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: March 23, 2021
IND NUMBER: 47857
NCT NUMBER: NCT04188730

STATISTICAL ANALYSIS PLAN

STUDY TITLE	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
PROTOCOL NO.	USWM-LX2-1001 (Amendment 4)
SPONSOR	USWM, LLC 4441 Springdale Rd. Louisville, KY 40241 United States of America (USA)
CLINICAL RESEARCH ORGANIZATION	
DATE AND VERSION	23 Mar 2021 – Version 1.0 - Final

SAP Final Version Approvals

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

Written By:	Date: 24 Mar 2021
Reviewed By:	Date: 23 Mar 2021
Approved By: Signature:	Date:

Revision History

VERSION	DATE	DESCRIPTION OF REVISIONS	REVISED BY
Draft 0.1	19 Feb 2021	New Document	[redacted]
Draft 0.2	05 Mar 2021	Incorporated Sponsor Comments	[redacted]
Draft 0.3	18 Mar 2021	Incorporated Sponsor Comments	[redacted]
Final 1.0	23 Mar 2021	Finalized Document	[redacted]

List of Abbreviations and Definition of Terms

ADAE	Analysis Dataset of Adverse Events
ADPC	Analysis Dataset of PK Concentrations
ADPP	Analysis Dataset of PK Parameters
ADSL	Subject Level Analysis Dataset
AE	Adverse Event
$AUC_{0-\infty}$	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 (t)
BMI	Body Mass Index
bpm	Beats per minute
CL/F	Apparent total clearance of the drug from plasma
C_{max}	Maximum observed plasma concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
C_t	Last measurable plasma concentration
CV	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EQ	Equivalent to
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
g	Gram
hr	Hour
ICH	International Council for Harmonisation
in	Inch
ISCV	Intra-subject coefficient of variation
kg	Kilogram
λ_z	Apparent first-order terminal elimination rate constant
m^2	Meters squared
Max.	Maximum
Mean	Arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
µg	Microgram
min	Minute
Min.	Minimum
mL	Milliliter
mmHg	Millimeter of mercury
msec	Millisecond
PI	Principal Investigator
PK	Pharmacokinetic(s)
PR	PR interval of the ECG
QRS	QRS interval of the ECG

QT	QT interval of the ECG
QTc	Corrected QT interval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
$T_{½}$	First-order terminal elimination half-life
TEAE	Treatment Emergent Adverse Event
T_{max}	Time of maximum observed plasma concentration
V_Z/F	Apparent volume of distribution during the terminal phase

TABLE OF CONTENTS

1. INTRODUCTION

This Statistical Analysis Plan (SAP) is based on the final Clinical Study Protocol USWM-LX2-1001 / Study No. [redacted] (Amendment 4) dated 25 Jan 2021. The SAP provides details on the planned statistical methodology for the analysis of the study data. The SAP also outlines the statistical programming specifications for the tables, listings and figures.

This SAP describes the study endpoints, derived variables, anticipated data transformations and manipulations, and other details of the analyses not provided in the study protocol. This SAP therefore outlines in detail all other aspects pertaining to the planned analyses and presentations for this study.

The following documents were reviewed in preparation of this SAP:

- Final Clinical Study Protocol USWM-LX2-1001 / Study No. [redacted] (Amendment 4) dated 25 Jan 2021
- Note to File/Memo to File dated 08 Feb 2021
- Electronic Case Report Form (eCRF) Spec Version 1.1 dated 04 Mar 2021

This SAP has been developed and finalized prior to database lock of the clinical database for Protocol USWM-LX2-1001 / Study No. [redacted]

2. 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.

3. OVERALL STUDY DESIGN

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.

† 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.

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 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.

For evaluation of the safety endpoint, the following assessments will be performed throughout the study: collection of medical history and Adverse Events (AEs), laboratory tests, vital signs, physical examination, 12-lead electrocardiograms (ECGs), and Columbia Suicidality Severity Rating Scale (C-SSRS) assessments. No formal statistical testing will be performed on safety variables.

STUDY SCHEMATIC

Study Phase	Screening	Periods I, II and III				End of Study
Activity	Within 28 days of Day 1	Check-In Day -1	Day 1	Day 2	Day 3	**Day 3 Period III**
Informed Consent	X					
Social, Medical History and Demographic Data	X					
Physical Examination[1]	X	X			X	X
C-SSRS[2]		X			X	X
Virology Testing	X					
FSH testing (if applicable)[3]	X					
12 Lead ECG[4]	X	X	X		X	X
Clinical Lab Tests[5]	X					X
Inclusion/Exclusion	X					
Eligibility		X				
Vital Signs[4]	X	X	X		X	X
Drug and Alcohol Screen[6]	X	X				
Serum Pregnancy Test[7]	X					X
Urine Pregnancy Test[7]		X				
Prior and Concomitant Medication	X	X	X	X	X	X
Confinement[8]		X	X	X	X	
Genotype sampling[9]			X			
High-fat, high-calorie breakfast[10]			X			
Dosing[11]			X			
Taste Assessment[12]			X			
PK sampling[13]			X	X	X	
Adverse Events[14]		X	X	X	X	X

