it might be (e.g., bronchospasms, laryngeal edema). Hospital admission and/or surgical operations planned before or during a study are not considered SAEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study. It should be noted that for this study, subjects with planned or anticipated surgery will not be enrolled into the study.

Important Medical Events: Important medical events are events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above. Examples of important medical events include adverse events that suggest a significant hazard, contraindication or precaution, occurrence of malignancy or development of drug dependency or drug abuse. Medical and scientific judgment should be exercised in deciding whether events qualify as medically important. All SAEs will be assessed and recorded by the Investigator as detailed in Sections 5.5.1.2 and 5.5.1.3.

5.5.1.2 Relationship of Adverse Event to IMP

For each AE, the Investigator must assess the attribution of the IMP to the AE and determine whether the AE is related or not related to the study or test drug as defined below. When in doubt, the AE will be considered "related" until further evidence becomes available to refute this assessment.

- **Unrelated:** Clinical event with an incompatible time relationship to IMP administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the IMP.
- **Related:** Clinical event with a reasonable or plausible time relationship to IMP administration and that is unlikely to be attributed to or cannot be explained by concurrent disease or other drugs or chemicals.

5.5.1.3 Recording Adverse Events

All AEs and details for the events will be recorded in the subject's source document and Adverse Event eCRF. An AE should be documented in terms of a medical diagnosis and reported in standard medical terminology when possible. When this is not possible, the AE will be documented in terms of signs and/or symptoms observed or reported. It is important for the Investigator to only record 1 AE per line on the eCRF. Combination events (e.g., nausea/vomiting), should not be entered as 1 event, but 2 events.

AEs can be collected by either the Investigator and/or designee; however, the Investigator must determine the intensity of the AE as defined by:

- **Mild:** no medical interventions required, short lasting discomfort, and does not interfere with subject's daily activities
- **Moderate:** activity may be limited and subject may require minimal medical therapy, intervention, or assistance
- **Severe:** definitely limits subject's daily activity that may require hospitalization and or intervention/therapy assess whether or not the IMP caused the AE

The Investigator or designee will record whether the AE or AEs led to discontinuation of the subject from the study, record the outcome of the AE (unresolved, resolved, resolved with sequelae, death, or unknown), and determine if the AE is serious.

For this study, AEs and SAEs will be collected beginning with the start of dosing on Day 1 and will end at study completion. All adverse events encountered during the study will be reported on the appropriate form and summarized in the final report.

5.5.1.4 Follow-up of Adverse Events

The clinical course of each AE will be followed until resolution, stabilization, until it has been determined that the study treatment or participation is not the cause, or if subject is declared lost to follow-up. SAEs that are still ongoing at the end of the study period must be followed to determine the final outcome. The Investigator must provide the Sponsor with all relevant follow-up information necessary to facilitate a thorough understanding of the event and judgment regarding the relationship to the IMP. If a subject discontinues participation due to an AE/SAE that is at least possibly related to the IMP, the subject will be followed until the event has resolved, stabilized or otherwise explained, or if subject is declared lost to follow-up. This telephone contact will be documented in source.

5.5.2 Expedited Reporting of Events

5.5.2.1 Events Requiring Expedited Reporting to [redacted]

The following events will be forwarded to the Sponsor's pharmacovigilance group, [redacted], via the study Event Form within 24 hours of becoming aware of any of the following events:

- All SAEs, regardless of causality
- Overdose (with or without an AE)
- Inadvertent or accidental exposure
- Pregnancy
- Unexpected therapeutic benefit

5.5.2.2 Timeframe for Collecting and Reporting Serious Adverse Events and Other Immediately Reportable Events

SAEs and other events requiring expedited reporting occurring after administration of the IMP and through study completion (or for discontinued subjects, within 7 days after his/her last dose of the IMP) must be reported to [redacted] ***within 24 hours*** of the time any study staff member is made aware of the event. The study SAE Form must be completed and emailed to [redacted] and to relevant study team members or faxed to [redacted] Additional eCRF and/or source documentation may need to be supplied to [redacted].

SAEs should also be reported to the [redacted] IRB within 24 hours (or 48 hours, if occurring on a weekend) of the time any study staff member is made aware of the event.

5.5.2.3 Regulatory Notification

USWM is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB or IEC of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events that occur during the

clinical trial. Each site is responsible for notifying his or her IRB or IEC of these additional SAEs.

