Title: A Randomized, Open-Label, 2×2 Crossover Phase 1 Study to Evaluate the Bioequivalence of Single Oral Dose of Lu AA21004 20 mg tablet and 2× Lu AA21004 10 mg tablets in Healthy Adult Subjects

NCT Number: NCT03437564

Statistical analysis plan Approve Date: 14 Jun-2018

Certain information within this statistical analysis plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
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If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

Note; This document was translated into English as the language on original version was Japanese.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Vortioxetine-1001

A Randomized, Open-Label, 2×2 Crossover Phase 1 Study to Evaluate the Bioequivalence of Single Oral Dose of Lu AA21004 20 mg tablet and 2×Lu AA21004 10 mg tablets in Healthy Adult Subjects

A Bioequivalence Study of the Lu AA21004 20 mg and 2×10 mg Tablets

PHASE 1

Version**:** 2

Date**:** 14 June 2018

Prepared by:

PPD

Based on:

Protocol Version: Amendment 1

Protocol Date: 15 February 2018

1.1 Approval Signatures

Study Title: A Randomized, Open-Label, 2×2 Crossover Phase 1 Study to Evaluate the Bioequivalence of Single Oral Dose of Lu AA21004 20 mg tablet and 2×Lu AA21004 10 mg tablets in Healthy Adult Subjects

A Bioequivalence Study of the Lu AA21004 20 mg and 2×10 mg Tablets

Approvals:

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

3.0 LIST OF ABBREVIATIONS

[This may be copied from the protocol and include all abbreviations used in the SAP]

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
CYP	cytochrome P450
ECG	electrocardiogram
GGT	γ-glutamyl transferase
HDL	high-density lipoprotein
ICH	International Conference on Harmonisation
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
SAE	serious adverse event
SAP	statistical analysis plan
SOC	System Organ Class

4.0 OBJECTIVES

4.1 Primary Objectives

To evaluate the bioequivalence of a single oral dose of a Lu AA21004 20 mg tablet in comparison with two Lu AA21004 10 mg tablets in Japanese healthy adult subjects

4.2 Secondary Objectives

To assess the safety of a single oral dose of Lu AA21004 20 mg in Japanese healthy adult subjects

4.3 Additional Objectives

Not applicable.

4.4 Study Design

This is a 2×2 crossover, open-label, comparative study in Japanese healthy adults to evaluate the bioequivalence of a single oral dose of the Lu AA21004 20 mg tablet and the Lu AA21004 10 mg tablet, and also to evaluate the safety of a single oral dose of Lu AA21004 20 mg.

Subjects will be randomized in a 1:1 ratio to either treatment sequence A or B.

This study consists of the screening period, Period 1, and Period 2. Subjects will receive one Lu AA21004 20 mg tablet or two Lu AA21004 10 mg tablets on Day 1 of Period 1 and Period 2. The interval between the Period 1 dosing and the Period 2 dosing of the study drug will be at least 3 weeks.

If the bioequivalence is not demonstrated with the initially planned number of subjects, an add-on subject study may be conducted in accordance with the “Partial Revision of Guideline for Bioequivalence Studies of Generic Products”.

Treatment sequence	Period 1		Period 2
	Day 1 to 4	Day 5 to 21[(a)]	Day 1 to 4
A	One Lu AA21004 20 mg tablet Single dose under fasted condition	Washout	Two Lu AA21004 10 mg tablets Single dose under fasted condition
B	Two Lu AA21004 10 mg tablets Single dose under fasted condition		One Lu AA21004 20 mg tablet Single dose under fasted condition

Period	Screening period		Administration term							
			Period 1					Period 2		
Day[(b)]	-28 to -2	-1	1	2 to 3	4	5 to 20	21	1	2 to 3	4
Days from the Period 1 study drug dosing[(a)]	-	-	1	2 to 3	4	5 to 20	21	22	23 to 24	25
Inpatient/Outpatient	Outpatient	Inpatient				No visit	Inpatient			
Procedure	Informed consent, screening	Admission	Study drug administration		Discharge		Admission	Study drug administration		Discharge

(a) When the interval between the Period 1 dosing and the Period 2 dosing of the study drug is 3 weeks.
(b) Day 1 is defined as the day of study drug administration in each of Period 1 and Period 2, with the day prior to Period 1 study drug administration referred to as Day -1 and the day prior to Period 2 study drug administration as Day 21.

