STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E2007-G000-238
Study Protocol Title:	An Open-Label Study with an Extension Phase to Evaluate the Pharmacokinetics of Perampanel (E2007) Oral Suspension When Given as an Adjunctive Therapy in Subjects From 1 Month to Less Than 4 years of Age with Epilepsy
Date:	13 February 2023
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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE(s)	adverse event(s)
AED	antiepileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomical therapeutic class
BMI	body mass index
BP	blood pressure
CGI	Clinical Global Impression
CGIC	Clinical Global Impression of Change
CGIS	Clinical Global Impression of Severity
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	electronic case report form
EIAED	enzyme-inducing antiepileptic drugs
EOT	End of treatment
FAS	Full Analysis Set
IGF-1	insulin-like growth factor-1
LLN	lower limit of normal
LNH	low/normal/high
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamics
PK	Pharmacokinetics
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
SAS	Safety Analysis Set
SD	Standard Deviation

Abbreviation	Term
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 DD	World Health Organization Drug Dictionary

3 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for the core study of Eisai Protocol E2007-G000-238 in pediatric subjects from 1 month to less than 4 years of age with epilepsy. The statistical methods for the Extension Phase will be described in a separate SAP.

3.1 Study Objectives

3.1.1 Primary Objective

To evaluate the pharmacokinetics (PK) of perampanel during the Maintenance Period of the Core Study following oral suspension administration given as an adjunctive therapy in pediatric subjects from 1 month to less than 4 years of age with epilepsy.

3.1.2 Secondary Objectives

- To evaluate the short- and long-term safety and tolerability of perampanel oral suspension, given as an adjunctive therapy, in subjects from 1 month to less than 4 years of age with epilepsy
- To evaluate the long-term effect of perampanel oral suspension, given as an adjunctive therapy, on growth from baseline to end of treatment in pediatric subjects from 1 month to less than 4 years of age with epilepsy

3.1.3 Exploratory Objective

The exploratory study objective was to explore the short- and long-term efficacy of perampanel oral suspension, given as an adjunctive therapy, in subjects from 1 month to less than 4 years of age with epilepsy as assessed by:

- Percent change in 28-day seizure frequency during the Titration + Maintenance Periods compared to baseline and during the Extension Phase compared to baseline
- Proportion of subjects with a 50% decrease in 28-day seizure frequency during the Maintenance Period compared to baseline and during the Extension Phase compared to baseline
- Proportion of subjects who are seizure-free during the Maintenance Period and during the Extension Phase
- Clinical Global Impression (CGI) of change (CGI-C)

