

**16.1.9            Documentation of Statistical Methods**

The final approved [Statistical Analysis Plan](#) for this study is provided in the following pages.



## STATISTICAL ANALYSIS PLAN

**Study Protocol  
Number:** E2082-A001-201

**Study Protocol  
Title:** A Multicenter, Double-Blind, Randomized, Cross-Over Study  
Evaluating Pharmacodynamics Activity of E2082 in Adult Subjects  
with Photosensitive Epilepsy

**Date:** 4 September 2019

**Version:** Final Version 1,0

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## 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)                                   |
| PGx          | pharmacogenomic                                      |
| 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 E2082-A001-201.

#### 3.1 Study Objectives

##### 3.1.1 Primary Objective

To assess pharmacodynamics (PD) activity of E2082 as measured by suppression of epileptic photoparoxysmal response (PPR) in the subject's most sensitive eye condition in the photosensitivity model as a proof of principle of efficacy in subjects with photosensitive epilepsy, compared to placebo

##### 3.1.2 Secondary Objectives

The secondary objectives of the study are:

- To assess the PD activity of E2082 as measured by suppression of PPR in each of the 3 eye conditions (eye closure, eyes closed, and eyes open), compared to placebo
- To assess PD activity of E2082 as measured by onset, maximum change, and duration of photosensitivity response in each of the 3 eye conditions (eye closure, eyes closed, and eyes open)
- To assess proportion of subjects with complete suppression, partial suppression, and no response of standardized photosensitivity response (SPR)
- To assess other central nervous system (CNS)-related effects of E2082 based on Bond-Lader Visual Analogue Scale (BL-VAS)
- To assess the safety and tolerability of E2082 following single oral dose administration
- To assess the pharmacokinetics (PK) of E2082 following single oral dose administration

##### 3.1.3 Exploratory Objective

To explore relationships between PK and PD.

#### 3.2 Overall Study Design and Plan

This is a multicenter, double blind, randomized, 6-sequence, 3-treatment, 3-period, crossover study with an Open-Label Treatment Period, in adult subjects with photosensitive epilepsy.

This study will have 2 phases: Pretreatment Phase and Treatment Phase.

The Pretreatment Phase will consist of a Screening Period (up to 3 weeks from Visit 1), during which each subject's study eligibility will be determined.

The Treatment Phase will consist of 3 blinded Treatment Periods for a randomized crossover design, followed by an Open-label Treatment Period. During the blinded Randomized Crossover Treatment Periods, there will be 3 Treatment Visits (Visit 2 [Treatment Period 1], Visit 3 [Treatment Period 2], and Visit 4 [Treatment Period 3]) evaluating single-dose administrations of either placebo, E2082 2.5 mg, or E2082 25 mg in a blinded manner. During the open-label treatment period, subjects will be administered a single dose of E2082 40 mg.

A recent protocol amendment ([Amendment 01; V2.0](#)) has modified the study design to allow for the evaluation of an open-label dose administration of E2082 10 mg in subjects as applicable, depending on the scenario the subject falls under and depending on the subject's response (photoparoxysmal response [PPR]) during blinded Treatment Periods, as described below.

**Scenario 1:** Newly enrolled or ongoing subjects who have completed up to the Treatment Period 3 at the time of Protocol Amendment 01 implementation, will undergo 1 treatment visit (Visit 5 [Treatment Period 4]) during the Open-label treatment period to receive a single-dose administration of E2082 40 mg or 10 mg; the dose to be administered will be provided by an independent unblinded biostatistician upon review of the subject's response data collected during Treatment Periods 1 through 3.

**Scenario 2:** Subjects who completed the open-label Treatment Period 4 (Visit 5), and have not completed the Follow-Up visit [Visit 6]) by the time of Protocol Amendment 01 implementation may continue the study as originally planned (ie, process to Follow-up Visit [Visit 6]) or may continue in the study to receive an additional open-label, single oral dose of E2082 10 mg in the Treatment Period 5 (Visit 8) before proceeding to Follow-up Visit (Visit 9).

**Scenario 3:** Subjects who completed the study (including Follow-Up visit [Visit 6]) before the implementation of Protocol Amendment 01 may be allowed to re-enter the study to receive an open-label, single-dose administration of E2082 10 mg after Screening 2 (Visit 7) dependent on the subject's response to treatment during the subject's initial study participation.