Figure 4.a Schematic of Study Design

5.0 ANALYSIS ENDPOINTS

5.1 PRIMARY ENDPOINTS

AUC_{last} of unchanged Lu AA21004

C_{max} of unchanged Lu AA21004

5.2 SECONDARY ENDPOINTS

AUC_{∞}, t_{max}, MRT, λ_z, and $t_{1/2z}$ of unchanged Lu AA21004

Adverse events, vital signs, 12-lead ECG, and laboratory test values

6.0 DETERMINATION OF SAMPLE SIZE

Planned number of subjects is 28 (14 for each sequence).

The planned sample size was calculated based upon the analysis of logarithmically transformed AUClast and Cmax. If the 90% CIs for the ratios of Lu AA 21004 20 mg tablets and 2×Lu AA 21004 10 mg tablets (2×Lu AA21004 10 mg tablets/ Lu AA21004 20 mg tablet) geometric mean value of AUClast and Cmax are both within the limits of 80.00% to 125.00%, the bioequivalence can be verified. It is hypothesize that there is no interaction between dosing formulation and administration period at AUClast and Cmax. Based on data from previous studies, the largest estimate of the within-subject coefficient of variation (CV) of AUClast and Cmax were 9.5% and 14.3%, and a sample size of 24 would then provide a power of 99.8% and 91.5% for each to correctly conclude the bioequivalence even if the true ratio is 1.1. Given that the 90% CIs for the ratio of the geometric means for AUClast and Cmax must both be contained in 80.00% to 125.00% in order to conclude the bioequivalence between the two treatments, 24 subjects provided an overall power of at least 91.3%, assuming that the two endpoints AUClast and Cmax are independent.

Taking into account possible occurrence of dropouts, planned number of subjects is 28.

In case the bioequivalence cannot be demonstrated with the number of subjects initially planned due to the insufficiency of the number of subjects, an add-on subject study will be conducted in accordance with the “Partial Revision of Guideline for Bioequivalence Studies of Generic Products”, if applicable. The maximum number of additional subjects in the add-on subject study is 28 (14 per sequence), which is determined based on study feasibility, but is not on statistical consideration.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

7.1.1 Study Definitions

- Treatment-emergent adverse event (TEAE): An adverse event which occurs on or after the start of study drug
- Pretreatment event (PTE): An adverse event which occurs on or after informed consent to participate in a study but prior to administration of study drug
- Descriptive statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles
- Coefficient of variation (CV) (%): Standard deviation / mean × 100
- Dose:
  - Lu AA21004 10 mg tablet
  - Lu AA21004 20 mg tablet
- Treatment sequence:
  - A (One Lu AA21004 20 mg tablet => Two Lu AA21004 10 mg tablets)
  - B (Two Lu AA21004 10 mg tablets => One Lu AA21004 20 mg tablet)

7.1.2 Definition of Study Days

- Study Time (hour): The date/time of tests/observation/evaluation – the date/time of first dose of the study drug (rounded to 3 decimal places)
- Study Day (day): The day before the first dose of the study drug will be defined as Day −1, and the day of the first dose of the study drug as Day 1.

7.1.3 Definition of Study Visit Windows

For all variables of test/observation/evaluation, evaluable data entered in the CRF according to the scheduled Study Time will be used as data.

7.2 Analysis Sets

- Safety analysis set: All subjects who received at least one dose of treatment period study drug
- Pharmacokinetic analysis set: All subjects who received at least one dose of treatment period study drug and did not have any of the major protocol deviations listed below, meet the minimum requirements of the protocol, and had measurable pharmacokinetics.
  - Violation of inclusion criteria: Subjects who did not meet inclusion criteria #1, #4, #5, or #6
  - Violation of exclusion criteria: Subjects who met exclusion criteria #1, #4, #6, #7, #8, #9, #12, #13, #14, #15, or #21
  - Use of excluded medications: Subjects who took drugs (prescription or over-the-counter drugs) listed in Table 7.a "Excluded Medications, Nutritional Supplements and Food" in section 7.3 of the protocol within the designated period
  - Violation of administration dose: Subjects who were given the study drug at a dose other than the dose specified in the protocol
  - Violation of dosing interval: Subjects who were given the Period 2 study drug without a washout period of at least 21 days after Period 1 study drug administration
  - Violation of dosing conditions: Subjects who were not given single oral doses under fasted condition in the morning (fasting of at least 10 hours prior to study drug administration) for all study drugs
  - Violation of pharmacokinetic measurement: Subjects who have one or more missing data or data determined to be non-evaluable for plasma concentration of Lu AA21004