Under 21 CFR 312.32(c)(l), the Sponsor must notify the FDA and all participating investigators in an IND safety report as soon as possible but no later than 15 calendar days after the Sponsor's safety physician determines that the unexpected or suspected adverse reaction or other information qualifies for reporting. The Sponsor must report any suspected adverse event that is both serious and unexpected. Before submitting an IND safety report, the Sponsor must report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the AE.[9]

Under 21 CFR 312.32(c)(2), any unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and, therefore, must be reported more rapidly to FDA. The requirement for reporting any unexpected fatal or life-threatening suspected adverse reaction by Sponsor to FDA is no later than 7 calendar days after the sponsor's safety physician initial receipt of the information. If the safety report submitted within 7 calendar days is complete, an additional submission within 15 days from day zero is not required (21 CFR 312.32(c)(1)(v)).[9]

5.5.3 Pregnancy

Although pregnancy is not considered an AE, it is the responsibility of the Investigator to report any pregnancy in a female subject (spontaneously reported to them or discovered during a protocol-defined pregnancy test) that occurs during the study or within 7 days after the day during which the subject received her last dose of the IMP to [redacted] within 24 hours (or 48 hours, if occurring on a weekend), using the contact information outlined in Section 5.5.2.2.

All female subjects who become pregnant must be discontinued immediately and must be followed, at appropriate intervals, until completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) and status of mother and child must also be reported to [redacted].

The [redacted] IRB should be reported about any pregnancies that occur in the study.

Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. Any SAE that occurs during pregnancy must be recorded on the SAE report form (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours (or 48 hours, if occurring on a weekend) to the Sponsor in accordance with the procedure for reporting SAEs.

5.5.4 Clinical Laboratory Evaluations

All subjects will be screened for alcohol, and marijuana (THC), cocaine, benzodiazepine, and opiate metabolites using immediate saliva/urine testing

at check-in each study period (see Appendix 8.1.4). Subjects with positive results will be withdrawn from the study.

All female subjects will have a urine pregnancy test performed at check-in each study period (see Appendix 8.1.5). Subjects with positive results will be withdrawn from the study.

A 12.5 mL sample of blood will be collected after the last pharmacokinetic blood sample in Period III (or early termination) for a post-study hematology and clinical chemistry determination and a urine sample for urinalysis (see Appendix 8.1.1). Subjects will be instructed to not donate blood or plasma until at least 30 days after the last dose of study medication.

In Period I, a blood sample for genotyping to determine CYP2D6 genotype/lofexidine metabolizer status will be obtained at the time of the pre-dose (Day 1, 0-hour) pharmacokinetic sample (see Appendix 8.1.2). This sample will only be analyzed, if needed, upon review of the PK results, as determined by the Sponsor.

All female subjects will have a serum pregnancy test performed at the end of the study (or early termination) (see Appendix 8.1.5).

5.5.5 Vital Signs and Other Safety Assessments

Additional vital sign assessments or safety evaluations may be performed at the discretion of the Investigator.

Vital Sign Assessments

Vital signs (temperature, pulse, and blood pressure) will be measured in the sitting position at check-in of each study period.

Blood pressure and pulse (sitting) will be measured at pre-dose (between -1.5 and -0.5 hours before dosing), and 3.5 and 7.5 hours (± 30 minutes) after dosing in each study period and before release from the clinical facility in Periods I and II.

The subject must have a pre-dose systolic blood pressure ≥ 90 mmHg to be eligible for dosing in the respective study period. If the subject's pre-dose systolic blood pressure is < 90 mmHg, the assessment must be repeated 2 additional times, 10 minutes apart. If two of the three systolic blood pressure measurements are < 90 mmHg, the subject will not be eligible to receive the study drug in the respective study period. The subject may participate in subsequent periods of the study, as applicable, at the discretion of the Investigator.

At the end of the study (i.e., release from the clinic in Period III or early termination) all subjects will have vital signs (temperature, pulse, and blood pressure) performed.

Any subject who experiences clinically significant hypotension (symptomatic orthostasis or as determined by the Investigator) will be required to remain

supine, provided supportive care (e.g., hydration), and closely monitored until symptoms are resolved. Subjects who experience symptomatic hypotension in a specific study period will be permitted to remain in the study and enrolled in a subsequent study period, as applicable, if systolic blood pressure is ≥ 90 mmHg at the pre-dose assessment in a subsequent study period and per the Investigator's discretion.

Subjects who experience a serious AE due to hypotension or bradycardia in a specific study period will not be eligible to participate in a subsequent study period, as applicable. In such a case, observations and sample collections should be completed for the subject following dosing in the respective study period and the subject will then be discontinued from the study (i.e., will not receive the dose in a subsequent study period).

