16.1.9 Documentation of Statistical Methods

The final approved Statistical Analysis Plan and other statistical documents, as applicable, for this study are provided in the following pages.

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E2730-A001-201
Study Protocol Title:	A Multicenter, Double-Blind, Randomized, Cross-Over Study Evaluating Pharmacodynamic Activity of E2730 in Adult Subjects with Photosensitive Epilepsy
Date:	13 FEB 2019
Version:	Version 1.0

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
AED	antiepileptic drug
ATC	anatomical therapeutic class
BMI	Body Mass Index
BP	blood pressure
CI	confidence interval
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
EEG-IPS	electroencephalogram intermittent photic stimulation
EOT	end of treatment
LNH	low/normal/high
LS	least square
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic(s)
CCI [redacted]	
PK	pharmacokinetic(s)
PPR	photoparoxysmal response
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SD	standard deviation
SI	Système International
SOC	system organ class
TEAE	treatment-emergent adverse event
TLG	tables, listings, and graphs
WHO DD	World Health Organization drug dictionary

3 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Eisai Protocol E2730-A001-201.

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective of the study is to assess the pharmacodynamics (PD) activity of E2730 as measured by suppression of epileptic PPR in the subject's most sensitive eye condition as a proof of principle of efficacy in subjects with photosensitive epilepsy.

3.1.2 Secondary Objectives

The secondary objectives of the study are:

- To assess the PD activity of E2730 as measured by suppression of epileptic PPR, onset, maximum change, and duration of response in 3 eye-conditions (eye closure, eyes closed, and eyes open) in subjects with photosensitive epilepsy.
- To assess the safety and tolerability of E2730 following a single oral dose in subjects with photosensitive epilepsy.
- To assess the pharmacokinetics (PK) of E2730 following a single oral dose in subjects with photosensitive epilepsy.
- To evaluate potential exposure-PD response relationships.

3.1.3 CCI

CCI [redacted]

3.2 Overall Study Design and Plan

This is a multicenter, double-blind, randomized, 6-sequence, 3-treatment, 3-period cross-over study in adult subjects with epilepsy. This study will use the photosensitivity proof of principle model to determine the potential of E2730 to reduce the photosensitive range in adult subjects. This study will have 2 phases: Prerandomization and Randomization. The Prerandomization Phase will consist of a Screening Period (up to 3 weeks), during which each subject's study eligibility will be determined and baseline assessments will be conducted. The Randomization Phase will consist of 3 Treatment Periods with a single dose in each period (placebo, E2730 40 mg, or E2730 120 mg, each separated by a 3-week (±3 days) washout interval for a total of approximately 6 weeks), and a Follow-up Period (a

single visit, 3 weeks ±3 days after the last day of study product administration). All visits will be conducted on an outpatient basis. Each subject will receive a single oral dose in a cross-over sequence according to his/her randomization code for the treatment sequence.

