



## STATISTICAL ANALYSIS PLAN

**Study Protocol Number:** E2007-G000-311

**Study Protocol Title:** An Open-Label, Multicenter Study with an Extension Phase to Evaluate the Safety, Tolerability, and Exposure-Efficacy Relationship of Perampanel Oral Suspension when Administered as an Adjunctive Therapy in Pediatric Subjects (Age 4 to less than 12 years) with Inadequately Controlled Partial-Onset Seizures or Primary Generalized Tonic-Clonic Seizures

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## 2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

<b>Abbreviation</b>	<b>Term</b>
ABNAS	A-B neuropsychological assessment schedule
AE(s)	adverse event(s)
AED	antiepileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomical therapeutic class
BMI	body mass index
CBCL	Child Behavior Checklist
CGI	Clinical Global Impression
CGIC	Clinical Global Impression of Change
CGIS	Clinical Global Impression of Severity
CRF	case report form
C <sub>ss,av</sub>	average steady-state drug concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EEG	Electroencephalogram
EQ-5D-Y	EuroQol 5 Dimensions – Youth
FAS	Full Analysis Set
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
GTC	Generalized Tonic-Clonic
HRQL	health-related quality of life
ICF	informed consent form
IP	Investigational Products
LGPT	Lafayette Grooved Pegboard Test
LLN	lower limit of normal
LNH	low/normal/high
MedDRA	Medical Dictionary for Regulatory Activities

<b>Abbreviation</b>	<b>Term</b>
PD	Pharmacodynamics
PGTC	primary generalized tonic-clonic
PK	Pharmacokinetics
POS	partial-onset seizures
PT	preferred term
QTc	corrected QT interval (time from the beginning of the QRS complex to the end of the T wave, corrected for heart rate)
SAE	serious adverse event
SAP	statistical analysis plan
SI	Système International
SMQ	standardized MedDRA queries
SOC	system organ class
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TLG	tables, listings, and graphs
ULN	upper limit of normal
WHO	World Health Organization

### 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 the core phase of Eisai Protocol E2007-G000-311. The statistical methods used in the extension phase will be described in a separate SAP.

#### 3.1 Study Objectives

##### 3.1.1 Primary Objective(s)

To evaluate the safety and tolerability of E2007/perampanel oral suspension when administered as an adjunctive therapy in children (ages 4 to <12 years) with inadequately controlled partial-onset seizures (POS) or primary generalized tonic-clonic seizures (PGTC)

##### 3.1.2 Secondary Objectives

1. To characterize the PK of perampanel and the relationship between perampanel plasma concentrations, efficacy, and safety using population PK/PD modeling
2. To evaluate the effects of perampanel on cognition, behavior, visuomotor skills, and growth and development in children during short-term (23 weeks) and long-term (up to 52 weeks) treatment
3. To evaluate the frequency of EEG abnormalities during awake and sleep state during 52 weeks of treatment
4. To evaluate suicidal ideation and suicidal behavior in children 6 years to less than 12 years as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS) during 52 weeks of treatment
5. To evaluate the efficacy of perampanel as measured by the median percent change per 28 days in seizure frequency, by the proportion of responders ( $\geq 25\%$ ,  $\geq 50\%$ , and  $\geq 75\%$ ), and by the proportion of subjects who are seizure-free for POS, PGTC, and Generalized Tonic-Clonic (GTC) seizures
6. To evaluate, in Japanese subjects, the efficacy of perampanel on partial onset seizures (POS) in the present study as compared with placebo in Study E2007-J000-335
7. To assess the effects of perampanel on the Clinical Global Impression (CGI), CGI of Severity (CGIS) and CGI of Change (CGIC)

### 3.1.3 Exploratory Objective

To assess the impact of perampanel on the health utility of children using the Euroqol 5 Dimensions-Youth (EQ-5D-Y) scale.

## 3.2 Overall Study Design and Plan

This was a multicenter, open-label single-arm study in children (ages 4 to <12 years) with inadequately controlled POS or PGTC. The study was to consist of a Core Study and Extension Phase (Extension A, for all countries in the study) with an Additional Extension Phase (Extension B) available for subjects enrolled in Japan only. Subjects were to be stratified by age ( $\geq 4$  to <7 years, 7 to <12 years) with at least 30% subjects enrolled in the equal or greater than 4 to less than 7 year age group for each seizure type (ie, at least 36 with POS and at least 12 with PGTC).

### Core Study

The Core Study was to consist of the following 2 phases: Pretreatment and Treatment Phase. The Pretreatment Phase was to consist of a Screening/Baseline Period that lasts up to 4 weeks  $\pm 3$  days outside of Japan. Subjects in Japan were required to complete 4 full weeks  $\pm 3$  days of the Screening/Baseline Period. However, subjects outside of Japan could begin treatment as soon as baseline procedures were completed and documentation of eligibility (such as a documented seizure diary entry for a qualifying seizure during the preceding 12 weeks prior to Visit 2 or a qualifying seizure during the prospective Screening/Baseline Period) had been established. During this phase, subjects were to be assessed for eligibility to participate in the study.

The Treatment Phase was to consist of 3 periods: Titration (up to 11 weeks), Maintenance (up to 12 weeks), and Follow-up (4 weeks; only for those subjects not rolling over into the Extension Phase).

### Extension A

The Extension Phase was to consist of a Maintenance Period (29 weeks) and a Follow-up Period (up to 4 weeks; only for those subjects not entering into Extension B [Japan only]).

An overview of the study design is presented in [Figure 1 of the protocol](#).

### Extension B

Extension B was to be available to subjects enrolled in Japan and in countries where an EAP cannot be implemented. Extension B consisted of an open-label Treatment Phase. In Japan, treatment was continued as long as clinically appropriate according to the judgment of the investigator. However, treatment of subjects in Extension B was to be completed when the subject reaches 12 years of age or when perampanel is commercially available in Japan for treatment of POS in pediatric subjects (4 to less than 12 years of age). In countries where an EAP cannot be implemented, participation in Extension B was continued as long as clinically appropriate according to the judgment of the

investigator, until the subject reaches 12 years of age or perampanel oral suspension is commercially available. Subjects who discontinue or choose not to switch to the commercial product was required a Follow-up Visit which was to be conducted 4 weeks ( $\pm 7$  days) after the discontinuation Visit.

## 4 DETERMINATION OF SAMPLE SIZE

A sample size of 160 subjects (with up to 40 subjects with PGTC and the balance with POS), is deemed sufficient for safety evaluation in this age group (age 4 to <12 years). This sample size matches the total number of adolescents who were enrolled in the 4 global Phase 3 efficacy and safety studies that support the POS and PGTC indications.

For purposes of registration in Japan, it has been determined that a sample size of 65 subjects enrolled in Japan will provide 80% power to exclude the possibility that there would be a reduction smaller than that observed in the placebo arm of Study E2007-J000-335 (ie, 10.5%).

The sample size calculation was examined based on two scenarios of 10%, 40% and 50% or 10%, 30% and 60% of subjects receiving E2007 doses of 4mg, 8mg or 12mg respectively, as allocation group dose. In addition, the ratio of inducer medication user was assumed to be 70%. In either scenario, a sample size set 65 subjects is powered above 80%. The power is calculated from the number of counts from 10,000 re-sampling simulation about the upper limit of 95% confidence interval below 10.5%.

## 5 STATISTICAL METHODS

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects. All summaries will be produced by age cohort (4-<7 and 7-<12), disease cohort (POS, PGTC, GTC) and inducer status (inducer, non-inducer) except TEAE summary by speed of titration. All analysis will be conducted for Japanese POS subjects in Japanese sites (Country=Japan).

### 5.1 Study Endpoints

#### 5.1.1 Primary Endpoints

Safety and tolerability, which include incidence of treatment-emergent adverse events (TEAEs) and SAEs, laboratory parameters, vital signs, and ECG parameters, of perampanel oral suspension in children (ages 4 to <7 years and  $\geq 7$  years to <12 years) with POS or PGTC

#### 5.1.2 Secondary Endpoints

The following endpoints will be analyzed:



1. The relationship between plasma levels of perampanel and efficacy endpoints (ie, change in average seizure frequency over 28 days, responder probability, and the proportion of subjects who are seizure-free in the Maintenance Period of the Core Study) separately for each seizure type
2. The relationship between plasma levels of perampanel and cognition endpoints including change from baselines in ABNAS, CBCL, and LGPT. In addition, depending on the AE data, the relationship between plasma levels of perampanel and select AEs will be assessed
3. Change from baseline at Week 23 and Week 52 in ABNAS, CBCL, and LGPT
4. Changes from baseline at Week 23 and Week 52 in growth and development parameters (height, weight, thyroid, and IGF-1)
5. Change from baseline in EEG and the frequency of EEG abnormalities during awake and sleep state
6. Proportion of subjects (aged 6 or older at time of consent/assent) with any treatment-emergent reports of suicidal ideation and behavior on the C-SSRS and intensity of these behaviors assessed using C-SSRS scores
7. The median percent change in seizure frequency per 28 days during Treatment Phase (Titration Period and Maintenance Period) of the Core Study, and during the long-term treatment (up to 52 weeks) relative to the Pretreatment Phase. Seizure frequency will be based on the number of seizures per 28 days, calculated as the number of seizures over the entire time interval divided by the number of days in the interval and multiplied by 28
8. Proportion of responders (25% responders defined as a decrease in 28-day seizure frequency of equal or greater than 25% compared to baseline seizure frequency; 50% responders defined as a decrease in 28-day seizure frequency of equal or greater than 50% compared to baseline seizure frequency; 75% responders defined as a decrease in 28-day seizure frequency of equal or greater than 75% compared to baseline seizure frequency) during Maintenance Period of Core Study, and during the long term treatment (up to 52 weeks)
9. Proportion of subjects who are seizure-free during Maintenance Period of Core Study, and during the long-term treatment (up to 52 weeks)
10. CGI of Change

### 5.1.3 Exploratory Endpoint

Change from baseline at Week 23 and Week 52 in EQ-5D-Y

## 5.2 Study Subjects

### 5.2.1 Definitions of Analysis Sets

The **Safety Analysis Set (SAS)** is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.

The **Full Analysis Set (FAS)** is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose primary efficacy measurement.

**PK Analysis Set** is the group of subjects receiving perampanel and with at least 1 quantifiable perampanel concentration at one of the visits during the Maintenance Period of the Core Study and with adequately documented dosing history.

**PK/PD Analysis Set** is the group of subjects receiving perampanel who have seizure frequency, cognition, or AE data with documented dosing history. Subjects receiving perampanel should have at least 1 quantifiable perampanel concentration at one of the visits during the Maintenance Period of the Core Study as per the PK Analysis Set.

### 5.2.2 Subject Disposition

The number of subjects enrolled and the reasons for screen failure will be summarized. The frequencies of occurrence of completion, discontinuation and each reason for discontinuation of primary and other will be summarized. The data will be described using incidence rate (number of subjects and percentage).