Physical Examinations

A brief physical examination will be performed at check-in of each study period and before release from the clinical facility in Periods I and II. At the end of the study (or early termination), all subjects will have a complete physical examination (including weight [NOT height]) performed.

12-lead ECG Assessments

A 12-lead ECG will be performed at pre-dose in Periods I, II and III (Day 1, before vital sign assessments) and 3.5 hours post-dose (± 30 minutes), at release from the clinic (Periods I and II), at check-in (Day -1) for Periods II and III, and at the end of the study (i.e., release from the clinic in Period III or early termination). ECGs will be performed prior to vital sign assessments when time points coincide.

The Period I pre-dose safety ECG will be collected in triplicate and must show QTcF findings that remain ≤ 440 msec on two of the three recordings for the subject to be eligible to receive study drug in Period I. If two of the three QTcF intervals exceed 440 msec, the subject will not be eligible to receive the study drug in Period I and will be discontinued from further participation in the study.

In the event that a post-dose QTcF reading is > 450 msec, two additional ECGs should be taken at 10- to 15-minute intervals. If two of the three QTcF intervals exceed 450 msec, the subject will be monitored hourly until the QTcF has returned to below 450 msec. If a subject's QTcF interval is > 500 msec at the post-dose ECG assessment or during hourly ECG monitoring, the subject will be discontinued from further participation in the study. Subjects with a post-dose QTcF interval > 450 msec in the respective study period that remains below 500 msec and resolves will be allowed to participate in subsequent study periods if the subject's respective check-in (Day -1) and pre-dose (Day 1, before vital sign assessments) ECGs are ≤ 440 msec (as outlined below).

The Periods II and III check-in and pre-dose safety ECGs will be collected in triplicate and must show QTcF findings that are ≤ 440 msec on two of the

three recordings for the subject to be eligible to receive study drug in the respective study period. If two of the three QTcF intervals exceed 440 msec, the subject will not be eligible to receive the study drug in the respective study period.. The subject may participate in subsequent periods of the study, as applicable, at the discretion of the Investigator.

C-SSRS Assessments

Subjects will complete the Columbia Suicidality Severity Rating Scale (C-SSRS) at check-in for each study period, at release from the clinical facility in Periods I and II, and at the end of study (i.e., release from the clinical facility in Period III or early termination). The C-SSRS: Baseline document should be used at check-in for Period I and the C-SSRS: Since Last Visit document should be used in all other instances.

5.6 Drug Concentration Measurements

Sample Size: 6 mL collections (K_2EDTA vacutainers)

Collection Times: Pre-dose samples will be collected within 45 minutes prior to dosing and before breakfast, if applicable. All times are relative to the dosing minute.

Pre-dose (0-hour, within 45 minutes prior to dosing) and at 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 7.0, 10.0, 16.0, 24.0, 30.0, 36.0, 48.0 and 54.0 hours post-dose

Total Number of Collections per Period/per Subject: 17

Total Blood Volume per Subject: The total maximum volume of blood collected for pharmacokinetic sampling may be up to 306 mL. [redacted] The total volume of blood collected during this study is anticipated to be approximately 352.5 mL for male subjects and approximately 367.5 mL for female subjects.

Sample Processing: Samples will be collected in 6 mL K_2EDTA vacutainers. [redacted] After collection until placement in the freezer, blood/plasma samples will be kept cooled in an ice/water bath.

Sample Shipment: Plasma samples will be sent to the bioanalytical laboratory for those subjects who were dosed with at least one of the study treatments (Treatment

A, B or C). Plasma samples will be shipped only Monday through Wednesday via overnight courier to:

[redacted]

5.7 Statistical Methods

5.7.1 Statistical and Analytical Plans

Concentrations of lofexidine in plasma will be measured by [redacted] using a fully validated analytical method. The analytical laboratory will be blinded to the randomization until after the analysis is completed. Samples will be analyzed by the bioanalytical laboratory for those subjects who were dosed with at least one of the study treatments (Treatment A, B or C), as indicated in Section 5.6.

Pharmacokinetic and statistical services will be performed by [redacted]. SAS®, Version 9.4 or higher will be used for all pharmacokinetic and statistical calculations.

Data from subjects who have sufficient plasma concentrations to characterize C_{max} and AUC_{0-t} of at least one of the study treatments (A, B or C) will be included in the pharmacokinetic analysis. Data from any subject/period that does not provide sufficient plasma concentrations to characterize C_{max} and AUC_{0-t} will be excluded from the pharmacokinetic analysis.

Data from subjects who have sufficient plasma concentrations to characterize C_{max} and AUC_{0-t} from at least two periods of the study, one of which includes Treatment A, will be included in the comparative statistical analysis.