1. To be performed as specified in Sections 5.3.1.1 (screening) and 5.5.5 of the Clinical Study Protocol.
2. C-SSRS to be obtained as specified in Section 5.5.5 of the Clinical Study Protocol.
3. To be performed as specified in Appendix 8.1.6 of the Clinical Study Protocol, if applicable.
4. ECGs and vital signs to be measured as specified in Sections 5.3.1.1 and 5.3.3 (screening) and 5.5.5 of the Clinical Study Protocol. Note: ECG to be conducted at check-in for Periods II and III **only**.
5. Clinical laboratory tests (see Appendix 8.1.1 of the Clinical Study Protocol) to be performed as specified in Sections 5.3.1.1 (screening) and 5.5.4 of the Clinical Study Protocol.
6. For all subjects, test results must be negative before drug will be administered to the subject. Alcohol tested at check-in only. Drug and alcohol tests, as appropriate, to be performed as specified in Appendix 8.1.3 of the Clinical Study Protocol (at screening) and Appendix 8.1.4 of the Clinical Study Protocol (at check-in).
7. Female subjects only. For all female subjects, test results must be negative before drug will be administered to the subject. Pregnancy tests to be performed as specified in Appendix 8.1.5 of the Clinical Study Protocol.
8. Subjects should enter the clinical facility at least 10.5 hours before dosing and will remain confined until at least 54 hours after dosing in each study period.
9. Blood sample to be collected in Period I as specified in Appendix 8.1.2 of the Clinical Study Protocol.
10. The standardized high-fat, high-calorie breakfast will be provided as specified in Section 5.4.4 of the Clinical Study Protocol.
11. Single dose to be administered as specified in Section 5.4.1 of the Clinical Study Protocol.
12. Treatments A or C only. To be performed as outlined in Section 5.4.1 and Appendix 8.2 of the Clinical Study Protocol.
13. Blood samples to be collected as specified in Section 5.6 of the Clinical Study Protocol.
14. From dosing in Period I until the end of the study.

4. RANDOMIZATION

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. 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. ANALYSIS POPULATIONS

6.1 Pharmacokinetic Population

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.

6.2 Safety Population

The safety population will include all subjects who are administered at least one dose of a study treatment (A, B or C).

7. STATISTICAL ANALYSIS METHODS

Data will be summarized with respect to demographic, baseline characteristics, safety, and pharmacokinetic (PK) variables.

For categorical variables, the number and percent of each category within a parameter will be calculated for non-missing data. For continuous variables, statistics will include number of observations, mean, standard deviation, median, minimum, and maximum values.

7.1 Baseline Characteristics

7.1.1 Baseline Demographics

Demographic information collected at screening includes age, sex, ethnicity, race, body weight (lbs), height (in), BMI, and tobacco use. Body weight and height will be converted into kg and cm, respectively, for presentation in listings and tables.

All data will be listed by subject. A summary table will be presented for the safety population.

7.1.2 Medical History

Only clinically significant medical history data, if they exist, will be presented and listed by subject.

7.2 Pharmacokinetic and Statistical Analyses

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

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.

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

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, although data will be summarized referencing the scheduled sample collection times.

7.2.1 Pharmacokinetic Parameters

The pharmacokinetic parameters will be determined from the plasma concentration data using a non-compartmental model.

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 / $AUC_{0-\infty}$.

Descriptive statistics (n, mean, SD, % coefficient of variation (%CV), geometric mean, minimum, median, maximum) will be reported for all PK parameters.

7.2.2 Statistical Analyses

A 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.

Two-sided 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.

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.

7.3 Safety Analysis

No formal statistical testing will be performed on safety variables.

7.3.1 Adverse Events

Adverse events (AEs) and Serious Adverse Events (SAEs) will be collected through both solicited and unsolicited means from dosing in Period I until the end of the study.

All reported AEs will be coded and classified according to the MedDRA Version 23.0 or higher adverse event dictionary. Each adverse event is to be evaluated for date of start and end, seriousness, severity, causal relationship to study treatment, action taken and outcome. The severity is characterized as mild, moderate or severe. The relationship to the study treatment is characterized as unrelated or related.

Adverse events will be listed by subject, treatment, system organ class, and preferred term. The incidence of AEs will be summarized by system organ class (SOC), preferred term (PT) and treatment. Subjects will be counted once per preferred term and once per system organ class, per treatment. The system organ classes will be ordered by decreasing total frequency then alphabetically. The preferred terms within each system organ class will be ordered by decreasing total frequency then alphabetically.

The summary table for Adverse Events will be based upon the safety population. AEs and SAEs will be summarized by overall number of AEs in the final report text, per treatment. The number of AEs leading to withdrawal from the study or SAEs will also be summarized in text.

7.3.2 Vital Signs

Sitting/supine vital signs assessment (temperature, respiration rate, pulse, and blood pressure) and orthostatic blood pressure assessment (within 3 minutes of standing from a sitting/supine position) will be performed at the screening visit. 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.

Descriptive statistics will be used to summarize the observed values by treatment at each time point and the change from baseline at each post-dose time point. Vital signs will be listed by subject.

7.3.3 ECG

A 12-lead ECG will be conducted in triplicate for all subjects at the screening visit. A 12-lead ECG will also be performed at pre-dose (in triplicate) 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).

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. Safety 12-lead ECG parameters will be listed by subject with any out of normal range values flagged.

7.3.4 Physical Examination

A complete physical examination (including height and weight) will be performed at screening. 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.

Physical examination results will be listed by subject.

7.3.5 Concomitant Medications

All prior and concomitant medications taken since screening until the end of the study will be listed by subject.

7.3.6 Clinical Laboratory Tests

All subjects will have chemistry, hematology, and urinalysis performed at screening and end of study.

Clinical laboratory results will be listed by subject and any clinically significant out of range laboratory results will be flagged.

7.3.7 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.

For 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.

7.4 Taste Assessment

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.

Taste Assessment Questionnaire results will be listed by treatment then by subject.

7.5 Multiple Comparisons

No multiple comparison adjustment will be made in this study.

7.6 Interim Analyses

There is no interim analysis planned in this study.

8. PK Reconciliation

Biostatistics team will reconcile the plasma concentration data sent by the bioanalytical laboratory

and the PK sample collection times from the SDTM dataset (i.e., BE domain). This reconcile step will be verified and documented appropriately.

9. TABLE, LISTING AND FIGURE SHELLS

The following shells are presented in order to provide a framework for the display of data from this study. These shells may not be reflective of every aspect of this study but are intended to show the general layout of the Tables, Listings and Figures that will be included in the final clinical study report. Tables, Listings, and Figures are numbered following the ICH structure. Table headers, variables names and footnotes will be modified as needed following data analyses. In addition to the standard SDTM datasets; the ADaM datasets; ADSL, ADAE, ADPC and ADPP will be programmed and submitted.