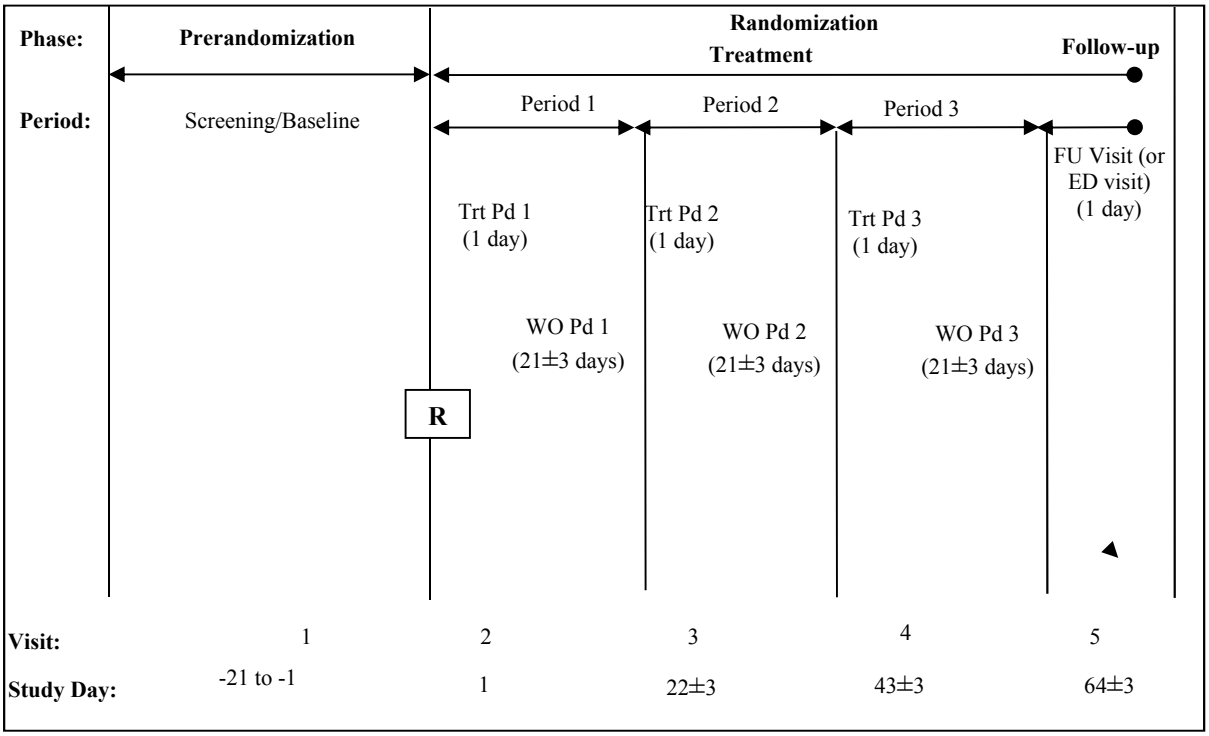
Table of Treatment Sequences

Sequence	Treatment Period 1	Treatment Period 2	Treatment Period 3
1: ABC	Placebo	E2730 40 mg	E2730 120 mg
2: BCA	E2730 40 mg	E2730 120 mg	Placebo
3: CAB	E2730 120 mg	Placebo	E2730 40 mg
4: ACB	Placebo	E2730 120 mg	E2730 40 mg
5: BAC	E2730 40 mg	Placebo	E2730 120 mg
6: CBA	E2730 120 mg	E2730 40 mg	Placebo

A = Placebo; B = E2730 40 mg; C = E2730 120 mg

An overview of the study design is presented by Figure 1 in the study protocol as follows.

Figure of Study Design for a Crossover Study



ED = Early discontinuation, FU = Follow Up, Pd = period, R = randomization, Trt = treatment, WO = washout.

4 DETERMINATION OF SAMPLE SIZE

Approximately 9 subjects with photosensitive epilepsy and a stable PPR will be needed to be randomized in the study in order to obtain 6 evaluable subjects. Based on a similar study in subjects with photosensitive epilepsy (NCT02564029), an estimated standard deviation of the treatment group difference of the SPR in the subject's most sensitive eye condition is 3.62. The width of a 90% CI of the mean group difference based on this standard deviation assumption and 6 subjects is 2.431. Therefore, a sample size of 6 would be sufficient to detect a mean group difference of 3 or larger with 90% confidence.

Subjects who discontinue from the study early may be replaced, after consultation with the sponsor. A subject will be defined as evaluable if the subject has completed at least 2 treatment periods (including one with placebo) and has more than 50% non-missing postdose PPR data in each period to get the average PPR value (ie, at least 3 of 5 posedose PPR data are valid in each period).

5 STATISTICAL METHODS

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, minimum and maximum unless otherwise specified. Categorical variables will be summarized as number (percentage) of subjects.

5.1 Study Endpoints

5.1.1 Primary Endpoint

The primary endpoint is mean change from baseline in the PPR range in each subject's most sensitive eye condition at each dose level of E2730 as compared to placebo.

5.1.2 Secondary Endpoints

- Mean changes from baseline in PPR ranges in each subject's eye closure, eyes closed, and eyes open condition at each dose level of E2730 as compared to placebo
- Onset, maximum change, and duration of photosensitivity response at each dose level in all 3 eye conditions at the time course of E2730 as compared to placebo
- Frequency and percentage of subjects with Complete Suppression, Partial Response, and no Response of PPR at each dose level of E2730 as compared to placebo
- Occurrence of AEs or changes in the neurological examination after single doses of E2730 compared to placebo
- Changes in vital signs, serum chemistries, complete blood counts, or liver function tests after single doses of E2730 compared to placebo

- PK of E2730 and its N-acetyl metabolite, M1

- Relationship between PK parameters of E2730 onset, maximum change, and duration of impact on photosensitivity

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.

The Pharmacokinetic Analysis Set is the group of randomized subjects who receive at least 1 dose of study drug and have sufficient PK data to derive at least 1 PK parameter.

The Pharmacodynamic Analysis Set is the group of randomized subjects who receive at least 1 dose of study drug and have sufficient PD data to derive at least 1 PD parameter.