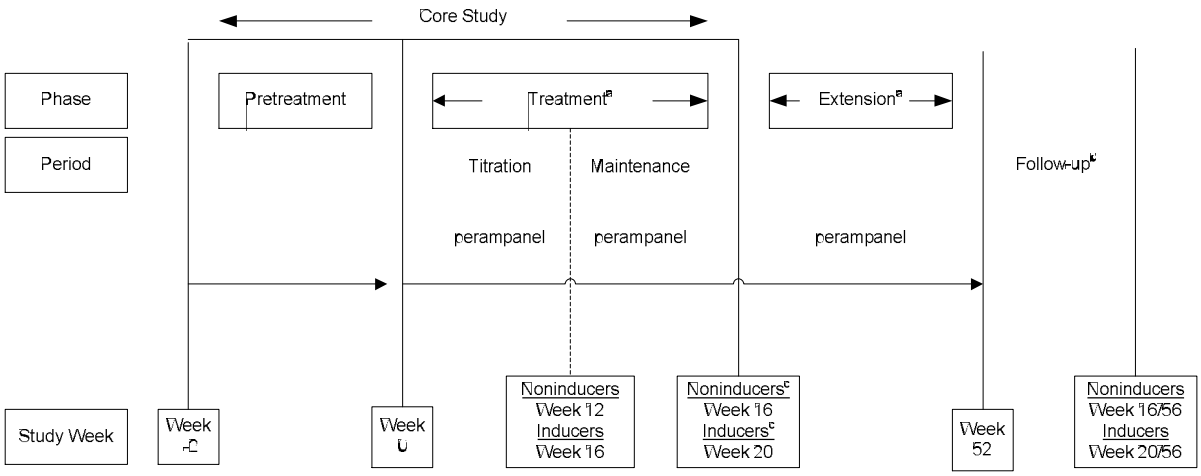
3.2 Overall Study Design and Plan

This was a multicenter, open-label study with an extension phase that was planned to enroll 16 to 24 pediatric subjects 1 to less than 24 months of age and at least 1 to a maximum of 26 pediatric subjects from 2 to less than 4 years of age with epilepsy. All subjects had been taking 1 to a maximum of 4 antiepilepsy drugs (AEDs) to participate in the study. For at least 6 but not more than 8 of the subjects in the age group of 1 to less than 24 months and for 13 subjects in the age group of 2 to less than 4 years (across studies), only 1 enzyme inducing antiepilepsy drug (EIAED) (ie, carbamazepine [CBZ], oxcarbazepine [OXC], phenytoin [PHT], or eslicarbazepine [ESL]) out of the maximum of 4 AEDs was allowed. These subjects were referred to as EIAED subjects. The remaining subjects were not taking any EIAEDs were referred to as non-EIAED subjects. For the age group of 1 to less than 24 months, the Sponsor aimed to ensure a reasonable representation of subject age (ie, at least 6 subjects in the age range ≥1 to ≤6 months, at least 5 subjects in the age range >6 to ≤12 months and at least 5 subjects in the age range >12 to <24 months). For the age group of 2 to less than 4 years, the required number of subjects (total of 26) can be pooled across multiple studies for PK and safety assessments in pediatric subjects of 2 to less than 4 years of age.

This study consisted of 3 phases: Pretreatment and Treatment (Core Study), and Extension. The Pretreatment Phase lasted up to 2 weeks, during which subjects were assessed for their eligibility to participate in the study. The Treatment Phase consisted of 3 periods: Titration (12-16 weeks), Maintenance (4 weeks), and Follow-Up (4 weeks; only for those subjects who completed the Maintenance Period but did not continue into the Extension Phase). The Extension Phase consisted of 2 periods: Maintenance (32-36 weeks) and Follow-Up (4 weeks). The end of the study was the date of the last study visit for the last subject.

The maximum total duration of treatment for each subject was 52 weeks and the maximum total duration of the study for each subject was 58 weeks.

An overview of the study design was presented in Figure below.



a: Subjects to receive study treatment starting at Week 0 of the Treatment Phase through Week 52 of the Extension Phase.
b: Follow-up Period Visit is to be completed at the end of the Treatment Phase for those subjects not rolling over to the Extension Phase of the study, for those subjects who early terminate from the study, and for all subjects completing the Extension Phase.
c: Prior to entry into the Maintenance Period, subjects have been maintained on their last Titration Period dose for at least 2 weeks.

4 DETERMINATION OF SAMPLE SIZE

Study E2007-G000-238 used population PK modeling to determine PK in pediatrics ≥1 to <24 months of age and from 2 to less than 4 years of age and compared these data to PK in adolescents and adults. In Study E2007-G000-232, data were obtained in 42 pediatric subjects ≥2 to <12 years of age, with approximate equal numbers enrolled in the age ranges of ≥2 to ≤6 and ≥7 to <12 years.

Given the narrower age range planned for Study 238 compared with Study 232, and the fact that the PK data from this study would be pooled with the data from subjects ≥2 to <12 years of age, it was proposed that PK data obtained in at least 16 subjects ≥1 to <24 months of age would be adequate to characterize the PK in this age group. In addition, Study 238 PK data in at least 16 subjects in this age group would account for more than 25% of the data obtained for perampanel overall in subjects ≥1 month to <12 years of age, confirming appropriate assessment and representation of this age group in the overall assessment of PK and safety in the pediatric population. The sample size was to be increased to at least 24 subjects if dose-normalized (to 8 mg) exposure in the Maintenance Period from the first 16 subjects in this study was not comparable to existing data in subjects aged ≥2 to 18 years.

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 performed by age cohort (1 to ≤ 6 months, > 6 to ≤ 12 months, >12 to < 24 months, and ≥24 to <48 months) and overall, unless stated otherwise.

5.1 Study Endpoints

5.1.1 Primary Endpoint

The primary endpoint of this study is to evaluate PK of perampanel during the Maintenance Period of the Core Study following oral suspension administration given as an adjunctive therapy in pediatric subjects from 1 month to less than 4 years of age with epilepsy, using a population PK approach. Details regarding PK analysis will not be described in this SAP but will be described in a separate analysis plan.