### 5.2.3 Protocol Deviations

The following major protocol deviations will be listed and summarized.

- Recruitment of a subject who did not satisfy the entry criteria
- Excluded medication administered
- Overdose of Investigational Products of 120% or above between two consecutive visits
- Continuation of treatment with investigational product after a treatment related withdrawal event
- IP compliance <80% between two consecutive visits.
- Unauthorized dose adjustment during Core Study
- Missing 2 or more PK samples during the Core Study
- Allowed concomitant AED(s) dose did not remain stable during core phase
- Other clinically relevant deviations to be decided before database lock

## 5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the SAS will be summarized using descriptive statistics. Continuous demographic and baseline variables include age, weight, height, and BMI; categorical variables include sex, age group (4-7, 7-12), race and ethnicity.

### **MEDICAL HISTORY**

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

Epilepsy-specific medical history for the SAS will be summarized using descriptive statistics, including time since diagnosis, suspected localization of the epileptogenic region and seizure type.

## 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). Latest Version before database lock will be used for analysis. The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by Anatomical Therapeutic Chemical (ATC) class and WHO DD preferred term (PT). Prior medications will be defined as medications that stopped before the 1st dose of study drug. Concomitant medications will be defined as medications that (1) started before the 1st dose of study drug and were continuing at the time of the 1st dose of study drug, or (2) started on or after the date of the 1st dose of study drug up until 28 days after the subject's last dose. All medications will be presented in subject data listings.

The number of baseline AEDs will be summarized and a summary of baseline and concomitant AEDs will be produced. A baseline AED is an AED taken at Day1. Concomitant AEDs are defined as above for concomitant medications.

Specifically, the number of subjects who take concomitant enzyme inducing antiepileptic drugs (EIAEDs) will be summarized using percentage and frequency.

## 5.2.6 Treatment Compliance

Percent compliance will be calculated for the treatment phase for the FAS as follows:

Compliance

$$= \frac{(\text{Study Med issued in grams} - \text{Study Med Returned in grams})}{(\text{Number of Days} \times \text{Prescribed Daily Dose in ml}) \times \text{Suspension density of 1.07g/ml}} \times 100$$

Overall compliance, each period compliance (Titration (Visit2-Visit6), Maintenance(Visit6-Visit9)) and per visit compliance (Visit2-Visit3, Visit3-Visit4, Visit4-Visit5, Visit5-Visit6, Visit6-Visit7, Visit7-Visit8, Visit8-Visit9) with study medication will be summarized using

descriptive statistics for. Subjects will also be categorized by compliance categories of <80%, 80%-120% and >120%.

### 5.3 Data Analysis General Considerations

#### 5.3.1 Pooling of Centers

Subjects from all centers will be pooled for all analyses.

#### 5.3.2 Adjustments for Covariates

Not applicable.

#### 5.3.3 Multiple Comparisons/Multiplicity

Not applicable.

#### 5.3.4 Examination of Subgroups

The efficacy endpoints will be summarized by disease cohorts (POS, PGTC, and GTC). Within the POS and PGTC disease cohorts, endpoints will also be summarized by age cohort (4 to <7 years,  $\geq 7$  to <12 years), and with or without use of concomitant EIAEDs,

All other endpoints will be summarized by disease cohorts (POS, PGTC, and GTC), age cohort (4 to <7 years,  $\geq 7$  to <12 years), and the presence or absence of concomitant EIAEDs.

#### 5.3.5 Handling of Missing Data, Dropouts, and Outliers

##### 5.3.5.1 Efficacy

For the last observation carried forward (LOCF) analyses, such as “Maintenance-LOCF” analyses of responder rate, if the overall duration of the Maintenance Period is less than 8 weeks, the diary data up to the last 8 weeks during the Titration and Maintenance Periods combined will be used to calculate the seizure frequency per 28 days for Maintenance-LOCF.

Since data is rank transformed prior to analysis, outliers will have no effect on the calculation for confidence interval of percent change in seizure frequency per 28 days.

##### 5.3.5.2 Safety

The algorithm on the assumptions used for imputing the missing dates for AEs is given in the programming specifications.

If the day and month are missing, events will be considered treatment-emergent if the year is equal to or after the year of the first dose date; if days are missing, events will be considered treatment-emergent if the year is after the year of the first dose, or if the year is equal to the year of the first dose date and the month is equal to or after the month of the first dose date.

For the purpose of summarizing maximum severity, if the severity of an adverse event (AE) is missing for a subject, then, if this subject has another AE with the same preferred term that has “severe” severity, the maximum severity of the AE will be noted as “severe”; otherwise the maximum severity will be noted as missing. Similarly, for the purpose of summarizing closest relationship, if the relationship of an AE to study drug is missing, the AE will be noted to be probably related if there is another probably related AE with the same preferred term, otherwise this relationship will be noted as missing.

For determining treatment emergent markedly abnormal lab values, a missing baseline lab value will be assumed to be of grade 0.

The algorithm to impute missing dates for concomitant medications is given in the programming specifications. No special handling of missing data is planned for the analysis of any of the other safety variables.

Data exceptions or outliers will be determined by inspection of the tables, listings, and graphs in consultation with the clinical study team. The effect of outliers on analyses may be assessed by re-analyzing the data without the outliers.

All the listings will display the original missing values.

### 5.3.6 Other Considerations

Not applicable.

## 5.4 Efficacy Analyses

Only “valid days” and “valid seizure counts” will be used in the calculations of seizure frequency per 28 days. A “valid day” is defined as the day where seizure counts information is present, that is, either a record with an answer of ‘No’ to the question ‘Did the subject experience any seizures?’ or a positive number of seizures for at least one of the seizure types collected. “Valid seizure counts” are the seizure counts that are read from the valid seizure days.

### 5.4.1 Primary Efficacy Analyses

Not applicable.

### 5.4.2 Secondary Efficacy Analyses

The percent change in seizure frequency per 28 days during Treatment Phase (Titration Period and Maintenance Period) of the Core Study with respect to during the Pretreatment Phase will be summarized using descriptive statistics (n, mean, median, minimum, maximum and 95% confidence interval). The percent change in seizure frequency per 28 days are calculated for Total seizure, POS total seizure and total complex partial seizure for POS cohort, for PGTC seizure, absence seizure, myoclonic seizure and total seizure for PGTC cohort and for Secondarily Generalized seizures for GTC cohort. Total Seizures is sum of all seizures, including POS, generalized and other seizures. Total POS Seizures is sum of all POS seizures, including simple partial seizures without motor signs, simple partial seizures

with motor signs, complex partial seizures and complex partial seizures with secondary generalization. Secondly Generalized seizures cohort is a subset of the POS cohort. The proportion of subjects who are seizure-free and the proportion of responders based on decrease from baseline (during the Pretreatment Phase) in 28-day seizure frequency of equal or greater than 25%, equal or greater than 50%, and equal or greater than 75% during Maintenance-LOCF Period of the Core Study will be summarized using frequency count (number and percentage). If subjects complete the Core study and have no seizure during the Maintenance Period, those will be treated as seizure-free.

The number of subjects with new seizure types compared to Baseline Period and Seizure history will be counted.

For analysis for the Japanese submission, all of analysis will be conducted for Japanese population but the following analysis also will be conducted.

The percent change in seizure frequency of POS total seizure per 28 days during Treatment Phase (Titration Period and Maintenance Period) of the Core Study with respect to the Pretreatment Phase will be summarized using descriptive statistics (n, mean, median, minimum, maximum and 95% confidence interval) by 4 week periods (1-4week, 5-8week, 9-12 week, 13-16 week, 17-20 week, 21-23 week, last 4 weeks of treatment).

The CGI-I and CGI-S will be summarized for each visit using frequency count (number and percentage).

#### 5.4.3 Other Efficacy Analyses

The score of EQ-5D-Y each items (Mobility, Looking after myself, Doing usual activities, Having pain or discomfort, Feeling worried, sad or unhappy) will be summarized for each visit using frequency count (number and percentage). The measurement and the change from baseline of EQ-5D-Y VAS at each visit will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum and maximum).

### 5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Perampanel plasma concentrations were obtained from blood samples drawn at any time during the treatment phase (Weeks 15, 19 and 23/EOT). Details of the analysis methods for population PK/PD modeling will not be described in this SAP but will be described in a separate analysis plan.

#### 5.5.1 Pharmacokinetic Analyses

Population PK analysis will be performed to characterize the PK of perampanel by pooling the concentration data with other studies, including 19 Phase 1 studies, 2 Phase 2 studies (232 and 235), and 5 Phase 3 studies (304, 305, 306, 332, and 335). A 2-compartment PK model will be fit to the data and the effect of intrinsic and extrinsic factors, including body weight and age, on the PK of perampanel will be evaluated. The post-hoc estimates of both

maximum observed concentration ( $C_{max}$ ) and area under the curve (AUC) from the final PK model will be derived for all subjects. In addition, average steady-state drug concentration ( $C_{ss,av}$ ) will be calculated. Subsequently, the dose-normalized derived exposure parameters will be summarized descriptively by age group ( $\leq 4$  years,  $>4$  to  $\leq 8$  years,  $>8$  to  $<12$  years,  $\geq 12$  to  $<18$  years, and  $\geq 18$  years) for subjects with and without inducing AEDs, and also presented in box-plots.

### 5.5.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

PD endpoints to be evaluated as part of PK/PD analyses include endpoints for efficacy, cognition, and selected safety parameters.

## 5.6 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set (SAS). Safety data will be summarized on an “as treated” basis using descriptive statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include TEAEs, clinical laboratory parameters, vital signs, 12-lead ECG results, C-SSRS, growth parameters, CBCL and LGPT. Study Day 1 for all safety analyses will be defined as the date of the 1st dose of study drug.

### 5.6.1 Extent of Exposure

The duration of treatment (Titration Period and Maintenance Period of the Core Study) will be calculated as the number of weeks between the date the subject receives their 1st treatment dose and the date the subject receives the last dose of treatment. These values will be used to summarize the extent of exposure to study medication.

Modal dose, mean daily dose, maximum daily dose and last daily dose will be presented using summary statistics and frequency using categories of  $< 4$ ,  $4$ ,  $>4-<8$ ,  $8-<12$ ,  $12=\leq$ . Number and percent of subjects who down-titrated or discontinued study at maximum daily dose exposed will be summarized using frequency count (number and percentage).

### 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 18.1 or higher) lower level term 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 from the date of first dose of study drug to 28 days after last end date of dose in prescribed dose entry, 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 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] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study treatment.

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

An overview of TEAEs and the number (percentage) of subjects with TEAEs by speed of titration, 'Fast' and 'Other', will be summarized by MedDRA SOC and PT for safety set. 'Fast' titrators are defined as subjects who spent less time on any one dose prior to attaining their maximum dose than was permitted by the protocol and 'Other' is defined as all other subjects.