Table 10.1.1 Subject Disposition

Subject Disposition	**Overall N = xx**
Subjects Randomized	xx (xx.x%)
Subjects included in Safety Population	xx (xx.x%)
Subjects included in Pharmacokinetic Population	xx (xx.x%)
Total Discontinued	xx (xx.x%)
Reason for Discontinuation	xx (xx.x%)
Adverse Event	xx (xx.x%)
Non-Compliance	xx (xx.x%)
Positive Substance Abuse Screen	xx (xx.x%)
Withdrawal by Subject	xx (xx.x%)
…	xx (xx.x%)

Created on: DDMMMYYYY Page 1 of N

Table 11.2.1 Summary of Demographic Data (Safety Population)

		Overall N = xx
Age (years)	Mean ± SD	xx.x ± xx.x
	Range (Min., Max.)	xx, xx
	Median	xx
Age Groups	< 18	x (xx.x%)
	18 – 40	x (xx.x%)
	41 – 64	x (xx.x%)
	65 – 75	x (xx.x%)
	> 75	x (xx.x%)
Sex	Male	x (xx.x%)
	Female	x (xx.x%)
Ethnicity*	Hispanic or Latino	x (xx.x%)
	Not Hispanic or Latino	x (xx.x%)
Race*	American Indian or Alaska Native	x (xx.x%)
	Asian	x (xx.x%)
	Black or African American	x (xx.x%)
	Native Hawaiian or Other Pacific Islander	x (xx.x%)
	White	x (xx.x%)
	Multiple	x (xx.x%)
BMI (kg/m^2)	Mean ± SD	xx.x ± xx.x
	Range (Min., Max.)	xx, xx
	Median	xx
Other Factors		
Height (cm)	Mean ± SD	xx.x ± xx.x
	Range (Min., Max.)	xx, xx
	Median	xx
Weight (kg)	Mean ± SD	xx.x ± xx.x
	Range (Min., Max.)	xx, xx
	Median	xx
Tobacco Users†	Yes	x (xx.x%)
	No	x (xx.x%)

* Categories based on FDA Guidance "Collection of Race and Ethnicity Data in Clinical Trials", Issue Date: October 26, 2016.
† Defined as current tobacco user (having used tobacco- or nicotine-containing products within 30 days before initial dosing).

Created on: DDMMMYYYY Page 1 of N

Table 11.4.1.1 Summary of Pharmacokinetic Parameters of Untransformed Data: Lofexidine (N = XX subjects)

Pharmacokinetic Parameter	Treatment	N (# datasets)	Arithmetic mean ± SD (%CV)*	Min.	Median	Max.
AUC_{0-t} (*units*·hr/mL)	A	x	xxx.xxxx ± xx.xxxx (xx.xxxx)	xxx.xxxx	xxx.xxxx	xxx.xxxx
	B	x	xxx.xxxx ± xx.xxxx (xx.xxxx)	xxx.xxxx	xxx.xxxx	xxx.xxxx
	C	x	xx.xxxx ± xx.xxxx (xx.xxxx)	xx.xxxx	xx.xxxx	xx.xxxx
$AUC_{0-\infty}$ (*units*·hr/mL)	A	x	xxx.xxxx ± xx.xxxx (xx.xxxx)	xxx.xxxx	xxx.xxxx	xxx.xxxx
	B	x	xxx.xxxx ± xx.xxxx (xx.xxxx)	xxx.xxxx	xxx.xxxx	xxx.xxxx
	C	x	xx.xxxx ± xx.xxxx (xx.xxxx)	xx.xxxx	xx.xxxx	xx.xxxx
AUC_{0-t}/ $AUC_{0-\infty}$	A	x	xxx.xxxx ± xx.xxxx (xx.xxxx)	xxx.xxxx	xxx.xxxx	xxx.xxxx
	B	x	xxx.xxxx ± xx.xxxx (xx.xxxx)	xxx.xxxx	xxx.xxxx	xxx.xxxx
	C	x	xx.xxxx ± xx.xxxx (xx.xxxx)	xx.xxxx	xx.xxxx	xx.xxxx
C_{max} (*units*/mL)	A	x	xxx.xxxx ± xx.xxxx (xx.xxxx)	xxx.xxxx	xxx.xxxx	xxx.xxxx
	B	x	xxx.xxxx ± xx.xxxx (xx.xxxx)	xxx.xxxx	xxx.xxxx	xxx.xxxx
	C	x	xx.xxxx ± xx.xxxx (xx.xxxx)	xx.xxxx	xx.xxxx	xx.xxxx
T_{max} (hr)	A	x	xxx.xxxx ± xx.xxxx (xx.xxxx)	xxx.xxxx	xxx.xxxx	xxx.xxxx
	B	x	xxx.xxxx ± xx.xxxx (xx.xxxx)	xxx.xxxx	xxx.xxxx	xxx.xxxx
	C	x	xx.xxxx ± xx.xxxx (xx.xxxx)	xx.xxxx	xx.xxxx	xx.xxxx
λ_z (hr^{-1})	A	x	xx.xxxx ± xx.xxxx (xx.xxxx)	xx.xxxx	xx.xxxx	xx.xxxx
	B	x	xx.xxxx ± xx.xxxx (xx.xxxx)	xx.xxxx	xx.xxxx	xx.xxxx
	C	x	xx.xxxx ± xx.xxxx (xx.xxxx)	xx.xxxx	xx.xxxx	xx.xxxx

Pharmacokinetic Parameter	Treatment	N (# datasets)	Arithmetic mean ± SD (%CV)*	Min.	Median	Max.
$T_{1/2}$ (hr)	A	x	xx.xxxx ± xx.xxxx (xx.xxxx)	xx.xxxx	xx.xxxx	xx.xxxx
	B	x	xx.xxxx ± xx.xxxx (xx.xxxx)	xx.xxxx	xx.xxxx	xx.xxxx
	C	x	xx.xxxx ± xx.xxxx (xx.xxxx)	xx.xxxx	xx.xxxx	xx.xxxx
CL/F (*units*)	A	x	xx.xxxx ± xx.xxxx (xx.xxxx)	xx.xxxx	xx.xxxx	xx.xxxx
	B	x	xx.xxxx ± xx.xxxx (xx.xxxx)	xx.xxxx	xx.xxxx	xx.xxxx
	C	x	xx.xxxx ± xx.xxxx (xx.xxxx)	xx.xxxx	xx.xxxx	xx.xxxx
V_z/F (*units*)	A	x	xx.xxxx ± xx.xxxx (xx.xxxx)	xx.xxxx	xx.xxxx	xx.xxxx
	B	x	xx.xxxx ± xx.xxxx (xx.xxxx)	xx.xxxx	xx.xxxx	xx.xxxx
	C	x	xx.xxxx ± xx.xxxx (xx.xxxx)	xx.xxxx	xx.xxxx	xx.xxxx