5.1.2 Secondary Endpoints

Secondary endpoints are safety and tolerability endpoints including incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), clinical laboratory parameters, vital signs, ECG parameters, and growth parameters (height, weight, head circumference, thyroid function, and IGF-1 levels).

5.1.3 Exploratory Endpoints

The efficacy endpoints are:

- Seizure frequency: Percent change in 28-day seizure frequency during the Treatment Phase and during the Extension Phase, compared to baseline.
- Responder rate: Proportion of subjects with a 50% decrease in 28-day seizure frequency during the Maintenance Period and during the Extension Phase, compared to baseline.
- Seizure-free rate: Proportion of subjects who are seizure-free during the Maintenance Period and during Extension Phase.
- Clinical Impression of change (CGI-C) at the end of core and extension phase.

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 study drug, had seizure frequency >0 during baseline period and had any seizure frequency data during the Treatment Phase.

The **Modified Full Analysis Set (Modified FAS)** is the group of subjects who received study drug and had any seizure frequency data during the Treatment Phase.

5.2.2 Subject Disposition

The number of subjects screened and the number (percentage) of subjects who failed screening and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition electronic case report form (eCRF). The distribution of the number of subjects enrolled by each site will be summarized.

The number (percentage) of treated subjects who completed the Core Study and who discontinued early from the Core Study will be summarized according to the primary reason for early discontinuation and other reason(s) for early discontinuation, based on data reported on the core study disposition eCRF.

5.2.3 Protocol Deviations

The number (percentage) of subjects with major protocol violations will be summarized. Major protocol deviation criteria include the following:

- Subject is less than 1 month or over 4 years of age at the time of consent/assent.
- Incorrect diagnosis of epilepsy according to the International League Against Epilepsy's Classification of Epileptic Seizures (1981).
- Subject was on more than 1 inducer AED (i.e., carbamazepine, oxcarbazepine, phenytoin) out of the maximum of 4 AEDs allowed.
- Subject stops or interrupted any approved AEDs the subject was on at baseline OR was on >4 AEDs.
- Non-compliance with study drug defined as overall compliance of <80% or >120%. For subjects where treatment compliance cannot be calculated, major deviations as recorded in the protocol deviation log for compliance will be used.
- Subjects with missing PK data at all PK timepoints, except when a subject was discontinued early from the study before reaching the first PK visit.

5.2.4 Demographic and Other Baseline Characteristics

The demographics and other baseline characteristics of the Safety Analysis Set will be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum) for continuous variables, and using numbers and percentages for categorical variables. Continuous demographic and baseline variables include age, weight, height, body mass index (BMI) and body surface area; categorical variables include sex, race, and ethnicity.

5.2.5 Medical History

The number (percentage) of subjects in the SAS reporting a history of any medical condition, as recorded on the eCRF, will be summarized.

Clinical Global Impression of Severity at baseline will be summarized.

Epilepsy-specific medical history (etiology, time from diagnosis to Visit 1, seizure type) will be summarized. A subject data listing of medical history will be provided.

5.2.6 Prior and Concomitant Therapy

Prior and concomitant medications will be assigned an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) drug codes. Concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. 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 (i.e., therapeutic class), and WHO DD preferred term. Prior medications are defined as medications that stopped before the first dose of study drug. Concomitant medications are defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 14 days after the subject's last dose.

Prior failed AEDs and AEDs taken at baseline, including the number of AEDs, will also be summarized on the Safety Analysis Set.

5.2.7 Treatment Compliance

Compliance with study medication during the Treatment Phase will be summarized using descriptive statistics. Overall percent compliance will be calculated as follows:

$$Compliance = \left(\frac{(\text{Wt. t of Study Drug Dispensed [g]} - \text{Wt. of Study Drug Returned [g]}) x \frac{0.5\ mg}{mL}}{(\text{No. of Days x Prescribed Daily dose [mg]}) \text{x} \frac{1.07\ \text{g}}{\text{mL}}} \right) x\ 100\%$$

where 0.5 mg/mL is the perampanel concentration in Fycompa oral suspension and
1.07 g/mL is the density of Fycompa oral suspension

Overall study medication compliance will also be summarized using the categories <80%, 80% to 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

All analyses will be provided by age cohort (1 to ≤ 6 months, > 6 to ≤ 12 months, >12 to < 24 months, and 24 to <48 months). Summaries of demography, seizure data, and TEAEs may be further presented by inducer/non-inducer subgroup. Growth parameters (height, weight, thyroid and insulin-like growth factor-1 [IGF-1] parameters) may also be summarized by sex.