Treatment visits (i.e., Visit 2, Visit 3, Visit 4, and Visit 5) will each be separated by a 2-week ( $\pm 3$  days) washout interval for a total of approximately 6 weeks. Treatment Period 5 (Visit 8) will be 2 weeks ( $\pm 3$  days) after Treatment Period 4 (Visit 5) for subjects in Scenario 2, and after Screening 2 for subjects in Scenario 3. All subjects will undergo a Follow-up Period of 2 weeks ( $\pm 3$  days) after the last day of study product administration (Visit 5 and/or Visit 8, as applicable). (revised per Amendment 01).

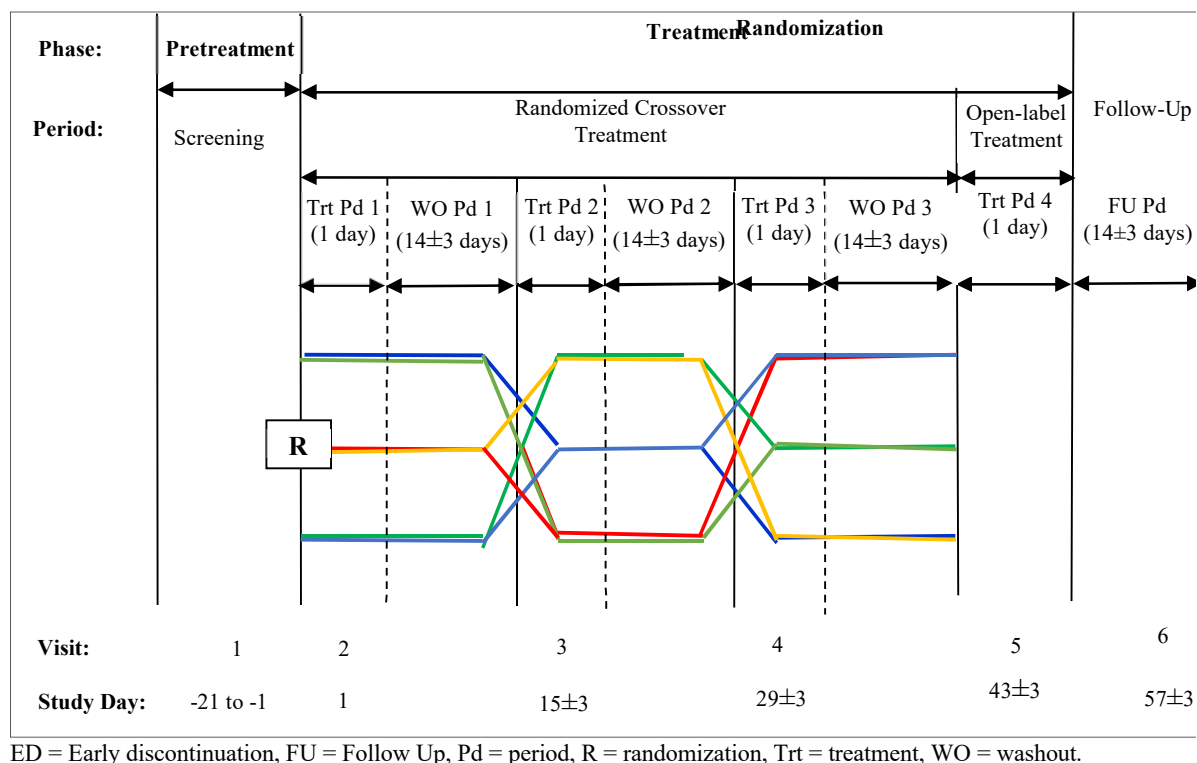
Each subject will receive a single oral dose in a crossover sequence according to his/her randomization code for the treatment sequence in 3 double-blinded treatment periods.