* %CV is calculated as 100*SD/Mean

Created on: DDMMMYYYY Page 1 of N

Table 11.4.1.2: Summary of Primary Endpoints Based on Plasma Lofexidine Concentrations (Ln-transformed): Treatment A vs. Treatment B (Fasted BE)

Parameter	Trt.	LS Geometric Mean	Standard Error	Geometric CV (%)	Contrast (# subjects)	LSGM Ratio (%)	90% Confidence Interval (%)	ISCV (%)*	P-value Period	P-value Sequence	90% CI within 80-125%
AUC_{0-t} (*units*·hr/mL)	A	xx	xx	xx.x	A vs B (n = xx)	xx. xx	xx. xx - xx. xx	xx.x	x.xxxx	x.xxxx	Yes/No
	B	xx	xx	xx.x							
$AUC_{0-\infty}$ (*units*·hr /mL)	A	xx	xx	xx.x	A vs B (n = xx)	xx. xx	xx. xx - xx. xx	xx.x	x.xxxx	x.xxxx	Yes/No
	B	xx	xx	xx.x							
C_{max} (*units*/mL)	A	xx	xx	xx.x	A vs B (n = xx)	xx. xx	xx. xx - xx. xx	xx.x	x.xxxx	x.xxxx	Yes/No
	B	xx	xx	xx.x							

* ISCV (Intra-subject coefficient of variation) is calculated as sqrt[exp(MSE)-1] using the model mean square error.

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Page 1 of N

Table 11.4.1.3: Summary of Primary Endpoints Based on Plasma Lofexidine Concentrations (Ln-transformed): Treatment C vs. Treatment A (Food Effect)

Parameter	Trt.	LS Geometric Mean	Standard Error	Geometric CV (%)	Contrast (# subjects)	LSGM Ratio (%)	90% Confidence Interval (%)	ISCV (%)*	P-value Period	P-value Sequence	90% CI within 80-125%
AUC_{0-t} (*units*·hr/mL)	C	xx	xx	xx.x	C vs A (n = xx)	xx. xx	xx. xx - xx. xx	xx.x	x.xxxx	x.xxxx	Yes/No
	A	xx	xx	xx.x							
$AUC_{0-\infty}$ (*units*·hr /mL)	C	xx	xx	xx.x	C vs A (n = xx)	xx. xx	xx. xx - xx. xx	xx.x	x.xxxx	x.xxxx	Yes/No
	A	xx	xx	xx.x							
C_{max} (*units*/mL)	C	xx	xx	xx.x	C vs A (n = xx)	xx. xx	xx. xx - xx. xx	xx.x	x.xxxx	x.xxxx	Yes/No
	A	xx	xx	xx.x							

* ISCV is calculated as sqrt[exp(MSE)-1] using the model mean square error.

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Table 12.2.2.1 Summary of Treatment-Emergent Adverse Events by System Organ Class and MedDRA Preferred Term

System Organ Class/MedDRA Preferred Term	Treatment A n (%)	Treatment B n (%)	Treatment C n (%)	Overall n (%)
Subjects having at least one TEAE	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
System Organ Class	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Preferred Term	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Preferred Term	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Preferred Term	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Preferred Term	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
…				

n = Number of subjects reporting AE
% = (Number of subjects reporting AE / number of subjects dosed with respective study drug) x 100
Subjects counted once per preferred term and once per system organ class, per treatment.
Treatment A = ## subjects dosed.
Treatment B = ## subjects dosed.
Treatment C = ## subjects dosed.

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Programming Note 1: Subjects with more than one PT for the same SOC will be counted only once. Subjects with more than one incidence of same PT will be counted only once.
Programming Note 2: The system organ classes will be ordered by decreasing overall frequency then alphabetically. The preferred terms within each system organ class will be ordered by decreasing overall frequency then alphabetically

Table 12.5.1 Summary of Vital Signs

			Observed Data				Change from Baseline			
Evaluation	**Treatment**	**Time Point**	**n**	**Mean (SD)**	**Median**	**Min, Max**	**n**	**Mean (SD)**	**Median**	**Min, Max**
Diastolic Blood Pressure (mmHg)	A	Pre-dose (Baseline)	xx	xx.x (xx.x)	xx.x	xx.x, xx.x				
	A	3.5 hr	xx	xx.x (xx.x)	xx.x	xx.x, xx.x	xx	xx.x (xx.x)	xx.x	xx.x, xx.x
	A	7.5 hr	xx	xx.x (xx.x)	xx.x	xx.x, xx.x	xx	xx.x (xx.x)	xx.x	xx.x, xx.x
		etc.								
	B	Pre-dose (Baseline)	xx	xx.x (xx.x)	xx.x	xx.x, xx.x				
	B	3.5 hr	xx	xx.x (xx.x)	xx.x	xx.x, xx.x	xx	xx.x (xx.x)	xx.x	xx.x, xx.x
	B	7.5 hr	xx	xx.x (xx.x)	xx.x	xx.x, xx.x	xx	xx.x (xx.x)	xx.x	xx.x, xx.x
		etc.								
	C	Pre-dose (Baseline)	xx	xx.x (xx.x)	xx.x	xx.x, xx.x				
	C	3.5 hr	xx	xx.x (xx.x)	xx.x	xx.x, xx.x	xx	xx.x (xx.x)	xx.x	xx.x, xx.x
	C	7.5 hr	xx	xx.x (xx.x)	xx.x	xx.x, xx.x	xx	xx.x (xx.x)	xx.x	xx.x, xx.x
		etc.								
Pulse (beats/min)	A	Pre-dose (Baseline)	xx	xx.x (xx.x)	xx.x	xx.x, xx.x				
	A	3.5 hr	xx	xx.x (xx.x)	xx.x	xx.x, xx.x	xx	xx.x (xx.x)	xx.x	xx.x, xx.x
	A	7.5 hr	xx	xx.x (xx.x)	xx.x	xx.x, xx.x	xx	xx.x (xx.x)	xx.x	xx.x, xx.x
		etc.								