5.2.2 Subject Disposition

The number of subjects screened and the number failing screening (overall and by reason for failure) will be summarized. Screen failure data will be listed. The number of subjects randomized along with the number of subjects administered each dose of E2730 will also be presented.

Subjects who prematurely terminate their participation in the study will be summarized by their primary reason as well as any other reasons(s) for study termination.

5.2.3 Protocol Deviations

Major protocol deviations will be presented as a listing.

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set will be summarized overall using descriptive statistics. Continuous demographic and baseline variables include age, height, and weight; categorical variables include sex, age group, race, and ethnicity.

Medical History

The number (percentage) of subjects in the Safety Analysis Set reporting a history of any medical condition, as recorded on the CRF, will be summarized overall. A subject data listing of medical and surgical history will be provided.

5.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD). The latest version before database lock will be used for analysis. The number (percentage) of subjects who took prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) class, and World Health Organization Drug Dictionary preferred term (PT). Prior medications will be summarized overall and concomitant medications will be summarized by treatment group. Prior medications will be defined as medications that stopped before the dose of study drug in treatment period 1. Concomitant medications for a treatment group will be defined as medications that started after the date of the dose of study drug up to 28 days after the subject's dose or the next dose date in next treatment period which is earlier. All prior and concomitant medications will be presented in subject data listings.

5.2.6 Treatment Compliance

Not Applicable.

5.3 Data Analysis General Considerations

Because of the crossover design of the study, analyses results will be summarized by treatment sequence (Sequence 1 to Sequence 6) and by treatment group (Placebo, E2730 40 mg, E2730 120 mg) as appropriate. When results are summarized by treatment, data from subjects receiving a given treatment in the corresponding period are combined. For example, placebo treatment comprises data from Treatment Period 1 of Sequence 1, Treatment Period 3 of Sequence 2, Treatment Period 2 of Sequence 3, Treatment Period 1 of Sequence 4, Treatment Period 2 of Sequence 5, and Treatment Period 3 of Sequence 6 (see Table of Treatment Sequences).

For those listings or data summaries where change from baseline measurements will be calculated and presented, unless stated otherwise, the last observed measurement, including unscheduled assessments, prior to the first dose of study drug in the first period will be considered the baseline measurement for all assessments except PPR related endpoints.

All descriptive statistics for continuous variables will be reported using number of observations (n), mean, standard deviation (SD), median, minimum, and maximum unless otherwise specified. Categorical variables will be summarized as number and percentage of subjects.

Listings will include all subjects, unless specified otherwise, and will be presented by sequence, treatment and subject.

5.3.1 Pooling of Centers

Subjects from all centers will be pooled for all analyses.

5.3.2 Adjustments for Covariates

Predose PPR value as baseline will be included in the mixed model as the adjustment for covariate.

5.3.3 Multiple Comparisons/Multiplicity

Not applicable.

5.3.4 Examination of Subgroups

Not applicable.

5.3.5 Handling of Missing Data, Dropouts, and Outliers

If there are more than 3 dropouts in the study, a subject discontinuing/discontinued from the study for any reason may be replaced at the discretion of the sponsor. Missing values in PPR will not be imputed in this study.

For PD analyses, two summaries for the primary and secondary PPR endpoints will be produced, if different, one for all data in PD analysis set and one for all completers.

For safety summaries, all data in Safety Analysis Set will be included.

5.3.6 Other Considerations

Not applicable.

5.4 Efficacy Analyses

Not Applicable.

5.5 Pharmacokinetic, Pharmacodynamic, CCI [redacted] Analyses

5.5.1 Pharmacokinetic Analyses

The Safety Analysis Set will be used for individual E2730 and M1 plasma concentration-time listings. The PK Analysis set will be used for summaries of E2730 and M1 plasma concentrations, summaries and listings of PK parameters. Plasma concentrations will be tabulated by nominal sampling time and summarized by treatment dose using summary statistics.

The following PK parameters will be derived by noncompartmental analysis using plasma concentrations of E2730 and M1. These parameters will include, but are not limited to:

- C_{max} maximum observed concentration
- $AUC_{(0\text{-}8h)}$ area under concentration x time curve from time 0 to 8 hours postdose
- t_{max} time to reach C_{max} following drug administration

The PK of E2730 will be analyzed based on available data from this study. The PK and PD Analysis datasets will be used to evaluate the relationship of PK of E2730 and change in PPR response. The PK-PD analyses may include the examination of the relationship of PK of E2730 and PPR response (eg, time of onset, maximum change, and duration of PPR; Bond and Lader data) using model-based approaches.

5.5.2 Pharmacodynamic Analyses

The following PD analyses will be performed on the PD Analysis Set.