### **AEs of special Interest**

A listing of subjects with AEs related to suicidality, identified by relevant Standardized MedDRA Query (SMQ) terms, will be provided. TEAEs of special interest listed below will be summarized by SOC and PT. SMQs will be used to identify relevant terms for the following TEAEs.

- TEAEs suggestive of abuse potential
- TEAEs related to alertness and cognition
- TEAEs related to psychosis / psychotic disorders
- TEAEs related to hostility/aggression



- TEAEs related to status epilepticus/convulsions
- TEAEs related to lab abnormalities
- Cardiac and ECG TEAEs
- TEAEs related to rash

TEAEs related to rash will be identified by medical review. Falls will be summarized for the Pretreatment Phase and Follow-up Period and will be summarized by actual dose of onset for the Titration and Maintenance Periods.

### 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 Safety Assessments \(Laboratory Measurements\)](#), 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 using descriptive statistics. Qualitative parameters listed in [protocol Section 9.5.1.5.3 Safety Assessments \(Laboratory Measurements\)](#) 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. For each laboratory parameter, shift from baseline (LNH) to each postbaseline visit and at the end of treatment will be presented. Similar shift tables from baseline (LNH) to the highest/lowest postbaseline value will also be presented.

[Protocol Appendix 2 \(Sponsor's Grading for Laboratory Values\)](#) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAV). Except for phosphate, a TEMAV was 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. The number and percentage of subjects with TEMAVs will be presented; each subject will be counted once in the laboratory parameter high and low categories, as applicable. Markedly abnormal laboratory values will be flagged in the subject data listings.

For ALT and AST analysis, the number of subjects with greater than 3 times, but less than 5 times the ULN and the number of subjects with greater than 5 times the ULN will be summarized. For bilirubin, a summary of the number of subjects with serum concentrations greater than 2 times the ULN will be created. These summaries will also be provided for the maximum value in the treatment duration. In addition, the number of subjects who meet the criteria for Hy's Law will be summarized by visit and during the treatment duration. A subject will be determined to have met Hy's Law if AST or ALT is  $> 3x$  ULN, bilirubin  $> 2x$

ULN, and alkaline phosphatase  $\leq 2x$  ULN at a visit. The number of subjects who meet each of the criteria for Hy's Law during treatment (but not all necessarily at the same visit) will also be summarized.

#### 5.6.4 Vital Signs

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

In addition, the criteria described in the table below will be used to determine clinically notable results for blood pressure and heart rate. The number (percentage) of subjects with clinically notable results over all scheduled and unscheduled visits will be summarized.

**Table 1: Criteria for Clinically Notable<sup>a</sup> Vital Signs**

Variable	Criterion Value	Change Relative to Baseline
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
Heart Rate	>120 bpm	Increase of $\geq 15$ bpm
	< 50 bpm	Decrease of $\geq 15$ bpm
Weight		Increase of > 7%
		Decrease of > 7%

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

The criteria in Table 2 will be used to determine abnormal results for blood pressure and heart rate. The number of subjects with abnormal results will be summarized.

**Table 2: Criteria for Abnormal Vital Signs**

Variable	Change Relative to Baseline
Systolic BP	Increase of $\geq 20$ mmHg
	Decrease of $\geq 20$ mmHg
	Increase of $\geq 40$ mmHg
	Decrease of $\geq 40$ mmHg
Diastolic BP	Increase of $\geq 10$ mmHg
	Decrease of $\geq 10$ mmHg
	Increase of $\geq 20$ mmHg
	Decrease of $\geq 20$ mmHg
Pulse	Increase of $\geq 15$ bpm

	Decrease of $\geq 15$ bpm
	Increase of $\geq 30$ bpm
	Decrease of $\geq 30$ bpm

### 5.6.5 Electrocardiograms

ECG parameters (QTcB, QTcF, PR interval, QRS duration and RR interval) and changes from baseline will be presented by visit.

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 Bazett and QTc Fridericia during the treatment period will be summarized.

Clinically borderline or abnormal ECG results in QTc Bazett and QTc Fridericia will be categorized as follows:

Absolute QTc interval prolongation:

- QTc interval 430-450 ms
- QTc interval  $>450$  ms
- QTc interval  $>500$  ms

Change from baseline in QTc interval:

- QTc interval increases from baseline 30-60 ms
- QTc interval increases from baseline  $>60$  ms.

### 5.6.6 Other Safety Analyses

#### **Aldenkamp-Baker Neuropsychological Assessment Schedule (ABNAS)**

The total ABNAS score (defined as the sum of the individual question scores) and sub-scores for fatigue, slowing, memory, concentration, motor-coordination and language (Brooks et al 2001) will be listed and summarized by visit. Changes from baseline ABNAS sub-scores will be summarized.

**Table 1: Definition between each aspect and question**

Aspect	# of items	Range	Item No
fatigue	5	0-15	1, 7, 13, 18, 24
slowing	5	0-15	2, 8, 14, 19, 23
memory	4	0-12	3, 9, 15, 20
concentration	4	0-12	4, 10, 16, 21
motor speed	3	0-9	5, 11, 17,
reading (language)	3	0-9	6, 12, 22

### Child Behavior Check List (CBCL 1.5/5 and CBCL 6/18)

The CBCL 1.5/5 measures problems in children (1,5 to 5 years old). The data are corrected the problems for children from CRF. To measure problems, 100 ‘problem items’ are rated on a scale to measure their occurrence. Higher scores indicate greater problems, as the scale ranges from 0, indicating ‘not true,’ to 2, indicating ‘often true.’ 67 of the items are then summed into seven syndrome scores (Emotionally Reactive, Anxious/Depressed, Withdrawn, Somatic Complaints, Attention Problems, Aggressive Behavior syndrome and Sleep problems.) The summation of the first four syndrome scores yields the Internalizing Syndrome composite score, and the summation of the next two syndrome scores yields the Externalizing Syndrome composite score. The total problems score is the summation of the two composite scores, the final three syndrome scores, and the 33 ‘problem items’ that were not included in any of the seven syndrome scores.

The total problems score, the Internalizing Syndromes score, the Externalizing Syndromes score, and each of the seven individual syndrome scores of the CBCL 1.5/5 will be evaluated using summaries of change from baseline (Week 0) by visit.

**Table 2: Definition CBCL 1.5-5 (Refer to link of CBCL/1 1/2-5 and LDS in profiles at website <http://www.aseba.org/forms.html>)**

Syndrome scale	#of items	Range	Items
Emotionally Reactive	9	(0-18)	21,46,51,79,82,83,92,97,99
Anxious/Depressed	8	(0-16)	10,33,37,43,47,68,87,90
Withdrawn	8	(0-16)	2,4,23,62,67,70,71,98
Somatic Complaints	11	(0-22)	1,7,12,19,24,39,45,52,78,86,93
Internalizing	36	(0-72)	sum of 4 previous scores
Attention Problems	5	(0-10)	5,6,56,59,95
Aggressive Behavior syndrome	19	(0-38)	8,15,16,18,20,27,29,35,40,42,44,53,58,66,69,81,85,88,96
Externalizing	24	(0-48)	sum of 2 previous scores
Sleep problems	7	(0-14)	22,38,48,64,74,84,94
Total	100	(0-200)	Sum of all problem items scores, including: Internalizing Syndromes, Externalizing Syndromes, Sleep problems, and 33 not yet accounted for problems

Also the CBCL 6/18 measures competencies and problems in children (6 to 18 years old) . To assess competence, sixteen items are scored for each child, with higher scores indicating better competence. The summed scores are grouped into three sub-scores for competence in

activities, social realms and school. The total competence score is the summation of all 16 items.

To measure problems, 120 ‘problem items’ are rated on a scale to measure their occurrence. Higher scores indicate greater problems, as the scale ranges from 0, indicating ‘not true,’ to 2, indicating ‘often true.’ 103 of the items are then summed into eight syndrome scores (Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Rule-Breaking Behavior, Aggressive Behavior, Social Problems, Thought Problems, and Attention Problems.) The summation of the first three syndrome scores yields the Internalizing Syndrome composite score, and the summation of the next two syndrome scores yields the Externalizing Syndrome composite score. The total problems score is the summation of the two composite scores, the final three syndrome scores, and the 17 ‘problem items’ that were not included in any of the eight syndrome scores.

The total competence score, the three sub-scores for competence, the total problems score, the Internalizing Syndromes score, the Externalizing Syndromes score, and each of the eight individual syndrome scores of the CBCL 6/18 will be evaluated using summaries of change from baseline (Week 0) by visit.

**Table 3: Definition CBCL 6-18 (Refer to link of CBCL/6-18 scored using three different societies in profiles at website : <http://www.aseba.org/forms.html>)**

#### Competency Scores

Sub-scores	# of Items	Score Range	Items
Activity	6	(0-15)	I.A, B, II.A, B, IV A, B
Social	6	(0-14)	III.A, B, V.1, 2, VI. A, B
School	4	(0-6)	VII. 1, 2,3,4
Total	16	(0-35)	Sum of 3 previous scores

#### Syndrome/ Problems Scores

Syndrome scale	#of items	Score Range	Items
Anxious/Depressed	13	(0-26)	14,29,30,31,32,33,35,45,50,52,71, 91,112
Withdrawn/Depressed	8	(0-16)	5,42,65,69,75,102,103,111
Somatic Complaints	11	(0-22)	47,49,51,54,56a,56b,56c,56d,56e, 56f,56g
Internalizing	32	(0-64)	sum of 3 previous scores
Rule-Breaking Behavior	17	(0-34)	2,26,28,39,43,63,67,72,73,81,82,9 0,96,99,101,105,106
Aggressive Behavior	18	(0-36)	3,16,19,20,21,22,23,37,57,68,86,8

			7,88,89,94,95,97,104
Externalizing	35	(0-70)	sum of 2 previous scores
Social Problems	11	(0-22)	11,12,25,27,34,36,38,48,62,64,79
Thought Problems	15	(0-30)	9,18,40,46,58,59,60,66,70,76,83,84,85,92,100
Attention Problems	10	(0-20)	1,4,8,10,13,17,41,61,78,80
Total	120	(0-240)	Sum of all problem items scores, including: Internalizing Syndromes, Externalizing Syndromes, Social Problem, Thought Problem, Attention Problem, and 17 not yet accounted for problems

Additionally, the borh CBCL results for each subject will be converted to a standardized T-score and classified at baseline and at each evaluation as normal, borderline clinical, or clinical, based on the thresholds provided in the CBCL manual. These classifications and their change from baseline will be presented in tables.

### Lafayette Grooved Pegboard Test (LGPT)

Time taken to perform the Lafayette Grooved Pegboard Test correctly (i.e. inserting 25 pegs for 8 years or older or 10 pegs for under 8 years old for each hand, ranges up to 300 seconds) will be summarized by visit. If the task cannot be completed correctly at 300 seconds, 300 seconds will be recorded.