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Programming Note: If any pre-dose assessment data are missing, the nearest non-missing pre-dose value will be used as the baseline.

Table 12.5.2 Shift Table for Changes from Baseline in ECGs

Treatment	Pre-dose (Baseline)	3.5 Hours Post-dose			Release		
		Normal n (%)	Abnormal (NCS) n (%)	Abnormal (CS) n (%)	Normal n (%)	Abnormal (NCS) n (%)	Abnormal (CS) n (%)
A	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal (NCS)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal (CS)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
B	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal (NCS)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Abnormal (CS)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…	…						

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Page 1 of N

Table 12.5.3 Columbia-Suicide Severity Rating Scale – Ideation and Behavior

C-SSRS Question	Period I Check-in – Lifetime n (%)	Period I Release – Since Last Visit n (%)	Period II Check-in – Since Last Visit n (%)	Period II Release – Since Last Visit n (%)	Period III Check-in – Since Last Visit n (%)	Period III Release/Early Termination – Since Last Visit n (%)
Suicidal Ideation						
Wish to be dead	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Non-specific active suicidal thoughts	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Active suicidal ideation with any methods (not plan) without intent to act	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Active suicidal ideation with some intent to act, without specific plan	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Active suicidal ideation with specific plan and intent	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Suicidal Behavior						
Engaged in non-suicidal self-injurious behavior	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Preparatory acts or behavior	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Suicidal behavior	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Actual attempt	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Interrupted attempt	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Aborted attempt	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Suicide	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)

n = Number of subjects who experience the event (i.e., respond 'Yes')
% = (Number of subjects who experience the event / number of subjects dosed) x 100

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Table 12.5.4 Columbia-Suicide Severity Rating Scale – Most Severe Ideation

C-SSRS Question	Visit	1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)	0 n (%)
Most severe ideation type no.	Period I Check-in – Lifetime	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Frequency	Period I Check-in – Lifetime	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Duration	Period I Check-in – Lifetime	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Controllability	Period I Check-in – Lifetime	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Deterrents	Period I Check-in – Lifetime	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Reasons for ideation	Period I Check-in – Lifetime	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Most severe ideation type no.	Period I Release – Since Last Visit	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Frequency	Period I Release – Since Last Visit	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
…							

n = Number of subjects in category
% = (Number of subjects in category / number of subjects dosed) × 100

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Table 14.2.1 Summary of Plasma Lofexidine Concentrations (units/mL) – (Treatment A)

Sub.	Per.	Seq.	Pre-dose	0.5 hr	0.75 hr	1.0 hr	1.5 hr	2.0 hr	3.0 hr	4.0 hr	5.0 hr	7.0 hr	10.0 hr	16.0 hr	24.0 hr	30.0 hr	…	54.0 hr
3001	x	x	x.xx	x.xx	x.xx													
3002	x	x	x.xx	x.xx	x.xx													
3003	x	x	x.xx	x.xx	x.xx	etc.												
3004	x	x	x.xx	x.xx	x.xx													
3005	x	x	x.xx	x.xx	x.xx													
…																		
N																		
Mean																		
St. Dev.																		
CV (%)																		
Min.																		
Median																		
Max.																		
Geometric Mean																		
Geometric CV (%)																		

Created on: DDMMMYYYY Page 1 of N

Note: Similar listings will be produced for Treatment B and Treatment C.

Table 14.2.2 Summary of Plasma Lofexidine Concentrations (units/mL) – (Treatment B)

Table 14.2.3 Summary of Plasma Lofexidine Concentrations (units/mL) – (Treatment C)

Table 14.2.4 Summary of PK Parameters Based on Plasma Lofexidine Concentrations – (Treatment A)

Sub.	Per.	Seq.	AUC $_{0\text{-}t}$ (*units*·hr/mL)	AUC $_{0\text{-}\infty}$ (*units*·hr/mL)	AUC $_{0\text{-}t}$/ AUC$_{0\text{-}\infty}$	C_{max} (*units*/mL)	T_{max} (h)	λ_z (hr^{-1})	$T_{1/2}$ (hr)	CL/F (units)	V_z/F (units)
3001	x	x	x.xxx	x.xxx	x.xxx	x.xxxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
3002	x	x	x.xxx	x.xxx	x.xxx	x.xxxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
3003	x	x	x.xxx	x.xxx	x.xxx	x.xxxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
3004	x	x	x.xxx	x.xxx	x.xxx	x.xxxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
3005	x	x	x.xxx	x.xxx	x.xxx	x.xxxx	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
…											
N											
Mean											
St. Dev.											
CV (%)											
Min.											
Median											
Max.											
Geometric Mean											
Geometric CV (%)											

Created on: DDMMMYYYY Page 1 of N

Note: A similar table will be produced for Treatment B and Treatment C.