5.7.1.1 Pharmacokinetic Analysis:

Linear and semi-logarithmic graphs of the concentration-time profiles for each subject will be provided, using the actual times of sample collections. Graphical presentations of mean results will use the scheduled times of sample

collections. Actual sample collection time will be used for calculating the pharmacokinetic parameters.

For the test and reference products, the peak exposure (C_{max}) will be the observed maximum plasma concentration; the time to peak exposure (T_{max}) will be the collection time at which C_{max} is first observed.

Areas under the plasma concentration-time curve from time zero to the time of last measurable concentration (AUC_{0-t}) will be calculated by the linear trapezoidal method. Area under the plasma concentration-time curve from time zero to time infinity ($AUC_{0-\infty}$) will be calculated as follows:

$AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda_z$, where C_t is the last measurable plasma concentration and λ_z is the apparent first-order terminal rate constant.

λ_z will be estimated, when possible, from the negative of the slope of the dataset with the best-fit least-squares linear regression analysis of the terminal ln-linear concentration-time data. The number of data points (3 or more) in the terminal phase (not including C_{max}) to be included in the final regression analysis for an evaluable λ_z will be determined from the dataset that has the highest adjusted R-squared (R^2) value of 0.7 or more.

λ_z will be considered non-evaluable if (1) the last three terminal points are used to determine λ_z and either the middle or the last point is higher than the preceding point or (2) the resulting adjusted R^2 value is less than 0.7.

An evaluable λ_z will be considered not reliable and not reportable if the resulting apparent first-order terminal half-life ($T_{½}$) value is longer than the time interval over which λ_z is estimated. If the resulting $T_{½}$ value is longer than the time interval over which λ_z is determined, an interval that is longer than the estimated $T_{½}$ will be explored. The interval with the next highest adjusted R^2 value will be chosen and the decrease in the adjusted R^2 value will be assessed to determine if a reliable estimation of the λ_z is possible. If λ_z is deemed not reliable then no $T_{½}$ and $AUC_{0-\infty}$ values will be reported for that dataset. $T_{½}$ will be calculated as $\ln(2)/\lambda_z$.

Apparent volume of distribution during the terminal phase (V_Z/F) of the drug from plasma will be calculated as follows: Dose / $[AUC_{0-\infty} \cdot \lambda_z]$).

Apparent total clearance of the drug from plasma (CL/F) will be calculated as follows: Dose / $AUC_{0-\infty}$.

No concentration estimates will be provided for missing sample values. Any sample with a missing value will be treated as if the sample had not been scheduled for collection. Data from subjects with missing concentration values (such as missing blood draws, lost samples, samples unable to be quantified) may be used if pharmacokinetic parameters can be estimated using the remaining data points, otherwise data from these subjects will be excluded from the final analysis.

5.7.1.2 Statistical Analyses

Descriptive statistics (n, mean, SD, % coefficient of variation (%CV), minimum, median, maximum) will be reported for lofexidine concentrations at each time point by treatment. Descriptive statistics (n, mean, SD, % coefficient of variation (%CV), geometric mean, minimum, median, maximum) will be reported for all PK parameters.

The statistical model will be conducted separately for Treatment A versus Treatment B analysis and for Treatment C versus Treatment A analysis using an incomplete block design.

If a subject has immediate pre-dose (0-hour sample) concentrations that are greater than 5% of the measured C_{max} value for that specific study period, the subject's data will be excluded from the statistical analysis. If a subject has measurable pre-dose concentrations that are 5% or less of the measured C_{max} value for that specific study period, the subject's data will be included in the analysis without adjustment.

Linear mixed effect model with treatment, sequence and period as fixed effects and random effects of subject nested within sequence will be used. Sequence effects will be tested against the Type III mean square term for subject-within sequence at the two-sided $\alpha = 10\%$ level of significance. Least squares means for the treatments (LSMEANS statement), the differences between adjusted treatment means, and the standard errors associated with these differences (ESTIMATE statement) will be estimated.

Confidence intervals (90%) on the geometric mean ratios (obtained from logarithmic transformed data) for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for the comparison of Treatment A to Treatment B (to compare the test formulation and reference product under fasted conditions) and the comparison of Treatment C to Treatment A (to compare the granules for reconstitution [test formulation] under fed and fasted conditions) will be constructed to test two one-sided hypotheses at the $\alpha = 0.05$ level of significance.[5-7]

A description of all of the statistical analyses will be provided in the Statistical Analysis Plan (SAP).

5.7.2 Safety Analysis

For safety, all AEs, ECGs, VS and safety laboratory values will be listed for each subject and tabulated by treatment. Physical examination data will also be listed.