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis Set:	All Subjects Who Signed the Informed Consent Form
Analysis Variable(s):	Date First Subject Signed Informed Consent Form MedDRA Version SAS Version Used for Creating the Datasets
Analytical Method(s):	Study information shown in the analysis variables section will be provided. (1) Study Information

7.3.2 Screen Failures

Analysis Set:	All Subjects Who Did Not Enter the Treatment Period
Analysis Variable(s):	[ ] shows categories (hereinafter, the same) Age (years) Gender [Male, Female]
Analytical Method(s):	The following summaries will be provided for the above analysis variable(s). (1) Frequency distributions for counting values and descriptive statistics for continuous variables

7.3.3 Subject Eligibility

Analysis Set:	All Subjects Who Signed the Informed Consent Form	
Analysis Variable(s):	Eligibility Status	[Eligible for Entrance into the Treatment Period, Not Eligible for Entrance into the Treatment Period]
	Primary Reason for Subject Not Being Eligible	[Adverse Event, Death, Lost to Follow-up, Pregnancy, Significant Protocol Deviation, Sample Size Sufficient, Screening Failure, Study Termination, Voluntary Withdrawal, Other]
Analytical Method(s):	The following summaries will be provided for the above analysis variable(s). When calculating percentages for the primary reasons for subject not being eligible, the total number of ineligible subjects will be used as the	

denominator.

(1) Frequency Distributions

7.3.4 Disposition of Subjects

Analysis Set:	All Subjects Who Entered the Treatment Period	
Analysis Variable(s):	Study Completion Status	[Completed All Planned Study Visits, Did Not Complete All Planned Study Visits]
	Reason for Discontinuation of Study Visits	[Adverse Event, Death, Lost to Follow-up, Pregnancy, Significant Protocol Deviation, Study Termination, Voluntary Withdrawal, Other]
Analytical Method(s):	Frequency distributions will be provided by group and overall. When calculating percentages for the reasons for discontinuation, the total number of subjects who did not complete all planned study visits will be used as the denominator. (1) Frequency Distributions	

7.3.5 Protocol Deviations and Analysis Sets

7.3.5.1 Protocol Deviations

Analysis Set:	All Subjects Who Entered the Treatment Period	
Analysis Variable(s):	Significant Protocol Deviation	[Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication/Dose, Withdrawal Criteria, Major GCP Violations]
Analytical Method(s):	Frequency distributions will be provided by group and overall. A number of subjects with protocol deviation and frequency distributions of each deviation according to the above categories will be provided. A subject who has several deviations will be counted once in each appropriate category (overlapping). (1) Frequency Distributions	

7.3.5.2 Analysis Sets

Analysis Set:	All Subjects Who Entered the Treatment Period	
Analysis Variable(s):	Handling of Subjects	[Categories are based on the specifications in Subject Evaluability List]
	Inclusion/Exclusion of Analysis Sets	
	Safety Analysis Set	[Included]
	Pharmacokinetic Analysis Set	[Included]
Analytical Method(s):	Frequency distributions will be provided by group for (1), and by group and overall for (2). For (1), a subject who corresponds to several categories will be counted once in each appropriate category (overlapping). (1) Frequency distributions for handling of subjects in each analysis set (2) Frequency distributions for number of subjects included in each analysis set	

7.4 Demographic and Other Baseline Characteristics

Analysis Set:	Safety Analysis Set Pharmacokinetic Analysis Set	
Analysis Variable(s):	Age (years)	
	Gender	[Male, Female]
	Height (cm)	
	Weight (kg)	
	BMI (kg/m^2)	
	Smoking Classification	[The subject has never smoked, The subject is a current smoker, The subject is an ex-smoker]
	Alcohol Classification	[Everyday, 2 to 3 Days a Week, 2 to 3 Days a Month, Never]
	Caffeine Classification	[Yes, No]
Analytical Method(s):	Frequency distributions will be provided by group and overall. (1) Frequency distributions for counting values and descriptive statistics for continuous variables	

7.5 Medical History and Concurrent Medical Conditions

Not applicable.

7.6 Medication History and Concomitant Medications

Not applicable.

7.7 Study Drug Exposure and Compliance

Analysis Set:	Safety Analysis Set
Analysis Variable(s):	Number of Times the Study Drug was Taken [1, 2]
Analytical Method(s):	Frequency distributions will be provided by group and overall. (1) Frequency distributions for counting values

7.8 Efficacy Analysis

Not applicable.