Table 14.2.5 Summary of PK Parameters Based on Plasma Lofexidine Concentrations – (Treatment B)

Table 14.2.6 Summary of PK Parameters Based on Plasma Lofexidine Concentrations – (Treatment C)

Table 14.2.7 Summary of Taste Assessment Questionnaire Results (Treatment A or C)

	Treatment A N = xx n (%)	**Treatment C N = xx n (%)**
Overall Taste		
Like very much	x (xx.x%)	x (xx.x%)
Like moderately	x (xx.x%)	x (xx.x%)
Like slightly	x (xx.x%)	x (xx.x%)
Neither like nor dislike	x (xx.x%)	x (xx.x%)
Dislike slightly	x (xx.x%)	x (xx.x%)
Dislike moderately	x (xx.x%)	x (xx.x%)
Dislike very much	x (xx.x%)	x (xx.x%)
Sourness		
Like very much	x (xx.x%)	x (xx.x%)
Like moderately	x (xx.x%)	x (xx.x%)
Like slightly	x (xx.x%)	x (xx.x%)
Neither like nor dislike	x (xx.x%)	x (xx.x%)
Dislike slightly	x (xx.x%)	x (xx.x%)
Dislike moderately	x (xx.x%)	x (xx.x%)
Dislike very much	x (xx.x%)	x (xx.x%)
Bitterness		
Like very much	x (xx.x%)	x (xx.x%)
Like moderately	x (xx.x%)	x (xx.x%)
Like slightly	x (xx.x%)	x (xx.x%)
Neither like nor dislike	x (xx.x%)	x (xx.x%)
Dislike slightly	x (xx.x%)	x (xx.x%)

	Treatment A **N = xx** **n (%)**	**Treatment C** **N = xx** **n (%)**
Dislike moderately	x (xx.x%)	x (xx.x%)
Dislike very much	x (xx.x%)	x (xx.x%)
Mouthfeel/Texture		
Like very much	x (xx.x%)	x (xx.x%)
Like moderately	x (xx.x%)	x (xx.x%)
Like slightly	x (xx.x%)	x (xx.x%)
Neither like nor dislike	x (xx.x%)	x (xx.x%)
Dislike slightly	x (xx.x%)	x (xx.x%)
Dislike moderately	x (xx.x%)	x (xx.x%)
Dislike very much	x (xx.x%)	x (xx.x%)
Grittiness		
Like very much	x (xx.x%)	x (xx.x%)
Like moderately	x (xx.x%)	x (xx.x%)
Like slightly	x (xx.x%)	x (xx.x%)
Neither like nor dislike	x (xx.x%)	x (xx.x%)
Dislike slightly	x (xx.x%)	x (xx.x%)
Dislike moderately	x (xx.x%)	x (xx.x%)
Dislike very much	x (xx.x%)	x (xx.x%)
Aftertaste		
Like very much	x (xx.x%)	x (xx.x%)
Like moderately	x (xx.x%)	x (xx.x%)
Like slightly	x (xx.x%)	x (xx.x%)
Neither like nor dislike	x (xx.x%)	x (xx.x%)

	Treatment A **N = xx** **n (%)**	**Treatment C** **N = xx** **n (%)**
Dislike slightly	x (xx.x%)	x (xx.x%)
Dislike moderately	x (xx.x%)	x (xx.x%)
Dislike very much	x (xx.x%)	x (xx.x%)

Listing 16.2.1 Discontinued Subjects

Subject No.	Discontinuation Reason	Date of Discontinuation	Time of Discontinuation	Discontinuation Related to COVID-19 Pandemic
xxxx	Withdrawal By Subject	dd/Mmm/yyyy	hh:mm	
xxxx	Withdrawal By Subject	dd/Mmm/yyyy	hh:mm	
…				

Created on: DDMMMYYYY Page 1 of N

Programming Notes: Listings will be presented by subject number. Secondary fields for AEs, PDs, and Other must be listed

Listing 16.2.2 Protocol Deviations

Subject No.	Type of Protocol Deviation	Deviation Date	PD Related to COVID-19 Pandemic
xxxx	Consumption or use of a restricted item	dd/Mmm/yyyy	
xxxx	Assessment performed out of window: Vital signs	dd/Mmm/yyyy	
…			

Created on: DDMMMYYYY Page 1 of N

Programming Note: Secondary fields for deviation categories of Assessment Not Performed and Assessment Performed Out of Window are required to be presented.

Listing 16.2.3 Subjects Excluded from Statistical Analysis

Sub.	Excluded from Analysis	Reason for Exclusion from Analysis	Applicable Treatment(s)
xxxx	A vs B	Subject did not have sufficient pharmacokinetic data for this analysis	B
xxxx	A vs B , C vs A	Pre-dose concentration > 5% of C_{max}	A
xxxx	C vs A	C_{max} observed at first post-dose sampling timepoint	C
xxxx	A vs B, C vs A	Data excluded because of protocol deviation	B, C
…			

Created on: DDMMMYYYY

Page 1 of N

Listing 16.2.4.1 Subject Demographics

Subject No.	Sex	Age (yrs)	Ethnicity	Race	Tobacco User	Height (in)	Weight (lbs)	BMI (kg/m^2)
xxxx	Male	43	Not Hispanic or Latino	Black or African American	No	xx	xx	xx.x
xxxx	Male	36	Not Hispanic or Latino	Black or African American	No	xx	xx	xx.x
…								

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Page 1 of N

Listing 16.2.4.2 Prior and Concomitant Medications

Subject No.	Medication	Indication	Dose	Route	Frequency*	Date Started	Date Stopped	Therapeutic Drug Class
xxxx	Vitamin D	General health	1000 IU	Oral	QD	--/Mmm/yyyy	Ongoing	
xxxx	Multivitamin	General health	1 Tablet	Oral	QD	dd/Mmm/yyyy	dd/Mmm/yyyy	
…								

*PRN - As needed; QD - Daily (once per day); Q4H - Every 4 hours; Q8H - Every 8 hours; Q12H - Every 12 hours; BID - Twice per day; TID - 3 times per day; QID - 4 times per day; QOD - Every other day; QS - Every week; QM - Every month; Q3M - Every 3 months

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Programming Note: Only the applicable abbreviations need to be included in the footnote.