Total number of pegs correctly placed and total number of pegs dropped will also be summarized separately for each hand by visit.

Total score for each hand (Trites) will be calculated as time to complete the test + total number of pegs dropped + total number of pegs correctly placed.

All summaries will be calculated by each age group (for 8 years or older, for under 8 years old) separately.

### Growth parameter

The actual value and change from baseline in growth parameter (height, weight, TSH, fT3, fT4 and IGF-1) will be summarized by visit. Height and weight will present summary statistics for overall percentile and overall z-score.

### EEG

The analysis of EEG parameters will be presented in a stand alone report and are covered in a separate analysis plan. .

## Columbia Suicide Severity Rating Scale (C-SSRS)

Scoring of the C-SSRS will be performed as suggested by the C-SSRS Columbia website [http://www.cssrs.columbia.edu/clinical\\_trials.html](http://www.cssrs.columbia.edu/clinical_trials.html).

The following summaries will be presented for the treatment duration (defined as the period from the date of first dose up to 28 days after the date of last dose, inclusive).

- Number (percentage) of subjects with any treatment-emergent report of suicidal behavior, suicidal ideation, and suicidality (suicidal behavior and/or ideation) will be displayed. A treatment-emergent report of suicidal behavior, suicidal ideation, or suicidality is an answer of 'Yes' to any question in the respective category during the treatment duration.
- Shift from baseline to the maximum suicidal ideation severity rating (0=no ideation present to 5=active ideation with plan and intent) in the treatment duration will assess worsening of suicidal ideation. Any score greater than 0 indicates the presence of suicidal ideation while a score of 4 (active suicidal ideation with some intent to act) or 5 (active suicidal ideation with specific plan and intent) can be used to indicate serious suicidal ideation.

Descriptive statistics and changes from baseline will be presented by visit for the suicidal ideation intensity score and the suicidal ideation severity rating (treated as a continuous variable) to assess change in suicidal ideation over time. The suicidal ideation intensity score ranges from 0 to 25 and is the sum of the 5 intensity items.

### 5.7 Other Analyses

Not applicable.

### 5.8 Exploratory Analyses

No exploratory analyses are planned for this study.

### 5.9 Extension Phase Analyses

The statistical methods used in extension phase will be described in a separate SAP.

## 6 INTERIM ANALYSES

An independent data monitoring committee (DMC) will be constructed to monitor the safety data. The responsibilities, membership, and purpose of the DMC, the timing of the meeting(s), and an outline of the plan for review of the safety data will be documented in the DMC Charter.

## 7 CHANGES IN THE PLANNED ANALYSES

The following major changes to the statistical methods in this analysis plan were made after version 2.0 of the SAP was approved.

- The study design was updated with the changes from latest protocol (V9.0).
- Efficacy analysis of the percent change in seizure frequency of POS total seizure in the subgroups of patients receiving at least 6mg, in the completer population, by age of onset, by duration of disease (month) and by CNS concomitant medication (Yes / No) was deleted since the overall efficacy analysis was deemed sufficient. .
- EEG analysis was defined another document.
- Overview of TEAE and TEAEs SOC/PT by speed of titration were added .

Other changes were editorial in nature, to add clarification or maintain consistency with the latest Eisai SAP template.

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 EFFICACY DATA HANDLING**

#### **8.1.1 Pre-randomization/baseline efficacy**

All diary data prior to first dose date will be used in the computation of Pretreatment Phase seizure frequency per 28 days. All subjects should have approximately 4 weeks of diary data prior to baseline (Visit 2). The baseline value for other efficacy endpoints will be the last nonmissing measurement occurring prior to the first dose of the study drug.

#### **8.1.2 Treatment Duration for Efficacy Analyses**

The date of first dose of the study drug is considered day 1 in the treatment duration.

The first dose date is the study drug start date and the last dose date is study drug end date from the study medication CRF page.

The treatment duration for efficacy variables is defined as follows:

- For diary seizure data: The duration between the day of first dose and the last day of study drug in treatment phase, inclusive.
- For non-diary efficacy data: The duration between the day of first dose and 7 days after the last visit of schedule in treatment phase, inclusive.

For all efficacy analyses, data reported only during the treatment duration will be analyzed. The diary seizure data during the Follow-up will be listed.

#### **8.1.3 Handling of Replicate Data**

For the CGIC and EQ-5D-Y assessment, the last visit, within the treatment duration will be used.



## 8.2 SAFETY DATA HANDLING

### 8.2.1 Baseline safety

The baseline value for all safety endpoints will be the last non-missing measurement occurring prior to the first dose of the study medication.

### 8.2.2 Treatment Duration for Safety Analyses

The treatment duration for non-AE safety variables is same of non-diary efficacy analysis in 8.1.2 Treatment Duration for Efficacy Analyses. For AEs, the treatment duration is considered to begin on Day 1 and ends 28 days after the last dose of treatment phase .

The post-treatment duration is considered to begin on the day after the treatment duration for safety. Since it is not always possible for all study participants to come in for their clinic visits on the exact day specified in the protocol schedule, the visit week of a subject's visit will be based on the actual visit occurring during the treatment duration. These visits will be used to create by visit summaries for laboratory, vital signs, electrocardiograms and other safety analyses data. The end of treatment value is the last non-missing value in the treatment duration.

Any concomitant medication taken within the 14 days after the last dose data will be listed/summarized as part of the concomitant medication listing/table.

AEs for the subject were collected and reported on CRF starting from the time subject signed informed consent to the last visit in the Treatment Phase following subject's last dose. Serious AEs were collected for 28 days after the last dose.

For summaries of safety by time points, the time points will be relative to date of first dose. For standardized reporting, study day windows relative to the first dose (Day 1) in the study will be applied to determine into which week the data will be mapped. Scheduled, unscheduled, and early withdrawal visits will be mapped to weeks. Table 2 below gives the mapping of relative day ranges to week for non-AE safety variables. If a subject did not have a recorded observation falling within a given range of days in order to be assigned to a week, the subject's data for that week will be regarded as missing for summarization purposes. If there are two or more assessments in the same window then:

- if the window is the baseline assessment, then the latest assessment will be used in the summary tables;
- if the window is the follow-up assessment, then the latest assessment will be used in the summary tables;

If the window is not the baseline or the follow-up assessment, then the assessment closest to the scheduled assessment will be used in the summary tables. Note that if two assessments are equidistant from the scheduled assessment then the last assessment of the two (within the allowable window) will be used.

**Table 1: Mapping of Study Day Ranges to Week**

Windowing Period	Study Day Range (Relative to First Dose)	Week
Pretreatment	Day $\leq 1^a$	0
Treatment	$2 \leq \text{Day} \leq 25$	2
Treatment	$26 \leq \text{Day} \leq 46$	5
Treatment	$47 \leq \text{Day} \leq 67$	8
Treatment	$68 \leq \text{Day} \leq 88$	11
Treatment	$89 \leq \text{Day} \leq 119$	15
Treatment	$120 \leq \text{Day} \leq 147$	19
Treatment	$148 \leq \text{Day} \leq 175$	23
End of Treatment(EOT) of Core Study	-	b
Follow up for completer of Core Study	$176 \leq \text{Day} \leq 203$	c
Follow up for discontinuation of Core Study	After the date of discontinuation $\leq \text{Day} \leq \text{last dose of study drug} + 35$	

- a: All assessments performed on the same date as the date of first dose were to be performed prior to dosing; results from these assessments will be regarded as Pretreatment values in the analyses.
- b: The last non-missing value measured in the Treatment Phase will be handled as the data of EOT of the Core Study. The Follow-up visit will not be included in this analysis visit.
- c For the safety assessment other than AE, the data assessed as the planned visit of the Follow-up will be handles as those of Follow-up visit. AE occurred on or after the date of discontinuation will be handles as that of Follow-up period.

### 8.2.3 Handling of Replicate Data

A subject having an AE coded to the same preferred term more than once during the study will be counted only once in the incidence calculations for that AE. Similarly, if a subject has more than one AE in a single body system, the incidence will be counted only once for that body system. If a subject has the same AE more than once, the occurrence that is of greatest severity will be used in the calculation of the incidence of individual AE by severity. Similarly, the AE considered most closely related to study drug will be used in the calculation of incidence of individual AE by relationship.

For the laboratory, vital signs, ECG and other safety variables datasets, the measurement noted as the scheduled visit measurement will be used in the analysis. If more than one assessment is present at a scheduled visit, then the nearest assessment for evaluation

visit(day) will be used in the summaries of the actual values and changes from baseline. In the event of two assessments being equally close to the scheduled visit day, the last assessment will be used.

### **Handling of prior/concomitant medication**

If the subject has taken the same concomitant medication (as coded to preferred WHO-drug term) more than once, the subject will be counted only once in the tabulation.

## **9 PROGRAMMING SPECIFICATIONS**

The rules for programming derivations and dataset specifications are 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**

Cancer Therapy Evaluation Program, CTCAE version 4.0 [published 28 May 2009 (v4.03: June 14, 2010)]. Available from: [http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03\\_2010-06-14\\_QuickReference\\_8.5x11.pdf](http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).

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)

Pellock JM, Carman WJ, Thyagarajan V, Daniels T, Morris DL, D'Cruz O. Efficacy of antiepileptic drugs in adults predicts efficacy in children: a systematic review. *Neurology*. 2012;79:1482-89.

## 13 APPENDICES

### 13.1 Sponsor's Grading for Determining Markedly Abnormal Laboratory Results

The following table is of Sponsor's Grading for Laboratory Values from the version in the [protocol, Appendix 1](#).

#### 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 <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 – $3.0 \times 10^9/L$ <LLN – 3000/mm <sup>3</sup>	<3.0 – $2.0 \times 10^9/L$ <3000 – 2000/mm <sup>3</sup>	<2.0 – $1.0 \times 10^9/L$ <2000 – 1000/mm <sup>3</sup>	< $1.0 \times 10^9/L$ <1000/mm <sup>3</sup>
Lymphocytes	<LLN – 800/mm <sup>3</sup> <LLN – $0.8 \times 10^9/L$	<800 – 500/mm <sup>3</sup> <0.8 – $0.5 \times 10^9/L$	<500 – 200/mm <sup>3</sup> <0.5 – $0.2 \times 10^9/L$	<200/mm <sup>3</sup> < $0.2 \times 10^9/L$
Neutrophils	<LLN – $1.5 \times 10^9/L$ <LLN – 1500/mm <sup>3</sup>	<1.5 – $1.0 \times 10^9/L$ <1500 – 1000/mm <sup>3</sup>	<1.0 – $0.5 \times 10^9/L$ <1000 – 500/mm <sup>3</sup>	< $0.5 \times 10^9/L$ <500/mm <sup>3</sup>
Platelets	<LLN – $75.0 \times 10^9/L$ <LLN – 75,000/mm <sup>3</sup>	<75.0 – $50.0 \times 10^9/L$ <75,000 – 50,000/mm <sup>3</sup>	<50.0 – $25.0 \times 10^9/L$ <50,000 – 25,000/mm <sup>3</sup>	< $25.0 \times 10^9/L$ <25,000/mm <sup>3</sup>
<b>METABOLIC/LABORATORY</b>				
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

### Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
				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
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), 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).