5.3.5 Handling of Missing Data, Dropouts, and Outliers

Analysis of percent change and responder rate for the seizure frequency per 28 days during the Maintenance Period will use a last observation carried forward (LOCF) type of imputation. If the overall duration of the Maintenance Period is less than 4 weeks, the diary data from the last 4 weeks during the Core Treatment Phase (Titration Period + Maintenance Period) will be used to calculate the seizure frequency per 28 days for Maintenance-LOCF. Subjects who didn't enter the Core Treatment Maintenance Period would be counted as non-responders in the maintenance period.

The seizure-free status during the Maintenance Period will only be counted for subjects who complete the Maintenance Period (i.e., those who complete the Core Study). A subject who dropped out early would be counted as 'No' for seizure-free status in the Maintenance period.

5.4 Exploratory Efficacy Analyses

This study is designed to assess PK and provide safety, tolerability and efficacy data in children with epilepsy aged 1 month to less than 4 years. Given the small sample size and lack of placebo or comparator, it will not be possible to draw definitive conclusions regarding the efficacy of perampanel oral suspension for the population in this study. As such, no formal statistical tests will be performed. Summary statistics will be displayed for all efficacy parameters in the Full Analysis Set unless stated otherwise.

The primary analysis will use data from the Pretreatment Phase to calculate baseline 28-day seizure frequency. A secondary analysis will use data from the Pretreatment Phase plus data from the 4 weeks prior to Visit 1 to calculate baseline 28-day seizure frequency. Seizure frequency will be based on the number of seizures per 28 days, calculated as the number of seizures over the time interval multiplied by 28 and divided by the number of days in the interval. Seizure frequency will refer to the overall seizure type, unless stated otherwise, obtained by combining across all seizure types.

Post-baseline data reported only during the **on-treatment** duration will be analyzed. The on-treatment duration is defined as follows:

- For diary data: The duration between the day of first study drug dose and the last

day of study drug dose, inclusive.

- For CGIC data: The duration after the day of first study drug dose up to 7 days after the last study drug dose, inclusive.

5.4.1 Primary Exploratory Efficacy Analyses

The efficacy seizure endpoints are the percent change in 28-day seizure frequency during the Treatment Phase compared to baseline, responder rate during the Maintenance Period, and seizure-free status during the Maintenance Period. The baseline 28-day seizure frequency for the primary analyses will use seizure data from the Pretreatment Phase.

The percent change and responder rate analyses will be based on a subset of FAS including subjects with baseline seizure data from the Pretreatment Phase. The seizure-free status will be performed on FAS and modified FAS including subjects who received study drug and had any seizure frequency data during the Treatment Phase.

5.4.2 Secondary Exploratory Efficacy Analyses

Secondary analyses for the percent change and responder rate endpoints in seizure frequency will use seizure data from the Pretreatment Phase plus the data from the 4 weeks prior to Visit 1 to calculate baseline 28-day seizure frequency.

5.4.3 Other Exploratory Efficacy Analyses

The percent change in 28-day seizure frequency during the Titration Period (no imputation) and Maintenance Period (using LOCF-type imputation described in Section 5.3.5) will also be summarized.

Percent change, seizure free and responder rate in 28-day seizure frequency analyses will also be repeated for each seizure type, as appropriate for subjects who have that seizure type during the baseline. Subjects who develop new seizure types during the study will be summarized by seizure type separately.

CGI-C scores at EOT compared to baseline will be summarized using frequency table. The EOT value is the last non-missing value while on treatment.

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Perampanel plasma concentrations were obtained from blood samples drawn during treatment. 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

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 using descriptive statistics (e.g., n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, 12-lead ECG parameters, growth parameters (height, weight, thyroid and insulin-like growth factor-1 [IGF-1] parameters). Study Day 1 for all safety analyses is defined as the date of the first dose of study drug.

5.6.1 Extent of Exposure

The duration of Treatment Phase (Titration Period and Maintenance Period) exposure to study drug will be defined as the number of days between the date of the first dose and the date of last dose of study drug, inclusive. The duration of exposure will be summarized as a continuous variable and by duration categories (>1 day, >1 week, >2 weeks, >4 weeks, >8 weeks, >12 weeks, >16 weeks). The dates of first and last dose of study drug will be determined from the Study eCRF.