**Table of Treatment Sequences**

| Sequence | Double-Blind Treatment Periods |              |              |
|----------|--------------------------------|--------------|--------------|
|          | 1 (V2)                         | 2 (V3)       | 3 (V4)       |
| 1: ABC   | Placebo                        | E2082 2.5 mg | E2082 25 mg  |
| 2: BCA   | E2082 2.5 mg                   | E2082 25 mg  | Placebo      |
| 3: CAB   | E2082 25 mg                    | Placebo      | E2082 2.5 mg |
| 4: ACB   | Placebo                        | E2082 25 mg  | E2082 2.5 mg |
| 5: BAC   | E2082 2.5 mg                   | Placebo      | E2082 25 mg  |
| 6: CBA   | E2082 25 mg                    | E2082 2.5 mg | Placebo      |

A = Placebo; B = E2082 2.5 mg; C = E2082 25 mg;

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

**Figure 1 : Design for a Crossover Study**



An overview of the changes related to amendment is described below in Figure 2.

|                               |                        |  |   |
|-------------------------------|------------------------|--|---|
| <b>Phase:</b>                 | <b>Pretreatment</b>    | <b>Treatment</b>                                   |   |
| <b>Period:</b>                | Screening 2<br>(SCR-2) | Open-label<br>Treatment<br><br>Trt Pd 5<br>(1 day) | Follow-Up 2<br>(FU-2)<br><br>FU Pd<br>(14±3 days) |
| <b>Visit:</b>                 | 7                      | 8  | 9   |
| <b>Study Day<sup>a</sup>:</b> | -21 to -1              | 1  | 15±3  |

FU = Follow-up, SCR = screening, Pd = Period

a: Study days are with respective to the day of Treatment Period 5 (Visit 8).

**Figure 2 : Study Design for Subjects in E2082-A001-201 - Scenario 3  
(Revised per Amendment 01)**

## 4 DETERMINATION OF SAMPLE SIZE

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.

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.

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 (i.e., at least 3 of 5 posedose PPR data are valid in each period).

Subjects who discontinue from the study early may be replaced after consultation with the sponsor.

## 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.

Study data will be unblinded once double-blind treatment period has completed. Two sets of analyses tables will be created: one set after the unblinding using all the available data until that point and another set after all the subjects have completed the last study visit.

### 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 E2082 as compared to placebo.

#### 5.1.2 Secondary Endpoints

- Mean change from baseline in the PPR range in each of the 3 eye conditions (eye closure, eyes closed, and eyes open) at each dose level of E2082 compared to placebo
- Onset, maximum change, and duration of response in each of the 3 eye conditions (eye closure, eyes closed, and eyes open) at each dose level of E2082
- Frequency and percentage of subjects with complete suppression, partial response, and no response of SPR at each dose level of E2082
- Changes from baseline in BL-VAS at each dose level of E2082
- Incidence of TEAEs at each dose level of E2082
- Clinically significant changes from baseline in vital signs, serum chemistries, complete blood counts, or liver function tests after single doses of E2082, compared to placebo
- PK parameters of E2082 ( $C_{\max}$ ,  $t_{\max}$ , area under concentration-time curve from time 0 to 8 hours postdose [ $AUC_{(0-8h)}$ ])
- Relationship between PK parameters of E2082 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

Number of subjects screened and screening failures (overall and by reason for failure) will be summarized. The number of subjects randomized along with the number of subjects received each dose of E2082 will also be presented.

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

### 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 by treatment groups and overall. Continuous demographic and baseline variables include age, height, and weight; categorical variables include sex, age group, race, and ethnicity.

### 5.2.5 Prior and Concomitant Therapy

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 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, whichever is earlier.

Prior medications will be summarized overall and concomitant medications will be summarized by treatment group. The latest version before database lock will be used for analysis.

### 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 presented by treatment

sequence (Sequence 1 to Sequence 6) and by treatment group (Placebo, E2082 2.5 mg, E2082 25 mg) as appropriate. For by treatment group summaries, data from subjects receiving a given treatment will be combined across various sequences.

For 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 (baseline) PPR values 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

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, Pharmacogenomic, and Other Biomarker Analyses

### 5.5.1 Pharmacokinetic Analyses

The Safety Analysis Set will be used for individual listings of E2082 plasma concentration-time data. The PK Analysis set will be used for descriptive statistics of E2082 plasma concentration-time data. Plasma concentrations will be tabulated by nominal sampling time and summarized by treatment group.

Various PK parameters will be derived and relationship between PK of E2082 and PD parameters will be explored. These analyses will be specified in separate PK SAP/report.