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## STATISTICAL ANALYSIS PLAN

**Study Protocol Number:** E2007-G000-311 (Extension Phase)

**Study Protocol Title:** An Open-Label, Multicenter Study with an Extension Phase to Evaluate the Safety, Tolerability, and Exposure-Efficacy Relationship of Perampanel Oral Suspension when Administered as an Adjunctive Therapy in Pediatric Subjects (Age 4 to less than 12 years) with Inadequately Controlled Partial-Onset Seizures or Primary Generalized Tonic-Clonic Seizures

**Date:** 6 February 2018

**Version:** Amendment 1

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## 2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

<b>Abbreviation</b>	<b>Term</b>
ABNAS	A-B neuropsychological assessment schedule
AE(s)	adverse event(s)
AED	antiepileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomical therapeutic class
BMI	body mass index
CBCL	Child Behavior Checklist
CGI	Clinical Global Impression
CGIC	Clinical Global Impression of Change
CGIS	Clinical Global Impression of Severity
CRF	case report form
C <sub>ss,av</sub>	average steady-state drug concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EEG	Electroencephalogram
EQ-5D-Y	EuroQol 5 Dimensions – Youth
FAS	Full Analysis Set
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
GTC	Generalized Tonic-Clonic
HRQL	health-related quality of life
ICF	informed consent form
IP	Investigational products
LGPT	Lafayette Grooved Pegboard Test
LLN	lower limit of normal
LNH	low/normal/high
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamics

<b>Abbreviation</b>	<b>Term</b>
PGTC	primary generalized tonic-clonic
PK	Pharmacokinetics
POS	partial-onset seizures
PT	preferred term
QTc	corrected QT interval (time from the beginning of the QRS complex to the end of the T wave, corrected for heart rate)
SAE	serious adverse event
SAP	statistical analysis plan
SI	Système International
SMQ	standardized MedDRA queries
SOC	system organ class
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TLG	tables, listings, and graphs
ULN	upper limit of normal
WHO	World Health Organization

### 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 the Extension Phase of Eisai Protocol E2007-G000-311. The SAP for the Core Study of Eisai Protocol E2007-G000-311 is a separate document.

#### 3.1 Study Objectives

##### 3.1.1 Primary Objective(s)

To evaluate the safety and tolerability of E2007/perampanel oral suspension when administered as an adjunctive therapy in children (ages 4 to <12 years) with inadequately controlled partial-onset seizures (POS) or primary generalized tonic-clonic seizures (PGTC)

##### 3.1.2 Secondary Objectives

1. To characterize the PK of perampanel and the relationship between perampanel plasma concentrations, efficacy, and safety using population PK/PD modeling
2. To evaluate the effects of perampanel on cognition, behavior, visuomotor skills, and growth and development in children during short-term (23 weeks) and long-term (up to 52 weeks) treatment
3. To evaluate the frequency of EEG abnormalities during awake and sleep state during 52 weeks of treatment
4. To evaluate suicidal ideation and suicidal behavior in children 6 years to less than 12 years as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS) during 52 weeks of treatment
5. To evaluate the efficacy of perampanel as measured by the median percent change per 28 days in seizure frequency, by the proportion of responders ( $\geq 25\%$ ,  $\geq 50\%$ , and  $\geq 75\%$ ), and by the proportion of subjects who are seizure-free for POS, PGTC, and Generalized Tonic-Clonic (GTC) seizures
6. To evaluate, in Japanese subjects, the efficacy of perampanel on partial onset seizures(POS) in the present study as compared with placebo in Study E2007-J000-335
7. To assess the effects of perampanel on the Clinical Global Impression (CGI), CGI of Severity (CGIS) and CGI of Change (CGIC)

### 3.1.3 Exploratory Objective

To assess the impact of perampanel on the health utility of children using the Euroqol 5 Dimensions-Youth (EQ-5D-Y) scale.

## 3.2 Overall Study Design and Plan

Details regarding the study design and plan for the Core Study and Extension Phase are in the Protocol. For a general overview, see the schema in [Section 13.1](#).

The Extension Phase will consist of a Maintenance Period (29 weeks) and a Follow-up Period (4 weeks).

All subjects who completed all scheduled visits up to and including Visit 9 in the Core Treatment Phase were eligible to participate in the Extension Phase of the study.

### Maintenance Period

During the Maintenance Period of the Extension Phase, all subjects were to continue with their optimal perampanel dose (ie, that dose level that they completed on during the Core Study). Multiple dose adjustment was allowed if a subject was experiencing intolerable AE(s) or a higher dose was deemed to be beneficial. The maximum dose of perampanel was 12 mg/day for subjects who were not receiving EIAEDs. For subjects who were receiving EIAEDs, the maximum dose was 16 mg except that for subjects enrolled in Japan, the maximum dose was 12 mg/day.

Addition, deletion, and dose changes to the concomitant antiepileptic drugs (AEDs) were allowed during Extension Maintenance Period. Conversion to monotherapy on perampanel was also permitted at the discretion of the investigator, if it was considered appropriate to control the seizures.

### Follow-Up Period

Follow-up was to be conducted 4 weeks ( $\pm 7$  days) after the last dose of study drug for all subjects.

## 4 DETERMINATION OF SAMPLE SIZE

As this was an extension study, it was not possible to accrue a predetermined number of patients; therefore, there was no a priori determination of sample size. The maximum possible number of subjects in Extension Phase is the total number of treated subject in Core Study.

## 5 STATISTICAL METHODS

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects. All summaries will be produced by age cohort (4-<7 and 7-<12), disease cohort (POS, PGTC, GTC) and inducer status (inducer, non-inducer). All

analysis will be conducted for all subjects who have completed the core study and participated in the Extension Phase.

In general, the scope of endpoints and analyses will be based on data collected throughout the entire duration of perampanel exposure (i.e., Core and Extension).

### **Analysis for CSR in Japan**

For CSR in Japan, all analyses defined in this document will be repeated using all subjects enrolled in the study, including those who did not participate in the Extension Phase, and will also be repeated using subjects enrolled in Japanese sites only.

## **5.1 Study Endpoints**

### **5.1.1 Primary Endpoints**

Safety and tolerability, which include incidence of treatment-emergent adverse events (TEAEs) and SAEs, laboratory parameters, vital signs, and ECG parameters, of perampanel oral suspension in children (ages 4 to <7 years and  $\geq 7$  years to <12 years) with POS or PGTC

### **5.1.2 Secondary Endpoints**

The following endpoints will be analyzed:

1. The relationship between plasma levels of perampanel and efficacy endpoints (ie, change in average seizure frequency over 28 days, responder probability, and the proportion of subjects who are seizure-free in the Maintenance Period of the Core Study) separately for each seizure type
2. The relationship between plasma levels of perampanel and cognition endpoints including change from baselines in ABNAS, CBCL, and LGPT. In addition, depending on the AE data, the relationship between plasma levels of perampanel and select AEs will be assessed
3. Change from baseline at Week 23 and Week 52 in ABNAS, CBCL, and LGPT
4. Changes from baseline at Week 23 and Week 52 in growth and development parameters (height, weight, thyroid, and IGF-1)
5. Change from baseline in EEG and the frequency of EEG abnormalities during awake and sleep state
6. Proportion of subjects (aged 6 or older at time of consent/assent) with any treatment-emergent reports of suicidal ideation and behavior on the C-SSRS and intensity of

these behaviors assessed using C-SSRS scores

7. The median percent change in seizure frequency per 28 days during Treatment Phase (Titration Period and Maintenance Period) of the Core Study, and during the long-term treatment (up to 52 weeks) relative to the Pretreatment Phase. Seizure frequency will be based on the number of seizures per 28 days, calculated as the number of seizures over the entire time interval divided by the number of days in the interval and multiplied by 28
8. Proportion of responders (25% responders defined as a decrease in 28-day seizure frequency of equal or greater than 25% compared to baseline seizure frequency; 50% responders defined as a decrease in 28-day seizure frequency of equal or greater than 50% compared to baseline seizure frequency; 75% responders defined as a decrease in 28-day seizure frequency of equal or greater than 75% compared to baseline seizure frequency) during Maintenance Period of Core Study, and during the long term treatment (up to 52 weeks)
9. Proportion of subjects who are seizure-free during Maintenance Period of Core Study, and during the long-term treatment (up to 52 weeks)
10. CGI of Change

### 5.1.3 Exploratory Endpoint

Change from baseline at Week 23 and Week 52 in EQ-5D-Y

## 5.2 Study Subjects

### 5.2.1 Definitions of Analysis Sets

The **Safety Analysis Set** is the group of subjects who received at least 1 dose of study drug in the Extension Phase and had at least one postdose safety assessment in the Extension Phase.

The **Full Analysis Set (FAS)** is the group of subjects who received at least 1 dose of study drug in the Extension Phase and had at least 1 postdose seizure measurement in the Extension Phase.

The **Enrolled Subjects** will consist of all subjects who chose to participate in the Extension Phase.

For CSR in Japan, the analysis sets defined in Core Study SAP will be used.

### 5.2.2 Subject Disposition

The frequencies of completion, discontinuation, ongoing and the primary and other discontinuation reasons will be summarized using incidence rate (number of subjects and percentage).

### 5.2.3 Protocol Deviations

Not applicable.

### 5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set will be summarized using descriptive statistics. Continuous demographic and baseline variables include age, weight, height, and BMI; categorical variables include sex, age group (4-7, 7-12), 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. A subject data listing of medical and surgical history will be provided.

Epilepsy-specific medical history for the Safety Analysis Set will be summarized using descriptive statistics, including time since diagnosis, suspected localization of the epileptogenic region and seizure type.

### 5.2.5 Prior and Concomitant Therapy

Concomitant medications are defined as medications that (1) started before the first dose of perampanel at Core Study and were continuing at the time of the first dose of perampanel, or (2) started on or after the date of the first dose of perampanel (or, started at the time of or after the first dose of perampanel) up to 14 days after the subject's last dose.

Concomitant medications taken during the study will be coded using the World Health Organization Drug Dictionary (WHO-DD) and further coded and summarized by Anatomical Therapeutic class, pharmacological class, pharmacological subclass, and WHO drug term.

A summary of concomitant AEDs, including the number of subjects who take concomitant enzyme inducing antiepileptic drugs (EIAEDs), will be produced. A shift table of number of AEDs from baseline to the end of treatment will also be produced.