Listing 16.2.5.1 Dosing Date, Time, and Treatment Schedule

Subject No.	Period	Date	Time	Treatment
xxxx	I	dd/Mmm/yyyy	hh:mm	A
xxxx	II	dd/Mmm/yyyy	hh:mm	B
xxxx	III	dd/Mmm/yyyy	hh:mm	C
xxxx	I	dd/Mmm/yyyy	hh:mm	C
xxxx	II	dd/Mmm/yyyy	hh:mm	A
xxxx	III	dd/Mmm/yyyy	hh:mm	B
xxxx	I	dd/Mmm/yyyy	hh:mm	B
xxxx	II	dd/Mmm/yyyy	hh:mm	A
xxxx	III	dd/Mmm/yyyy	hh:mm	C
…				

Created on: DDMMMYYYY Page 1 of N

Listing 16.2.5.2 Deviations from Scheduled Collection Times

Subject No.	Treatment	Period	Sample Time (hrs)	Deviation*
xxxx	A	I	10.0	+3
xxxx	B	II	0.5 – 54.0†	DFP
xxxx	C	III	5.0	+4
xxxx	B	I	16.0	+3
xxxx	A	II	48.0	NS
…				

* Minutes assessment was performed late (+) or early (-).
DFP: Dropped from Period
DFS: Dropped from Study
NS: No Sample Collected
†Subject did not participate in this portion of the study

Created on: DDMMMYYYY Page 1 of N

Listing 16.2.5.3 Taste Assessment Questionnaire (Treatment A or C)

Subject No.	Treatment*	Overall Taste	Smell	Sweetness	Sourness	Bitterness	Mouthfeel/ Texture	Grittiness	Aftertaste
xxxx	A	Like very much	Like very much	Like very much	Like very much	Like very much	Like very much	Like very much	Like very much
xxxx	A	Like moderately	Like moderately	Like moderately	Like moderately	Like moderately	Like moderately	Like moderately	Like moderately
xxxx	A	Like slightly	Like slightly	Like slightly	Like slightly	Like slightly	Like slightly	Like slightly	Like slightly
xxxx	A	Neither like nor dislike	Neither like nor dislike	Neither like nor dislike	Neither like nor dislike	Neither like nor dislike	Neither like nor dislike	Neither like nor dislike	Neither like nor dislike
xxxx	C	Dislike slightly	Dislike slightly	Dislike slightly	Dislike slightly	Dislike slightly	Dislike slightly	Dislike slightly	Dislike slightly
xxxx	C	Dislike moderately	Dislike moderately	Dislike moderately	Dislike moderately	Dislike moderately	Dislike moderately	Dislike moderately	Dislike moderately
xxxx	C	Dislike very much	Dislike very much	Dislike very much	Dislike very much	Dislike very much	Dislike very much	Dislike very much	Dislike very much
…									

*Taste Assessment Questionnaire completed once by each subject, only after the subject's first dose of lofexidine granules (Treatment A or C).

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Page 1 of N

Listing 16.2.7 Adverse Events

Subject No.	System Organ Class/ MedDRA Preferred Term/ AE Term	Treatment	Onset Date Time	Onset Date Time	Severity	Relationship	Outcome	Action Taken with Study Treatment	Other Action Taken	SAE
xxxx	Nervous system disorders / Headache / Headache	A	dd/Mmm/yyyy hh:mm	dd/Mmm/yyyy hh:mm	Mild	Unrelated	Recovered/ Resolved	Dose Not Changed	None	No
xxxx	Investigations / Blood pressure increased / Blood pressure increased	C	dd/Mmm/yyyy hh:mm	dd/Mmm/yyyy hh:mm	Moderate	Related	Recovered/ Resolved	Dose Not Changed	None	No
…										

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Listing 16.2.8.1 Serum Chemistry Laboratory Test Results

Subject No.	Visit	Date	Time	Test	Result	Units	Clinically Significant (if out of range)
xxxx	Screening	dd/Mmm/yyyy	hh:mm	Alanine Aminotransferase	xx.x	U/L	
xxxx	Screening	dd/Mmm/yyyy	hh:mm	Alkaline Phosphatase	xx.x	U/L	
xxxx	Screening	dd/Mmm/yyyy	hh:mm	Aspartate Aminotransferase	xx.x	U/L	
xxxx	Screening	dd/Mmm/yyyy	hh:mm	Bilirubin	xx.x	mg/dL	
xxxx	Screening	dd/Mmm/yyyy	hh:mm	Creatinine	xx.x	mg/dL	
xxxx	Screening	dd/Mmm/yyyy	hh:mm	Glucose	xx.x	mg/dL	
xxxx	Screening	dd/Mmm/yyyy	hh:mm	Potassium	xx.x	mmol/L	
xxxx	Screening	dd/Mmm/yyyy	hh:mm	Urea Nitrogen	xx.x	mg/dL	
xxxx	Screening	dd/Mmm/yyyy	hh:mm	Magnesium	xx.x	mg/dL	
xxxx	Screening	dd/Mmm/yyyy	hh:mm	Sodium	xx.x	mEq/L	
xxxx	Screening	dd/Mmm/yyyy	hh:mm	Chloride	xx.x	mEq/L	
xxxx	End of Study/ Early Termination	dd/Mmm/yyyy	hh:mm	Alanine Aminotransferase	xx.x	U/L	
…	…			…			

Created on: DDMMMYYYY

Page 1 of N

Note: Similar listings will be produced for hematology and urinalysis.