Safety (12-lead) ECG changes from baseline will be presented in a shift table (i.e., normal to abnormal) at each post-dose time point. For vital signs, descriptive statistics will be used to summarize the observed values at each time point and the change from baseline at each post-dose time point.

No formal statistical testing will be performed on safety variables.

5.7.3 C-SSRS Assessments

Subjects will complete the Columbia Suicidality Severity Rating Scale (C-SSRS) at check-in for each study period, at release from the clinical facility in Periods I and II, and at the end of study (i.e., release from the clinical facility in Period III or early termination).

Categorical variables for C-SSRS data, the number and percent of each category within a parameter, will be calculated for non-missing data and tabulated by time point.

5.7.4 Determination of Sample Size

A sample size of 16 subjects enrolled to complete 12 subjects is considered, by the Sponsor, sufficient to meet the objectives of this study. The sample size for this study was determined based on clinical and practical considerations and not on a formal statistical power calculation.

6.0 REGULATORY OBLIGATIONS

6.1 Compliance

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and all applicable regulations, including the Federal Food, Drug and Cosmetics Act., U.S. applicable Code of Federal Regulations (Title 21), ICH Guidelines, and IRB requirements relative to clinical studies.

6.2 Quality Assurance

All aspects of the clinical and statistical phases of the study including all associated documentation will be reviewed by the quality assurance unit of [redacted] following their appropriate SOPs for QA methods and procedures. The final report will be audited to ensure that the methods described and the results reported accurately reflect the raw data generated during the study.

6.3 Institutional Review Board

The study protocol, informed consent form, Investigator's brochure, or package insert (as applicable), and any specific advertising will be submitted to and approved by the [redacted] Institutional Review Board ([redacted] IRB) before the start of the study. [redacted]

6.4 Audits, Inspections and Monitoring

In accordance with the principles of GCP, [redacted] will ensure that it will permit trial related monitoring, audits, IRB/IEC review and regulatory inspection(s) by providing direct access to the clinical facility while the study is in progress and source data/ documents. Monitoring may occur virtually through electronic monitoring means.

6.5 Study Documentation

6.5.1 Protocol

The Investigator indicated on Form FDA 1572 will act as the Principal Investigator. [redacted]

6.5.2 Informed Consent

An Informed Consent Form (ICF) that includes all of the relevant elements currently required by FDA or state regulations will be provided to each prospective study subject at screening and before enrollment into the study. [redacted] A copy of the ICF will be provided to the subject. [redacted]

6.5.3 Protocol and Informed Consent Changes

Changes to the protocol or the ICF will be implemented as amendments to the original document and approved by the [redacted] IRB. [redacted] Any addenda, amendment, or revision that substantially alters the study design or increases potential risk to the subject requires the subject's consent to continue in the study.

6.5.4 Source Documents and Case Report Forms

All subjects will be identified by initials, date of birth, and the last four digits of his/her social security number, and will be assigned a study subject number. Source documents will be used to record all study-related data. Source document entries will be used to complete electronic Case Report Forms (eCRFs). [redacted] All data and eCRFs will be reviewed, evaluated, and signed by the Investigator, as required.

6.5.5 Final Report

At the conclusion of the study, a final report will be issued to the Sponsor. Where applicable, it will contain a narrative description of the clinical

conduct of the study. Appropriate tables and graphs will be created to summarize the data.

[redacted]

6.6 Drug Accountability

All drug receipt, inventory, dispensing, dosing and reconciliation records will be maintained in compliance with [redacted] Standard Operating Procedures. The study drugs will be used by the Investigator or by a qualified individual under the Investigator's direct supervision [redacted] At the end of the study, all study drug will be accounted for; any unused drug will be inventoried and retained on site. [redacted]

6.7 Record Retention

All drug accountability records, eCRFs, source data, and related regulatory documents must be retained for at least two years following marketing approval by the FDA. The Sponsor must notify the Investigator when approval of this formulation is received.

6.8 Financing and Insurance

[redacted]

6.9 Confidentiality

This document contains trade secrets and commercial information that is confidential and may not be disclosed to third parties. Persons to whom this study protocol is disclosed must be informed that all the information herein is confidential and may not be further divulged. These restrictions will apply as well to all future communications if deemed privileged or confidential. Publication of the study results may only be allowed with written permission from the Sponsor.

All subject information related to this study will remain confidential. Outside of [redacted], subjects will be identified, at all times, by a number and initials. Sponsor, study monitors, auditors, the IRB, FDA, and applicable regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by applicable laws and regulations.

7.0 REFERENCES

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