### 5.2.6 Study Medication Treatment Compliance

In general, study medication treatment compliance (%) for a given period of time will be calculated as follows with respect to (*i.e.*, within) the given period of time:



$$\text{Study Medication Treatment Compliance (\%)} = \frac{(\text{Study Med issued in grams} - \text{Study Med Returned in grams})}{(\text{Number of Days} \times \text{Prescribed Daily Dose in ml}) \times \text{Suspension density of 1.07g/ml}} \times 100$$

Study medication treatment compliance (%) will be presented for the SAS by visit in the Maintenance Period of Extension Phase. Subjects will also be categorized by compliance categories of <80%, 80%-120% and >120%.

### 5.3 Data Analysis General Considerations

#### 5.3.1 Pooling of Centers

Subjects from all centers will be pooled for all analyses. For analysis specifically planned for Japan subjects, only Japan centers will be pooled.

#### 5.3.2 Adjustments for Covariates

Not applicable.

#### 5.3.3 Multiple Comparisons/Multiplicity

Not applicable.

#### 5.3.4 Examination of Subgroups

The efficacy seizure endpoints will be summarised by disease cohorts (POS, PGTC, and GTC). Within the POS and PGTC disease cohorts, endpoints will also be summarized by age cohort (4 to <7 years, ≥7 to <12 years), and the presence or absence of concomitant EIAEDs,

All other endpoints will be summarised by disease cohorts (POS, PGTC, and GTC), age cohort (4 to <7 years, ≥7 to <12 years), and with or without use of concomitant EIAEDs.

#### 5.3.5 Handling of Missing Data, Dropouts, and Outliers

The algorithm on the assumptions used for imputing the missing dates for AEs is given in the programming specifications.

If the day and month are missing, events will be considered treatment-emergent if the year is equal to or after the year of the first dose date; if days are missing, events will be considered treatment-emergent if the year is after the year of the first dose, or if the year is equal to the year of the first dose date and the month is equal to or after the month of the first dose date.

For the purpose of summarizing maximum severity, if the severity of an adverse event (AE) is missing for a subject, then, if this subject has another AE with the same preferred term that has “severe” severity, the maximum severity of the AE will be noted as “severe”; otherwise the maximum severity will be noted as missing. Similarly, for the purpose of summarizing the closest relationship in AE causality, if the relationship of an AE to study drug is missing,

the AE will be noted to be probably related if there is another probably related AE with the same preferred term, otherwise this relationship will be noted as missing.

For determining treatment emergent markedly abnormal lab values, a missing baseline lab value will be assumed to be of grade 0.

The algorithm to impute missing dates for concomitant medications is given in the programming specifications. No special handling of missing data is planned for the analysis of any of the other safety variables.

Data exceptions or outliers will be determined by inspection of the tables, listings, and graphs in consultation with the clinical study team. The effect of outliers on analyses may be assessed by re-analyzing the data without the outliers.

All the listings will display the original missing values.

### 5.3.6 Other Considerations

#### 5.3.6.1 Safety

A subject who has an AE coded to the same preferred term more than once during the Extension Phase and the Core Study will be counted only once in the incidence calculations for that AE. Similarly, if a subject has more than one AE in a single system organ class (SOC), the incidence will be counted only once for that SOC. If a subject has the same AE more than once, the occurrence that is of greatest severity will be used in the calculation of the incidence of individual AE by severity. The AE considered most closely related to study treatment will be used in the calculation of incidence of individual AE by relationship.

If a subject has taken the same concomitant medication (as coded to preferred WHO-drug term) more than once, the subject will be counted only once in the tabulation.

#### 5.3.6.2 Efficacy

If no diary data is observed during a period, then the seizure frequency per 28 days for that period will be set to missing. Missing diary data should not be interpreted as equivalent to a non-missing record of zero.

## 5.4 Efficacy Analyses

Only “valid days” and “valid seizure counts” will be used in the calculations of seizure frequency per 28 days. A “valid day” is defined as the day where seizure counts information is present, that is, either a record with an answer of ‘No’ to the question ‘Did the subject experience any seizures?’ or a positive number of seizures for at least one of the seizure types collected. “Valid seizure counts” are the seizure counts that are read from the valid seizure days.

The baseline for a given seizure type (or total) is defined as seizure frequency per 28 days of the given type (or total) based on all valid seizure diary data dated before the first dose date

of perampanel. This means that the baseline will be based on all valid seizure diary data occurring during the Core Study Pretreatment Phase.

#### 5.4.1 Primary Efficacy Analyses

Not applicable.

#### 5.4.2 Secondary Efficacy Analyses

The percent change in seizure frequency per 28 days during the Core Study and Maintenance Period of the Extension Phase with respect to baseline assessment collected during the Pretreatment Phase of the Core Study will be summarized using descriptive statistics (n, mean, median, minimum, maximum and 95% confidence interval). The percent change in seizure frequency per 28 days are calculated for total seizure, POS total seizure and total complex partial seizure for POS cohort, for PGTC seizure, absence seizure, myoclonic seizure and total seizure for PGTC cohort and for Secondarily Generalized seizures for GTC cohort. Total Seizures is sum of all seizures, including POS, generalized and other seizures. Total POS Seizures is sum of all POS seizures, including simple partial seizures without motor signs, simple partial seizures with motor signs, complex partial seizures and complex partial seizures with secondary generalization. Secondarily Generalized seizures cohort is a subset of POS cohort.

The proportion of subjects who are seizure-free and the proportion of responders based on decrease from baseline (during the Pretreatment Phase) in 28-day seizure frequency of equal or greater than 25%, equal or greater than 50%, and equal or greater than 75% during Maintenance Period of the Extension Phase will be summarized using frequency count (number and percentage). If subjects complete the Extension Phase and have no seizure during the Maintenance Period, those will be treated as seizure-free.

The number of subjects with new seizure types compared to Baseline Period and Seizure history will be summarized.

The CGIC and CGIS will be summarized for each visit using frequency count (number and percentage).

For Japan submission, all of the analysis will be repeated for Japanese population.

#### 5.4.3 Other Efficacy Analyses

The score of EQ-5D-Y each items (Mobility, Looking after myself, Doing usual activities, Having pain or discomfort, Feeling worried, sad or unhappy) will be summarized for each visit using frequency count (number and percentage). The measurement and the change from baseline of EQ-5D-Y VAS at each visit will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum and maximum).

## 5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

### 5.5.1 Pharmacokinetic Analyses

Not applicable.

### 5.5.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable.

## 5.6 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data will be summarized on an “as treated” basis using descriptive statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include TEAEs, clinical laboratory parameters, vital signs, 12-lead ECG results, C-SSRS, growth parameters, CBCL, LGPT, and EEG. Study Day 1 for all safety analyses will be defined as the date of the 1st dose of study drug.

### 5.6.1 Extent of Exposure

Exposure will be evaluated for the Safety Analysis Set.

Duration of Extension Phase exposure will be calculated as the number of week between the date the subject received the first dose of perampanel in the Extension Phase and the date the subject received the last dose of perampanel in the Extension Phase. Total perampanel exposure will be calculated as the number of week between the date the subject received the first dose of perampanel in Core Study and the date the subject received the last dose of study drug in the Extension Phase.

Modal dose, mean daily dose, maximum daily dose and last daily dose will be presented using summary statistics and frequency using categories of <4, 4, >4-<8, 8-<12, 12=<. Number and percent of subjects who down-titrated or discontinued study at maximum daily dose exposed will be summarized using frequency count (number and percentage).

### 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). Adverse events will be coded to the MedDRA (version 18.1 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) will also be captured in the database.

A TEAE is defined as an AE that:

- Emerges from the date of first dose of study drug in Core Study to 28 days after last end date of dose in prescribed dose entry in Extension Phase, having been absent at pretreatment (Baseline) in Core Study, or
- Reemerges during treatment, having been present at pretreatment (Baseline) in Core Study but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state in Core Study, 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.

TEAEs will be summarized 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 a SOC and PT, even if the subject experienced more than one 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 [possibly related, probably related] and No [not related]).

AEs will be analyzed by the actual dose at AE onset.

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study treatment.

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

### **AEs of special Interest**

A listing of subjects with AEs related to suicidality, identified by relevant Standardized MedDRA Query (SMQ) terms, will be provided. TEAEs of special interest listed below will be summarized by SOC and PT. SMQs will be used to identify relevant terms for the following TEAEs.

- TEAEs suggestive of abuse potential
- TEAEs related to alertness and cognition

- TEAEs related to hostility/aggression
- TEAEs related to psychosis/psychotic disorders
- TEAEs related to status epilepticus/convulsions
- TEAEs related to lab abnormalities
- Cardiac and ECG TEAEs
- TEAEs related to rash

TEAEs related to rash will be identified by medical review. Falls, regardless of causality, will be summarized for the treatment period (including Titration phase and Maintenance phase of the Core Study, as well as Maintenance through Follow-up Period of the Extension phase) by the actual dose at onset.

### 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 Safety Assessments \(Laboratory Measurements\)](#), the actual value and the change from baseline to each post baseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit using descriptive statistics. Qualitative parameters listed in [protocol Section 9.5.1.5.3 Safety Assessments \(Laboratory Measurements\)](#) will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each post baseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both non-missing baseline and relevant post baseline 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. For each laboratory parameter, shift from baseline (LNH) to each post baseline visit and at the end of treatment will be presented. Similar shift tables from baseline (LNH) to the highest/lowest post baseline value will also be presented.

The Sponsor's Grading for Laboratory Values ([Protocol Appendix 2](#)) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAV). Except for phosphate, a TEMAV was 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 post baseline value with an increase from baseline to a grade of 3 or higher. The number and percentage of subjects with TEMAVs will be presented; each subject will be counted once in the laboratory parameter high and low categories, as applicable. Markedly abnormal laboratory values will be flagged in the subject data listings..

For ALT and AST analysis, the number of subjects with greater than 3 times, but less than 5 times the ULN and the number of subjects with greater than 5 times the ULN will be summarized. For bilirubin, a summary of the number of subjects with serum concentrations greater than 2 times the ULN will be created. These summaries will also be provided for the

maximum value in the treatment duration. In addition, the number of subjects who meet the criteria for Hy's Law will be summarized by visit and during the treatment duration. A subject will be determined to have met Hy's Law if AST or ALT is  $> 3x$  ULN, bilirubin  $> 2x$  ULN, and alkaline phosphatase  $< 2x$  ULN at a visit. The number of subjects who meet each of the criteria for Hy's Law during treatment (but not all necessarily at the same visit) will also be summarized.

#### 5.6.4 Vital Signs

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

In addition, the criteria described in the table below will be used to determine clinically notable results for blood pressure and heart rate. The number (percentage) of subjects with clinically notable results over all scheduled and unscheduled visits will be summarized.