No multiplicity adjustments will be made. The 5 PPR measured postdose on a treatment day will be averaged and used for both primary endpoint and secondary endpoints. The predose PPR data from the respective treatment period will be used as the baseline data for that period.

Primary PD Analyses

The primary endpoint of mean change from baseline of the average PPR for each E2730 dose compared with placebo in the most sensitive eye condition will be performed using a mixed effects model for crossover study. The model will include treatment, period, and sequence as fixed effects, baseline (predose) measurement as a covariate, and subject nested within sequence as a random effect. Where data are normally distributed, least squares (LS) means, difference in LS means of each E2730 dose compared to placebo, and 90% CIs will be presented with no adjustments for multiplicity.

Secondary PD Analyses

The secondary endpoints of mean change from baseline of the average PPR for each E2730 dose compared with placebo in all 3 different eye conditions (eye closure, eyes closed, and eyes open) will be analyzed and summarized by using the same mixed effects model as for primary PD analyses.

Additional analysis by graphical exploration on onset, maximum change, and duration of photosensitivity response at each dose level will be performed for all 3 eye conditions at the time course of E2730 as compared to placebo. This analysis will provide further information on the frequency and percentage of subjects with Complete Suppression, Partial Response, and No Response of PPR (see Section 8.3 Definitions of Derived PPR Variables) at each dose level of E2730 as compared to placebo.

Sensitivity analyses for PPR may be conducted, for example, of PPR for subjects who completed all Treatment Periods 1-3 versus those who are included in the PD Analysis Set. CCI [redacted]

5.6 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. Safety data that will be evaluated include adverse events (AEs), clinical laboratory results, vital signs, ECGs, C-SSRS, and neurological/physical examinations. Treatment-emergent adverse events (TEAEs) will be summarized by presenting for each treatment group, the incidence of AEs.

Descriptive summary statistics (eg, mean, SD, median, minimum, and maximum for continuous variables, and the number and percent for categorical variables) of the laboratory, vital signs, and ECG parameters, and changes from baseline will be evaluated by treatment group. The proportion of subjects with any treatment-emergent report of suicidal ideation and behavior and intensity of these behaviors will be summarized.

All safety data will be presented in listings. Study Day 1 for all safety analyses will be defined as the date of the dose of study drug in treatment period 1.

5.6.1 Extent of Exposure

The number of subjects exposed to each study drug dose and placebo will be summarized descriptively by treatment and treatment period and provided in a listing.

5.6.2 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA (Version 20.0 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group, using the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of

subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] or No [not related]).

The number (percentage) of patients with treatment-emergent SAEs will be summarized by the latest edition of MedDRA SOC, and PT. A subject data listing of all SAEs, including deaths, will be provided.

A subject data listing of all AEs leading to discontinuation from study drug will be provided.

5.6.3 Laboratory Values

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in protocol section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in protocol section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment.

Appendix 1 (Sponsor's Grading for Laboratory Values) below presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

5.6.4 Vital Signs

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, and temperature) and changes from baseline will be presented by visit and treatment group.

Clinically notable ranges are defined as follows.

Variable	Criterion value[a]	Change relative to baseline[a]
Heart rate	>120 bpm	Increase of ≥15 bpm

	<50 bpm	Decrease of ≥15 bpm
Systolic BP	>180 mmHg	Increase of ≥20 mmHg
	<90 mmHg	Decrease of ≥20 mmHg
Diastolic BP	>105 mmHg	Increase of ≥15 mmHg
	<50 mmHg	Decrease of ≥15 mmHg

[a] Clinically notable means that a value must have met both the criterion value and satisfied the magnitude of change relative to baseline.

Vital sign values will be listed on an individual basis by sequence, treatment and subject. Clinically notable vital sign values will be identified on the listings as those above (H) or below (L) a clinically notable range.

5.6.5 Electrocardiograms

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTc Fridericia during the treatment period will be summarized. Clinically abnormal ECG results in QTc Fridericia will be categorized as follows:

For the QT interval assessment, clinically abnormal ECG results for QT interval corrected for heart rate using Fridericia's formula (QTcF) will be categorized as follows: QTcF values >450 msec, >480 msec, and >500 msec, and time-matched change from baseline in QTcF >30 msec and >60 msec.

5.6.6 Other Safety Analyses

The results of C-SSRS assessments will be listed for each subject. The incidence of suicidal ideation or suicidal behavior will be summarized by treatment group as appropriate.

5.7 Other Analyses

Not applicable.

6 INTERIM ANALYSES

No formal interim analyses are planned for this study.