Listing 16.2.8.2 Hematology Laboratory Test Results

Listing 16.2.8.3 Urinalysis Laboratory Test Results

Listing 16.2.8.4 Vital Signs

Subject No.	Treatment	Visit	Time Point	Date	Time	Vital Sign	Result	Units	Clinically Significant (if out of range)
xxxx		Screening		dd/Mmm/yyyy	hh:mm	Diastolic Blood Pressure	xx	mmHg	
xxxx		Screening		dd/Mmm/yyyy	hh:mm	Pulse	xx	beats/min	
xxxx		Screening		dd/Mmm/yyyy	hh:mm	Respiration Rate	xx	breaths/min	
xxxx		Screening		dd/Mmm/yyyy	hh:mm	Systolic Blood Pressure	xxx	mmHg	
xxxx		Screening		dd/Mmm/yyyy	hh:mm	Temperature	xx.x	F	
xxxx		Screening Repeat 1		dd/Mmm/yyyy	hh:mm	Diastolic Blood Pressure	xx	mmHg	
xxxx		Screening Repeat 1		dd/Mmm/yyyy	hh:mm	Systolic Blood Pressure	xxx	mmHg	
xxxx	A	Period I	Check-in	dd/Mmm/yyyy	hh:mm	Diastolic Blood Pressure	xx	mmHg	
xxxx	A	Period I	Check-in	dd/Mmm/yyyy	hh:mm	Pulse	xx	beats/min	
xxxx	A	Period I	Check-in	dd/Mmm/yyyy	hh:mm	Systolic Blood Pressure	xxx	mmHg	
xxxx	A	Period I	Check-in	dd/Mmm/yyyy	hh:mm	Temperature	xx.x	F	
xxxx	A	Period I	Pre-dose	dd/Mmm/yyyy	hh:mm	Diastolic Blood Pressure	xx	mmHg	
xxxx	A	Period I	Pre-dose	dd/Mmm/yyyy	hh:mm	Pulse	xx	beats/min	
xxxx	A	Period I	Pre-dose	dd/Mmm/yyyy	hh:mm	Systolic Blood Pressure	xxx	mmHg	
xxxx	A	Period I	3.5 hr	dd/Mmm/yyyy	hh:mm	Diastolic Blood Pressure	xx	mmHg	
xxxx	A	Period I	3.5 hr	dd/Mmm/yyyy	hh:mm	Pulse	xx	beats/min	
xxxx	A	Period I	3.5 hr	dd/Mmm/yyyy	hh:mm	Systolic Blood Pressure	xxx	mmHg	
xxxx	A	Period I	7.5 hr	dd/Mmm/yyyy	hh:mm	Diastolic Blood Pressure	xx	mmHg	
…	…	…	…						

Listing 16.2.8.5 Electrocardiogram Results

Subject No.	Treatment	Visit	Time Point	Date	Time	Vent. Rate (bpm)	Intervals (msec)				Result	Clinical Significance (if abnormal)
							PR	QRS	QT	QTc		
xxxx		Screening		dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Normal	
xxxx		Screening		dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Normal	
xxxx		Screening		dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Normal	
xxxx	A	Period I	Pre-dose	dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Normal	
xxxx	A	Period I	Pre-dose	dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Normal	
xxxx	A	Period I	Pre-dose	dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Normal	
xxxx	A	Period I	3.5 hr	dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Normal	
xxxx	A	Period I	Release	dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Normal	
xxxx		Period II	Check-in	dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Normal	
xxxx		Period II	Check-in	dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Normal Variant	
xxxx		Period II	Check-in	dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Normal	
xxxx	B	Period II	Pre-dose	dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Normal	
xxxx	B	Period II	Pre-dose	dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Normal	
xxxx	B	Period II	Pre-dose	dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Normal	
xxxx	B	Period II	3.5 hr	dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Abnormal	Clinically Significant
xxxx	B	Period II	Release	dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Normal	
xxxx		Period III	Check-in	dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Normal	
xxxx		Period III	Check-in	dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Normal	
xxxx		Period III	Check-in	dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Normal	
xxxx	C	Period III	Pre-dose	dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Normal	
xxxx	C	Period III	Pre-dose	dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Normal	
xxxx	C	Period III	Pre-dose	dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Normal	
xxxx	C	Period III	3.5 hr	dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Normal	

							Intervals (msec)					
Subject No.	**Treatment**	**Visit**	**Time Point**	**Date**	**Time**	**Vent. Rate (bpm)**	**PR**	**QRS**	**QT**	**QTc**	**Result**	**Clinical Significance (if abnormal)**
xxxx	C	Period III	Release	dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Abnormal	Not Clinically Significant
xxxx		Screening		dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Normal	
xxxx	B	Period I	Pre-dose	dd/Mmm/yyyy	hh:mm	xx	xxx	xxx	xxx	xxx	Normal	
…		…	…									

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Listing 16.2.8.6 Physical Examination Results

Subject No.	Treatment	Visit	Time Point	Category	Result	Description (if abnormal/changed)
xxxx				General Appearance		
xxxx		Screening		Skin	Abnormal	
xxxx		Screening		EENT		
xxxx		Screening		Head		
xxxx		Screening		Neurological		
xxxx		Screening		Cardiovascular		
xxxx		Screening		Lungs/Thorax		
xxxx		Screening		Abdominal		
xxxx		Screening		Musculoskeletal		
xxxx		Screening		Extremities		
xxxx	A	Period I	Check-in	General Appearance	No Change	
xxxx	A	Period I	Check-in	Cardiovascular	Change	
xxxx	A	Period I	Check-in	Lungs/Thorax		
xxxx	A	Period I	Check-in	Abdominal		
xxxx	A	Period I	Release	General Appearance		
xxxx	A	Period I	Release	Cardiovascular		
xxxx	A	Period I	Release	Lungs/Thorax		
xxxx	A	Period I	Release	Abdominal		
xxxx	B	Period II	Check-in	General Appearance		
…	…	…	…	…		

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Listing 16.2.8.7 Genotyping Results (If Applicable)

Subject No.	CYP2D6 Metabolizer Status
xxxx	Extensive Metabolizer
xxxx	Intermediate Metabolizer
xxxx	Poor Metabolizer
xxxx	Ultrarapid Metabolizer
…	

Created on: DDMMMYYYY Page 1 of N

Figure 11.4.1.1 Mean Plasma Lofexidine Concentrations

Figure 11.4.1.2 Mean Plasma Lofexidine Concentrations – Semi-logarithmic Scale

Figure 14.2.1 Mean Plasma Lofexidine Concentrations (Including Error-bars) – Treatment A

Figure 14.2.2 Mean Plasma Lofexidine Concentrations (Including Error-bars) – Treatment B

Figure 14.2.3 Mean Plasma Lofexidine Concentrations (Including Error-bars) – Treatment C

Appendix 16.1.9 Individual Plasma Lofexidine Concentrations by Subject

Appendix 16.1.9 Individual Plasma Lofexidine Concentrations by Subject – Semi-logarithmic Scale