### 5.5.2 Pharmacodynamic Analyses

No multiplicity adjustments will be made. The PPR measurements collected at the 5 postdose timepoints on a given treatment day will be averaged and the arithmetic average value will be used for both primary endpoint and secondary endpoint analyses. The predose PPR data from the respective treatment period will be used as the baseline data for that period. The following PD analyses will be performed on the PD Analysis Set.

#### Primary PD Analyses

The reduction in PPR response will be evaluated for 8 hours postdose during each Treatment Period. A diminution in response is anticipated with the dose range.

The primary endpoint, mean change from baseline of the average PPR in the most sensitive eye condition, will be summarized by treatment group, and analyzed using a mixed effects model for crossover part of the study. The mixed effects model for the crossover part of the study will include treatment (E2082 2.5 mg, 25 mg, and placebo), period, and sequence as fixed effects, baseline (predose) measurement as a covariate, and subject nested within sequence as a random effect. Least squares (LS) means, difference in LS means of each E2082 dose (2.5 mg or 25 mg) 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 E2082 dose for all 3 different eye conditions (eye closure, eyes closed, and eyes open) will be summarized by treatment group and compared with placebo by using the same mixed effects model as for primary PD analyses.

Table and figure for the proportions of subjects with complete suppression, partial response, or no response will be displayed by treatment group (see [section 8.3](#) for definition of complete, partial suppression or no response).

Evaluation of onset, maximum change, and duration of photosensitivity response at each dose level will be performed for all 3 eye conditions for each treatment using summary and graphical displays.

Sensitivity analyses may be conducted for photosensitivity response, for example, in subjects who completed all 3 Treatment Periods 1 through 3 versus those who are included in the PD Analysis Set. Other exploratory analyses may be conducted as data permit.

All other PD data (ie, BL-VAS data) may be summarized by treatment groups using standard summary statistics.

PK-PD analyses may include examination of relationship between PK of E2082 and SPR (eg, time of onset, maximum change, and duration of response; and BL-VAS data) using model-based approaches as permitted by data. Details of the PK/PD analyses will be described in a separately prepared analysis plan and its report.

## 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 for each treatment group by incidence of each AE.

Descriptive summary statistics of the laboratory, vital signs, and ECG parameters, and changes from baseline will be presented 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.

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 group and treatment period.

### 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 treatment-emergent adverse event (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 TEAEs will be included in the 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 subjects 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 at that dose) 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 visit via shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Number and percentage of subjects with markedly abnormal laboratory values will be summarized. [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.

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 and presented in the listings.

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.

In addition, the number (percentage) of subjects with at least 1 clinically notable vital sign results will be summarized by treatment groups. Clinically notable ranges are defined as follows:

| Variable     | Criterion value <sup>a</sup> | Change relative to baseline <sup>a</sup> |
|--------------|------------------------------|--|
| Heart rate   | >120 bpm                     | Increase of $\geq 15$ bpm                |
|              | <50 bpm                      | Decrease of $\geq 15$ bpm                |
| Systolic BP  | >180 mmHg                    | Increase of $\geq 20$ mmHg               |
|              | <90 mmHg                     | Decrease of $\geq 20$ mmHg               |
| Diastolic BP | >105 mmHg                    | Increase of $\geq 15$ mmHg               |
|              | <50 mmHg                     | Decrease of $\geq 15$ mmHg               |

<sup>a</sup> Clinically notable means that a value must have met both the criterion value and satisfied the magnitude of change relative to baseline.

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.

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 may 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. However, there is no data with 10 mg thus the statistical analyses and TLGs do not include 10 mg.

## 8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

### 8.1 Definitions of Baseline Values

For PPR analyses in all 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 4 are one-day treatment periods which will include single dose of study drug on Day 1 (Visit 2) for treatment period 1, Day 15 (Visit 3) for treatment period 2, Day 29 (Visit 4) for treatment period 3, and Day 43 (Visit 5) for treatment period 4.

### 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.
- Response: 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

Rules for handling PK data for derivation of PK parameters will be defined in separate PK report. 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](http://www.cssrs.columbia.edu/scales_cssrs.html)

## 13 APPENDICES

### 13.1 Sponsor's Grading for Laboratory Values

#### Sponsor's Grading for Laboratory Values

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

### Sponsor's Grading for Laboratory Values

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

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT =  $\gamma$ -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
  pdiff=control('Placebo') ;
run;
```

**SIGNATURE PAGE**

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| Neurology Business Group       |      |
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