7 CHANGES IN THE PLANNED ANALYSES

There are no changes to the statistical methods in this analysis plan compared to the latest protocol. Any future changes to the analysis will be documented separately and will be addressed in the Clinical Study Report.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

8.1 Definitions of Baseline Values

For PPR analyses in all 3 treatment periods, the predose PPR data from the respective treatment period will be used as baseline data for that period. If predose PPR data is not valid, the average PPR value at screening visit will be used as baseline for PPR analyses.

The baseline value for all safety endpoints will be the last non-missing measurement occurring prior to the first dose of study drug in the treatment period 1.

8.2 Definitions of Treatment Periods

Treatment periods 1 to 3 are one-day treatment periods which will include single dose of study drug on Day 1 (Visit 2) for treatment period 1, Day 22 (Visit 3) for treatment period 2, and Day 43 (Visit 4) for treatment period 3.

8.3 Definitions of Derived PPR Variables

The followings are definitions for PPR related analyses:

- Standard Photosensitivity Response (SPR): a standardized derived measure of the range of frequencies of IPS that elicits epileptiform EEG responses in a subject. The range is assigned a number, representing the number of frequency steps, from 0 to 14 between the lowest to the highest frequencies of IPS that elicits epileptiform activity by EEG. If the upper and lower limit of measured frequencies is the same, SPR will be set = 1.
- Most sensitive eye condition: SPR is measured in each of 3 eye states: eye closure, eyes closed, and eyes open. That eye condition that yields the largest SPR before dosing is defined as the most sensitive eye condition.
- Duration of suppression: The difference in hours between the onset of suppression and the end of suppression of photosensitivity. The onset of suppression is defined as the first time point at which the SPR was at least 3 units below the mean SPR at baseline. The end of suppression is defined as the last time (second time) with two successive reductions in SPR of at least 3 units lower than the mean SPR at baseline.
- Complete suppression is defined as a standardized photosensitivity response (SPR) reduction to 0 over at least 1 time point for all three eye conditions. Partial response is defined as a reduction in SPR of at least 3 units from baseline for at least 3 time points, and no time points with at least 3 units of increase, in the most sensitive eye condition; without meeting the complete suppression definition. No response is

defined as the response not meeting complete suppression or partial suppression definitions.

8.4 Definitions of PK Data Handling

8.4.1 Lower Limit of Quantification (LLOQ) of E2730 Plasma Concentration

The LLOQ of E2730 plasma concentration is 1.00 ng/mL. The LLOQ of M1 plasma concentration is 0.300 ng/mL.

8.4.2 Below Limit of Quantification (BLQ) Handling for Calculation of PK Parameters

While calculating PK parameters in Phoenix-WinNonlin, BLQ values will be handled according to the NCA-MNL.

8.4.3 BLQ Handling for Developing Concentration-Time Profiles

When developing individual concentration-time profiles, BLQ values will be handled according to the NCA-MNL.

8.4.4 Handling of Anomalous Concentration Values

The handling of anomalous concentration values will follow the guidance in the NCA-MNL.

8.4.5 General Rules for Presentation of Drug Concentration and PK Parameters

When presenting individual/raw values and summary statistics, the following rule will be applied: for drug concentrations and all summary statistics will have 3 significant digits except for tmax will have 2 decimal places.

9 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications will be provided in separate documents.

10 STATISTICAL SOFTWARE

All statistical analyses will be performed using SAS v 9.3 or later.

11 MOCK TABLES, LISTINGS, AND GRAPHS

The study TLG shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

12 REFERENCES

1. Columbia-Suicide Severity Rating Scale (C-SSRS). Columbia University. Available from: http://www.cssrs.columbia.edu/scales_cssrs.html

2. NCA-MNL: 302-104.01-MNL Non-Compartmental Analysis User Manual, June 2018

13 APPENDICES

13.1 Sponsor's Grading for Laboratory Values

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

13.2 SAS Code of Mixed Model for Primary PD Analyses

```
proc mixed data= xxx;
  class USUBJID TRTPN PERIOD SEQUENCE ;
  model AVAL = TRTPN PERIOD SEQUENCE BASE /SOLUTION ddfm= kr;
  random USUBJID(SEQUENCE) ;
  lsmeans TRTPN/alpha= 0.1 PDIFF CL ;
run;
```

SIGNATURE PAGE

Author:

[electronic signature in eDMS]

PPD

Date

Neurology Business Group

Approval:

[electronic signature in eDMS]

PPD

Date

Neurology Business Group

[electronic signature in eDMS]

PPD

Date

Neurology Business Group