**Table 1: Criteria for Clinically Notable<sup>a</sup> Vital Signs**

Variable	Criterion Value	Change Relative to Baseline
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
Heart Rate	$> 120$ bpm	Increase of $\geq 15$ bpm
	$< 50$ bpm	Decrease of $\geq 15$ bpm
Weight		Increase of $> 7\%$
		Decrease of $> 7\%$
a: Clinically notable means that a value must have met both the criterion value and satisfied the magnitude of change relative to baseline.		

The criteria in [Table 2](#) will be used to determine abnormal results for blood pressure and heart rate. The number of subjects with abnormal results will be summarized.

**Table 2: Criteria for Abnormal Vital Signs**

<b>Variable</b>	<b>Change Relative to Baseline</b>
Systolic BP	Increase of $\geq 20$ mmHg
	Decrease of $\geq 20$ mmHg
	Increase of $\geq 40$ mmHg
	Decrease of $\geq 40$ mmHg
Diastolic BP	Increase of $\geq 10$ mmHg
	Decrease of $\geq 10$ mmHg
	Increase of $\geq 20$ mmHg
	Decrease of $\geq 20$ mmHg
Pulse	Increase of $\geq 15$ bpm
	Decrease of $\geq 15$ bpm
	Increase of $\geq 30$ bpm
	Decrease of $\geq 30$ bpm

### 5.6.5 Electrocardiograms

ECG parameters (QTcB, QTcF, PR interval, QRS duration and RR interval) and changes from baseline will be presented by visit.

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 one post baseline abnormal ECG result in QTc Bazett and QTc Fridericia during the treatment period will be summarized.

Clinically borderline or abnormal ECG results in QTc Bazett and QTc Fridericia will be categorized as follows:

Absolute QTc interval prolongation:

- QTc interval 430-450 ms
- QTc interval  $>450$  ms
- QTc interval  $>500$  ms

Change from baseline in QTc interval:

- QTc interval increases from baseline 30-60 ms
- QTc interval increases from baseline  $>60$  ms



### 5.6.6 Other Safety Analyses

#### **Aldenkamp-Baker Neuropsychological Assessment Schedule (ABNAS)**

The total ABNAS score (defined as the sum of the individual question scores) and sub-scores for fatigue, slowing, memory, concentration, motor-coordination and language (Brooks et al 2001) will be listed and summarized by visit. Changes from baseline ABNAS sub-scores will be summarized.

**Table 3: Definition between each aspect and question**

<b>Aspect</b>	<b># of items</b>	<b>Range</b>	<b>Item No</b>
fatigue	5	0-15	1, 7, 13, 18, 24
slowing	5	0-15	2, 8, 14, 19, 23
memory	4	0-12	3, 9, 15, 20
concentration	4	0-12	4, 10, 16,21
motor speed	3	0-9	5, 11, 17,
reading (language)	3	0-9	6, 12, 22

#### **Child Behavior Check List (CBCL 1.5/5 and CBCL 6/18)**

The CBCL 1.5/5 measures problems in children (1.5 to 5 years old). To measure problems, 100 ‘problem items’ are rated on a scale to measure their occurrence. Higher scores indicate greater problems, as the scale ranges from 0, indicating ‘not true,’ to 2, indicating ‘often true.’ 67 of the items are then summed into seven syndrome scores (Emotionally Reactive, Anxious/Depressed, Withdrawn, Somatic Complaints, Attention Problems, Aggressive Behavior syndrome and Sleep problems.) The summation of the first four syndrome scores yields the Internalizing Syndrome composite score, and the summation of the next two syndrome scores yields the Externalizing Syndrome composite score. The total problems score is the summation of all 100 item scores. .

The total problems score, the Internalizing Syndromes score, the Externalizing Syndromes score, and each of the seven individual syndrome scores of the CBCL 1.5/5 will be evaluated using summaries of change from baseline (Week 0) by visit.

**Table 4: Definition CBCL 1.5-5 (Refer to link of CBCL/1 1/2-5 and LDS in profiles at website <http://www.aseba.org/forms.html>)**

Syndrome scale	#of items	Range	Items
Emotionally Reactive	9	(0-18)	21,46,51,79,82,83,92,97,99
Anxious/Depressed	8	(0-16)	10,33,37,43,47,68,87,90
Withdrawn	8	(0-16)	2,4,23,62,67,70,71,98
Somatic Complaints	11	(0-22)	1,7,12,19,24,39,45,52,78,86,93
Internalizing	36	(0-72)	sum of 4 previous scores
Attention Problems	5	(0-10)	5,6,56,59,95
Aggressive Behavior syndrome	19	(0-38)	8,15,16,18,20,27,29,35,40,42,44,53,58,66,69,81,85,88,96
Externalizing	24	(0-48)	sum of 2 previous scores
Sleep problems	7	(0-14)	22,38,48,64,74,84,94
Total	100	(0-200)	Sum of all problem items scores

Also the CBCL 6/18 measures competencies and problems in children (6 to 18 years old). To assess competence, sixteen items are scored for each child, with higher scores indicating better competence. The summed scores are grouped into three sub-scores for competence in activities, social realms and school. The total competence score is the summation of all 16 items.

To measure problems, 120 ‘problem items’ are rated on a scale to measure their occurrence. Higher scores indicate greater problems, as the scale ranges from 0, indicating ‘not true,’ to 2, indicating ‘often true.’ 103 of the items are then summed into eight syndrome scores (Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Rule-Breaking Behavior, Aggressive Behavior, Social Problems, Thought Problems, and Attention Problems.) The summation of the first three syndrome scores yields the Internalizing Syndrome composite score, and the summation of the next two syndrome scores yields the Externalizing Syndrome composite score. The total problems score is the summation of the two composite scores, the final three syndrome scores, and the 17 ‘problem items’ that were not included in any of the eight syndrome scores.

The total competence score, the three sub-scores for competence, the total problems score, the Internalizing Syndromes score, the Externalizing Syndromes score, and each of the eight individual syndrome scores of the CBCL 6/18 will be evaluated using summaries of change from baseline (Week 0) by visit.

**Table 5: Definition CBCL 6-18 (Refer to link of CBCL/6-18 scored using three different societies in profiles at website : <http://www.aseba.org/forms.html>)****Competency Scores**

Sub-scores	# of Items	Score Range	Items
Activity	6	(0-15)	I.A, B, II.A, B, IV A, B
Social	6	(0-14)	III.A, B, V.1, 2, VI. A, B
School	4	(0-6)	VII. 1, 2,3,4
Total	16	(0-35)	Sum of 3 previous scores

**Syndrome/ Problems Scores**

Syndrome scale	#of items	Score Range	Items
Anxious/Depressed	13	(0-26)	14,29,30,31,32,33,35,45,50,52,71,91,112
Withdrawn/Depressed	8	(0-16)	5,42,65,69,75,102,103,111
Somatic Complaints	11	(0-22)	47,49,51,54,56a,56b,56c,56d,56e,56f,56g
Internalizing	32	(0-64)	sum of 3 previous scores
Rule-Breaking Behavior	17	(0-34)	2,26,28,39,43,63,67,72,73,81,82,90,96,99,101,105,106
Aggressive Behavior	18	(0-36)	3,16,19,20,21,22,23,37,57,68,86,87,88,89,94,95,97,104
Externalizing	35	(0-70)	sum of 2 previous scores
Social Problems	11	(0-22)	11,12,25,27,34,36,38,48,62,64,79
Thought Problems	15	(0-30)	9,18,40,46,58,59,60,66,70,76,83,84,85,92,100
Attention Problems	10	(0-20)	1,4,8,10,13,17,41,61,78,80
Total	120	(0-240)	Sum of all problem items scores

Additionally, both CBCL results for each subject will be converted to a standardized T-score and classified at baseline and at each evaluation as normal, borderline clinical, or clinical, based on the thresholds provided in the CBCL manual. These classifications and their change from baseline will be presented in tables.

**Lafayette Grooved Pegboard Test (LGPT)**

Time taken to perform the Lafayette Grooved Pegboard Test correctly (i.e. inserting 25 pegs for 8 years or older or 10 pegs for under 8 years old for each hand, ranges up to 300 seconds) will be summarized by visit. If the task cannot be completed correctly at 300 seconds, 300 seconds will be recorded.

Total number of pegs correctly placed and total number of pegs dropped will also be summarized separately for each hand by visit.

Total score for each hand (Trites) will be calculated as time to complete the test + total number of pegs dropped + total number of pegs correctly placed.

All summaries will be calculated by each age group (for 8 years or older, for under 8 years old) separately.

### **Growth parameter**

The actual value and change from baseline in growth parameter (height, weight, TSH, fT3, fT4 and IGF-1) will be summarized by visit. Height and weight will be presented using summary statistics for overall percentile and overall z-score.

### **EEG**

EEG parameters will be summarized and listed as appropriate.

### **Columbia Suicide Severity Rating Scale (C-SSRS)**

Scoring of the C-SSRS will be performed as suggested by the C-SSRS Columbia website [http://www.cssrs.columbia.edu/clinical\\_trials.html](http://www.cssrs.columbia.edu/clinical_trials.html).

The following summaries will be presented for the treatment duration (defined as the period from the date of first dose at Core Study up to 28 days after the date of last dose at Extension Phase, inclusive).

- Number (percentage) of subjects with any treatment-emergent report of suicidal behavior, suicidal ideation, and suicidality (suicidal behavior and/or ideation) will be displayed. A treatment-emergent report of suicidal behavior, suicidal ideation, or suicidality is an answer of 'Yes' to any question in the respective category during the treatment duration.
- Shift from baseline to the maximum suicidal ideation severity rating (0=no ideation present to 5=active ideation with plan and intent) in the treatment duration will assess worsening of suicidal ideation. Any score greater than 0 indicates the presence of suicidal ideation while a score of 4 (active suicidal ideation with some intent to act) or 5 (active suicidal ideation with specific plan and intent) can be used to indicate serious suicidal ideation.

Descriptive statistics and changes from baseline will be presented by visit for the suicidal ideation intensity score and the suicidal ideation severity rating (treated as a continuous variable) to assess change in suicidal ideation over time. The suicidal ideation intensity score ranges from 0 to 25 and is the sum of the 5 intensity items.

## 5.7 Exploratory Analyses

The change from baseline in EQ-5D-Y will be summarized by age and disease cohorts, and by the presence or absence of concomitant EIAED, using descriptive statistics.

## 6 INTERIM ANALYSES

An independent data monitoring committee (DMC) will be constructed to monitor the safety data. The responsibilities, membership, and purpose of the DMC, the timing of the meeting(s), and an outline of the plan for review of the safety data will be documented in the DMC Charter.

## 7 CHANGES IN THE PLANNED ANALYSES

There are currently no changes in the planned analyses.

## 8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

### 8.1 Efficacy Data Handling

#### 8.1.1 Pre-randomization/baseline efficacy

All diary data prior to first dose date at Core Study will be used in the computation of Pretreatment Phase seizure frequency per 28 days. The baseline value for other efficacy endpoints will be the last non-missing measurement occurring prior to the first dose of the study drug at Core Study.