7.8.1 Primary Efficacy Endpoint(s)

Not applicable.

7.8.2 Secondary Efficacy Endpoint(s)

Not applicable.

7.8.3 Additional Efficacy Endpoint(s)

Not applicable.

7.8.4 Statistical/Analytical Issues

7.8.4.1 Adjustments for Covariates

Not applicable.

7.8.4.2 Handling of Dropouts or Missing Data

Missing test results and data determined to be non-evaluable according to this document will not be used for hypothesis testing and estimations.

For plasma concentrations and laboratory test results, values below the lower limit of quantification will be treated as zero when calculating the descriptive statistics. For laboratory test results, values above the upper limit of quantification will be treated as the upper limit value when calculating the descriptive statistics.

7.8.4.3 Multicenter Studies

Not applicable.

7.8.4.4 Multiple Comparison/Multiplicity

Not applicable.

7.8.4.5 Use of an "Efficacy Subset" of Subjects

Not applicable.

7.8.4.6 Active-Control Studies Intended to Show Equivalence or Non-Inferiority

The bioequivalence for Lu AA21004 will be assessed based on “Partial Revision of Guideline for Bioequivalence Studies of Generic Products”. Formulations are considered to be bioequivalent if any of the following criteria are met. If the bioequivalence cannot be verified, it will be considered adding additional subjects.

For the primary endpoints (AUC_{last} and C_{max}) of unchanged Lu AA21004, the two-sided 90% CIs of the difference in the mean values of logarithmic parameters to be assessed between two treatments is within the acceptable range of ln(0.80) to ln(1.25).

7.8.4.7 Examination of Subgroups

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

7.9.1.1 Plasma Concentrations

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variable(s): Plasma Concentrations of Unchanged Lu AA21004

Visit: Predose, 1, 2, 4, 6, 8, 10, 12, 14, 16, 24, 36, 48, and 72 Hours Postdose

Analytical Method(s): The following summaries will be provided.

(1) Descriptive Statistics of Plasma Concentrations for each treatment by Visit

(2) Mean and Standard Deviation Plot of Plasma Concentrations for each treatment (vertical axis: normal scale)

(3) Mean Plot of Plasma Concentrations for each treatment (vertical axis: common logarithmic scale)

7.9.1.2 Pharmacokinetic Parameters

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variable(s): Pharmacokinetic Parameters of Unchanged Lu AA21004

AUClast	AUCinf	Cmax
tmax	t1/2z	MRTinf, ev
MRTlast, ev	λz	

Treatment Ratio of Test Product to Reference Product in AUClast and Cmax of Unchanged Lu AA21004 (One Lu AA21004 20 mg tablet / Two Lu AA21004 10 mg tablets)
(R(AUClast), R(Cmax))

Analytical Method(s): The following summaries will be provided by treatment.

(1) Summary of Pharmacokinetic Parameters

For AUClast, Cmax, and AUCinf, descriptive statistics, geometric mean, and CV will be provided.

For tmax, descriptive statistics will be provided.

For all other variables other than AUClast, Cmax, AUCinf, and tmax, descriptive statistics and CV will be provided.

7.9.1.3 Assessment of Bioequivalence

Primary Endpoints

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variable(s): Pharmacokinetic Parameters of Unchanged Lu AA21004

AUClast Cmax

Analytical Method(s): The following analysis will be performed for the above analysis variable(s)

(1) The difference in the least square means between treatments (One Lu AA21004 20 mg tablet – Two Lu AA21004 10 mg tablets) and the two-sided 90% CIs will be provided using a crossover ANOVA model. The ANOVA model will include log-transformed (natural log) analysis variable as dependent variable, and treatment, group, and period as independent variables.

Secondary Endpoints

Analysis Set: Pharmacokinetic Analysis Set

Analysis Variable(s): Pharmacokinetic Parameters of Unchanged Lu AA21004

AUCinf tmax t1/2z

MRTinf, ev MRTlast, ev λz

Analytical Method(s): The following analysis will be performed for the above analysis variable(s).

(1) For analysis variables other than tmax, the difference in the least square means between treatments (One Lu AA21004 20 mg tablet – Two Lu AA21004 10 mg tablets) and the two-sided 90% and 95% CIs will be provided using a crossover ANOVA model. The ANOVA model will include log-transformed (natural log) analysis variable as dependent variable, and treatment, group, and period as independent variables.