#### 8.1.2 Treatment Duration for Efficacy Analyses

The date of first dose of the study drug is considered day 1 in the treatment duration.

The first dose date is the study drug start date and the last dose date is study drug end date from the study medication CRF page.

The treatment duration for efficacy variables is defined as follows:

- For diary seizure data: The duration between the day of first dose at Core Study and the last day of study drug at Maintenance Period in Extension Phase, inclusive.
- For non-diary efficacy data: The duration between the day of first dose at Core Study and 7 days after the last day of study drug at Maintenance Period in Extension Phase, inclusive.

For all efficacy analyses, data reported during Core Study and the Maintenance Period in Extension Phase will be analyzed. The diary seizure data during the Follow-up will be listed.

#### 8.1.3 Handling of Replicate Data

For the CGIC and EQ-5D-Y assessment, the last visit within the treatment duration will be used.

## 8.2 Safety Data Handling

### 8.2.1 Baseline Safety

The baseline value for safety endpoints will be the last non-missing measurement occurring prior to the first dose of the study medication at Core Study.

### 8.2.2 Treatment Duration for Safety Variables

The treatment duration for non-AE safety variables is the same as non-diary efficacy analysis in [Section 8.1.2 Treatment Duration for Efficacy Analyses](#). For AEs, the treatment duration is considered to begin on Day 1 at Core Study and ends 14 days after the last dose of Maintenance Period in Extension Phase.

The post-treatment duration is considered to begin on the day after the treatment duration for safety. Since it is not always possible for all study participants to come in for their clinic visits on the exact day specified in the protocol schedule, the visit week of a subject's visit will be based on the actual visit occurring during the treatment duration. These visits will be used to create by visit summaries for laboratory, vital signs, electrocardiograms and other safety analyses data. The end of treatment value is the last non-missing value in the treatment duration.

Any concomitant medication taken within the 14 days after the last dose data will be listed/summarized as part of the concomitant medication listing/table.

AEs for the subject were collected and reported on CRF starting from the time subject signed informed consent to the last visit in the Follow-up following subject's last dose. Serious AEs were collected for 28 days after the last dose.

For summaries of safety by time points, the time points will be relative to date of first dose. For standardized reporting, study day windows relative to the first dose (Day 1) in the study will be applied to determine into which week the data will be mapped. Scheduled, unscheduled, and early withdrawal visits will be mapped to weeks. [Table 6](#) below gives the mapping of relative day ranges to week for non-AE safety variables. If a subject did not have a recorded observation falling within a given range of days in order to be assigned to a week, the subject's data for that week will be regarded as missing for summarization purposes. If there are two or more assessments in the same window then:

- if the window is the baseline assessment, then the latest assessment will be used in the summary tables;
- if the window is the follow-up assessment, then the latest assessment will be used in the summary tables;

If the window is not the baseline or the follow-up assessment, then the assessment closest to the scheduled assessment will be used in the summary tables. Note that if two assessments are equidistant from the scheduled assessment then the last assessment of the two (within the allowable window) will be used.

**Table 6: Mapping of Study Day Ranges to Week**

<b>Windowing Period</b>	<b>Study Day Range (Relative to First Dose)</b>	<b>Week</b>
Pretreatment	Day $\leq 1^a$	0
Treatment	$2 \leq \text{Day} \leq 25$	2
Treatment	$26 \leq \text{Day} \leq 46$	5
Treatment	$47 \leq \text{Day} \leq 67$	8
Treatment	$68 \leq \text{Day} \leq 88$	11
Treatment	$89 \leq \text{Day} \leq 119$	15
Treatment	$120 \leq \text{Day} \leq 147$	19
Treatment	$148 \leq \text{Day} \leq 175$	23
Extension	$176 \leq \text{Day} \leq 208$	28
Extension	$209 \leq \text{Day} \leq 293$	40
Extension	$294 \leq \text{Day} \leq 378$	52
End of Treatment(EOT) of Extension Phase	-	b
Follow up for discontinuation of Extension Phase	After the date of discontinuation $\leq \text{Day}$ $\leq$ last dose of study drug +35	c

- a: All assessments performed on the same date as the date of first dose were to be performed prior to dosing; results from these assessments will be regarded as Pretreatment values in the analyses.
- b: The last non-missing value measured in the Maintenance Period will be handled as the data of EOT of the Extension Phase. The Follow-up visit will not be included in this analysis visit.
- c For the safety assessment other than AE, the data assessed as the planned visit of the Follow-up will be handled as those of Follow-up visit. AE occurred on or after the date of discontinuation will be handled as that of Follow-up period.

## 9 PROGRAMMING SPECIFICATIONS

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

## 10 STATISTICAL SOFTWARE

All data analyses will be performed by the Sponsor or designee (Symbiance) after the study is completed and the database is released. Statistical programming and analyses will be performed using SAS® and/or other validated statistical software as required.

## 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.

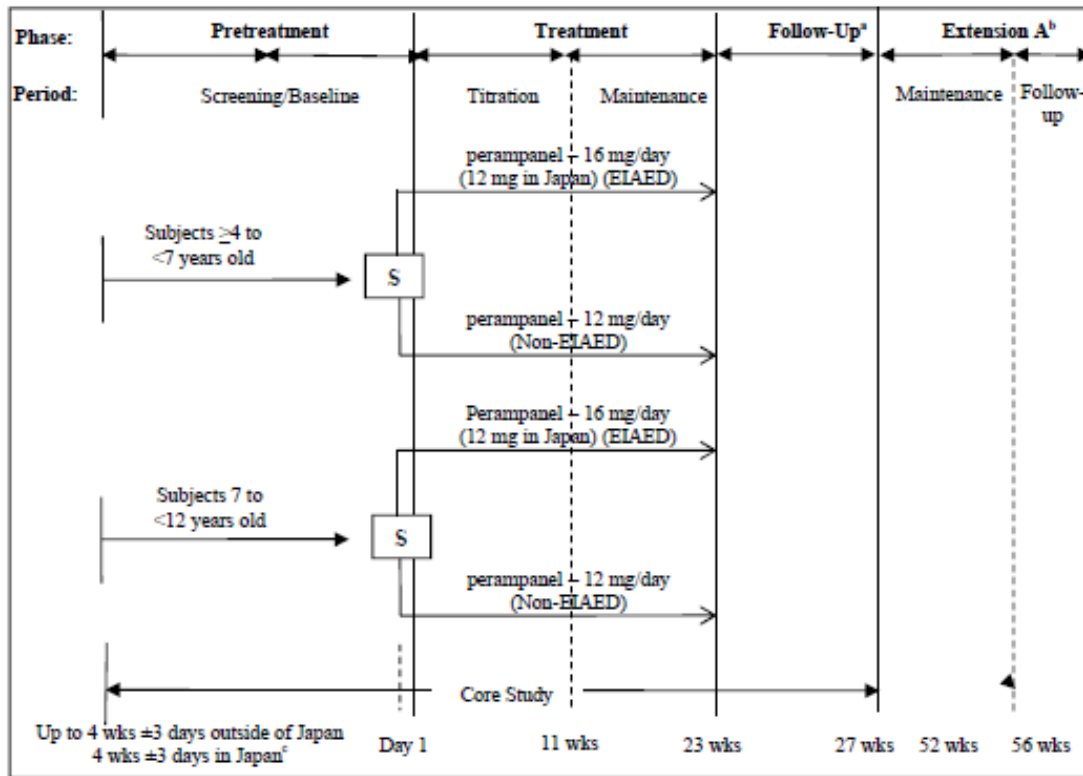
## 12 REFERENCES

[Clinical Study Protocol: E2007-G000-311](#), An Open-Label, Multicenter Study with an Extension Phase to Evaluate the Safety, Tolerability, and Exposure-Efficacy Relationship of Perampanel Oral Suspension when Administered as an Adjunctive Therapy in Pediatric Subjects (Age 4 to less than 12 years) with Inadequately Controlled Partial-Onset Seizures or Primary Generalized Tonic-Clonic Seizures, 20 Apr 2017 v5.0 Amendment 01.



## 13 APPENDICES

### 13.1 Study Design for E2007-G000-311



**Figure 1 Study Design for Study E2007-G000-311**

Note: (revised per Amendments 02 and 03)

Follow-up can occur during the Core Study (if the subject discontinued during the Core Study), or during Extension A or Extension B, after the termination of study treatment.

EIAED = enzyme inducing antiepileptic drug, S = stratified, wks = weeks.

- Subjects will have a Follow-up Visit 4 weeks (±7 days) after the end of the treatment and a final assessment completed if they are not rolling over into Extension A.
- Subjects who are enrolled in Japan and have completed the Extension A may be eligible to enroll in Extension B, as detailed in Appendix 2. (revised per Amendment 03)
- Subjects in Japan are required to complete 4 full weeks ±3 days of the Screening/Baseline Period. (revised per Amendment 02)

## 13.2 Sponsor's Grading for Determining Markedly Abnormal Laboratory Results

The following table is of Sponsor's Grading for Laboratory Values from the version in the [protocol, Appendix 1](#).

### 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 <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 – $3.0 \times 10^9/L$ <LLN – 3000/mm <sup>3</sup>	<3.0 – $2.0 \times 10^9/L$ <3000 – 2000/mm <sup>3</sup>	<2.0 – $1.0 \times 10^9/L$ <2000 – 1000/mm <sup>3</sup>	< $1.0 \times 10^9/L$ <1000/mm <sup>3</sup>
Lymphocytes	<LLN – 800/mm <sup>3</sup> <LLN – $0.8 \times 10^9/L$	<800 – 500/mm <sup>3</sup> <0.8 – $0.5 \times 10^9/L$	<500 – 200/mm <sup>3</sup> <0.5 – $0.2 \times 10^9/L$	<200/mm <sup>3</sup> < $0.2 \times 10^9/L$
Neutrophils	<LLN – $1.5 \times 10^9/L$ <LLN – 1500/mm <sup>3</sup>	<1.5 – $1.0 \times 10^9/L$ <1500 – 1000/mm <sup>3</sup>	<1.0 – $0.5 \times 10^9/L$ <1000 – 500/mm <sup>3</sup>	< $0.5 \times 10^9/L$ <500/mm <sup>3</sup>
Platelets	<LLN – $75.0 \times 10^9/L$ <LLN – 75,000/mm <sup>3</sup>	<75.0 – $50.0 \times 10^9/L$ <75,000 – 50,000/mm <sup>3</sup>	<50.0 – $25.0 \times 10^9/L$ <50,000 – 25,000/mm <sup>3</sup>	< $25.0 \times 10^9/L$ <25,000/mm <sup>3</sup>
<b>METABOLIC/LABORATORY</b>				
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

**Sponsor's Grading for Laboratory Values**

	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
				life-threatening consequences; seizures
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), 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).

# SIGNATURE PAGE

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