(2) For tmax, the difference in the least square means between treatments (One Lu AA21004 20 mg tablet – Two Lu AA21004 10 mg tablets) and the two-sided 90% and 95% CIs will be provided using a crossover ANOVA model. The ANOVA model will include analysis variable as dependent variable, and treatment, group, and period as independent variables.

7.9.1.4 Individual Plasma Concentrations

Analysis Set:	All Subjects Who Entered the Treatment Period
Analysis Variable(s):	Plasma Concentrations of Unchanged Lu AA21004
Visit:	Predose, 1, 2, 4, 6, 8, 10, 12, 14, 16, 24, 36, 48, and 72 Hours Postdose
Analytical Method(s):	The following case plots will be provided. (1) Plot Over Time for Each Subject of Plasma Concentrations of Lu AA21004 (vertical axis: normal scale)

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

Not applicable.

7.11 Safety Analysis

7.11.1 Adverse Events

7.11.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set: Safety Analysis Set

Analysis Variable(s): TEAE

Categories: Relationship to Study Drug [Related, Not Related]
Intensity [Mild, Moderate, Severe]

Analytical Method(s): The following summaries will be provided by treatment.

(1) Overview of TEAEs

1) All TEAEs (number of events, number and percentage of subjects)
2) Relationship of TEAEs to study drug (number of events, number and percentage of subjects)
3) Intensity of TEAEs (number of events, number and percentage of subjects)
4) TEAEs leading to study drug discontinuation (number of events, number and percentage of subjects)
5) Serious TEAEs (number of events, number and percentage of subjects)
6) Relationship of serious TEAEs to study drug (number of events, number and percentage of subjects)
7) Serious TEAEs leading to study drug discontinuation (number of events, number and percentage of subjects)
8) TEAEs resulting in death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below.

When calculating percentages of subjects with occurrence of TEAE, the number of subjects who were treated by that treatment in the safety analysis set will be used as the denominator.

[Number of subjects]

- Summaries for 2) and 6)
  A subject with occurrences of TEAE in both categories (i.e., Related and Not Related) will be counted once in the Related category.
- Summary for 3)
  A subject with multiple occurrences of TEAE will be counted once for the

TEAE with the maximum intensity.

- Summaries other than 2), 3), and 6)
  A subject with multiple occurrences of TEAE will be counted only once.

[Number of events]

For each summary, the total number of events will be calculated.

7.11.1.2 Displays of Treatment-Emergent Adverse events

Analysis Set:	Safety Analysis Set
Analysis Variable(s):	TEAE
Categories:	Intensity [Mild, Moderate, Severe]
Analytical Method(s):	The following summaries will be provided using frequency distribution by treatment.

TEAEs will be coded using the MedDRA and will be summarized using System Organ Class (SOC) and Preferred Term (PT). SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by SOC only or PT only.

(1) TEAEs by SOC and PT
(2) TEAEs by SOC
(3) TEAEs by PT
(4) Drug-Related TEAEs by SOC and PT
(5) Intensity of TEAEs by SOC and PT
(6) Intensity of Drug-Related TEAEs by SOC and PT
(7) TEAEs Leading to Study Drug Discontinuation by SOC and PT
(8) Serious TEAEs by SOC and PT

The frequency distribution will be provided according to the rules below.

[Number of subjects]

- Summary tables other than (5) and (6)
  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. When calculating percentages of subjects with occurrence of TEAE, the number of subjects who were treated by that treatment in the safety analysis set will be used as the denominator.

- Summary tables for (5) and (6)
  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity. When calculating percentages of subjects with occurrence of TEAE, the number of subjects who were treated by that treatment in the safety analysis set will be used as the denominator.

7.11.1.3 Displays of Pretreatment Events

Analysis Set:	All Subjects Who Signed the Informed Consent Form
Analysis Variable(s):	PTE
Analytical Method(s):	The following summaries will be provided using frequency distribution. PTEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency. (1) PTEs by SOC and PT (2) Serious PTEs by SOC and PT The frequency distribution will be provided according to the rules below. [Number of subjects] A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT.

7.11.2 Clinical Laboratory Evaluations

7.11.2.1 Hematology and Serum Chemistry

Analysis Set:	Safety Analysis Set		
Analysis Variable(s):	Hematology		
	Erythrocytes (RBC)	Hemoglobin	Hematocrit
	Platelets	Leukocytes (WBC)	
	WBC Differentials (Neutrophils/Leukocytes, Eosinophils/Leukocytes, Basophils/Leukocytes, Lymphocytes/Leukocytes, Monocytes/Leukocytes)		
	Serum Chemistry		
	Albumin	ALT (GPT)	ALP
	AST (GOT)	GGT	Total Bilirubin
	Direct Bilirubin	Total Protein	Creatinine
	Creatine Kinase (CPK)	Blood Urea Nitrogen	Potassium
	Sodium	Chloride	Calcium
	Phosphate	Glucose	Total Cholesterol
	HDL-Cholesterol	LDL-Cholesterol	Triglycerides
	Urate		
Categories:	Adjudication Result Based on the Normal Reference Range	[Low, Normal, or High Relative to the Normal Reference Range]	
Visit:	Predose, 72 Hours Postdose		
Analytical Method(s):	The following summaries will be provided by treatment.		

(1) Descriptive statistics for observed values and changes from baseline (each postdose visit – Predose) by visit
(2) Plots over time for each subject
(3) Shift tables on adjudication results based on the normal reference range showing the number of subjects in each category at Predose and each postdose visit

7.11.2.2 Urinalysis

Analysis Set:	Safety Analysis Set	
Analysis Variable(s):	Specific Gravity	
	pH	
	Protein	[-, +-, 1+, 2+, 3+]
	Glucose	[-, +-, 1+, 2+, 3+, 4+]
	Occult blood	[-, +-, 1+, 2+, 3+]
	Urobilinogen	[+-, 1+, 2+, 3+]
	Ketones	[-, +-, 1+, 2+, 3+]
Categories:	Adjudication Result Based on the Normal Reference Range	[Low, Normal, or High Relative to the Normal Reference Range]
Visit:	Predose, 72 Hours Postdose	
Analytical Method(s):	For specific gravity, summaries (1), (2), and (4) will be provided by treatment. For pH, summaries (4) will be provided by treatment. For each variable other than specific gravity and pH, summaries (3) will be provided by treatment. (1) Descriptive statistics for observed values and changes from baseline (each postdose visit – Predose) by visit (2) Plots over time for each subject (3) Shift tables showing the number of subjects in each category at Predose and each postdose visit (4) Shift tables on adjudication results based on the normal reference range showing the number of subjects in each category at Predose and each postdose visit	

7.11.3 Vital Signs

Analysis Set:	Safety Analysis Set
Analysis Variable(s):	Temperature (Armpit) Systolic Blood Pressure Diastolic Blood Pressure Pulse Rate
Visit:	Predose, 24 and 72 Hours Postdose

Analytical Method(s): The following summaries will be provided by treatment.

(1) Descriptive statistics for observed values and changes from baseline (each postdose visit – Predose) by visit
(2) Plots over time for each subject

7.11.4 12-Lead ECGs

Analysis Set: Safety Analysis Set

Analysis Variable(s): Heart Rate
RR Interval
PR Interval
QT Interval
QRS Interval
QTcF Interval
Interpretation [Within Normal Limits, Abnormal but not Clinically Significant, Abnormal and Clinically Significant]

Visit: Predose (Screening) and 72 Hours Postdose

Analytical Method(s): For each variable other than 12-lead ECG interpretations, summaries (1) and (2) will be provided by treatment.
For 12-lead ECG interpretation, summary (3) will be provided by treatment.

(1) Descriptive statistics for observed values and changes from baseline (each postdose visit – Predose) by visit
(2) Plots over time for each subject
(3) Shift tables showing the number of subjects in each category at Predose and each postdose visit

7.11.5 Other Observations Related to Safety

Not applicable.

7.12 Interim Analysis

Not applicable.

7.13 Changes in the Statistical Analysis Plan

Statistical Analysis Plan (Version 1: 13 March 2018→Version 2: 14 June 2018)

Before change

7.11.2.2 Urinalysis

Analytical Method(s):	For specific gravity, summaries (1), (2), and (4) will be provided by treatment. For each variable other than specific gravity, summaries (3) will be provided by treatment.

After change

Analytical Method(s):	For specific gravity, summaries (1), (2), and (4) will be provided by treatment. For pH, summaries (4) will be provided by treatment. For each variable other than specific gravity and pH, summaries (3) will be provided by treatment.

Reason for change

Due to error in writing

8.0 REFERENCES

Not applicable.