The mean daily dose, maximum dose received, last dose, and modal dose for each subject over the Treatment Phase and for each period (Titration, Maintenance) will be summarized. The mean daily dose will be calculated by taking the average of all the doses taken during the time period weighted by the number of days on each dose (i.e., sum of [days on each dose*dose]/during the time period).

5.6.2 Adverse Events

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 25.1 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 treatment-emergent AE (TEAE) is defined as an AE that emerged during treatment, having been absent at pretreatment (Baseline) or

- Re-emerged during treatment, having been present at pre-treatment (Baseline) but stopped before treatment, or
- Worsened in severity during treatment relative to the pre-treatment state, when the AE was 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.

Treatment-emergent AEs (TEAEs) will be summarized by age group and by EIAED and non-EIAED. 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 (related, and not related). The number (percentage) of subjects with TEAEs will also be summarized by the onset periods of Titration, Maintenance, and Follow-up.

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 treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

5.6.2.1 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

The number (percentage) of subjects with treatment-emergent serious adverse events (SAEs) will be summarized by MedDRA SOC and PT. A subject data listing of all SAEs will be provided. A subject data listing of all AEs leading to death 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.

5.6.2.2 AEs of Special Interest

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 psychiatric 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 will be identified by medical review and summarized. Falls will be listed 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 9.7.1.8, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and by age group using descriptive statistics. Qualitative parameters listed in protocol Section 9.7.1.8 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 non-missing baseline and relevant postbaseline results.

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

Appendix 1 (Sponsor's Grading for Laboratory Values) in Section 13.1 presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

5.6.4 Vital Signs

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]) will be presented by visit and by age group.

5.6.5 Electrocardiograms

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

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

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

Absolute QTc interval prolongation:

- QTc interval 430-450 msec
- QTc interval >450 msec
- QTc interval >500 msec

Change from baseline in QTc interval:

- QTC interval increases from baseline 30-60 msec
- QTC interval increases from baseline >60 msec

5.6.6 Other Safety Analyses

GROWTH

Descriptive summary statistics of changes from baseline in height, weight, and head circumference will be evaluated for each age cohort and overall. This data will be compared with normative scores to assess clinical relevance.

Absolute and percentile changes from baseline in height and weight will be presented by visit and to EOT. The sex and age specific percentiles are calculated from z-scores based on the 2000 Center for Disease Control Growth Charts for the United States.

Some calculation details are provided in Section 13.2. The average of the 2 height measurements from a visit will be used for these summaries. Changes from baseline to EOT in thyroid function and IGF-1 testing will be summarized.

5.7 Other Analyses

Not applicable.

5.8 Exploratory Analyses

Other exploratory analyses may be conducted as appropriate. Any exploratory analyses that are performed will be appropriately titled/labelled as exploratory and will be clearly distinguished from planned analyses when results are reported in the Clinical Study Report.

5.9 Extension Phase Analyses

The statistical methods for the Extension Phase will not be described in this SAP but will be described in a separate SAP.

6 INTERIM ANALYSES

After every 4th subject completes the Maintenance Period an interim analysis (safety, tolerability, and PK) will be conducted where dose-normalized exposure will be compared to that observed in other studies in subjects between ≥2 and <18 years of age for evidence of

systematic deviations potentially warranting dose adjustment in this age group or for other subjects enrolled in the study.

All data from the Pretreatment and Treatment Phases (Core Study) will be analyzed when all subjects have completed the Maintenance Period. In addition, data from the Pretreatment, Treatment, and Extension Phases will be analyzed when all subjects have completed the Extension Phase.

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 are documented in the DMC Charter.

7 CHANGES IN THE PLANNED ANALYSES

There are no major changes in the planned analyses from the protocol at the time of the finalization of this SAP.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

8.1 EFFICACY DATA HANDLING

8.1.1 Baseline efficacy Data

Baseline seizure frequency per 28 days will be calculated two ways.

For the primary analysis of seizure endpoints, baseline seizure frequency per 28 days will be calculated using seizure data from the 2-week Pretreatment Phase. Seizures per 28 days during these 2-week pretreatment phase will be calculated as the number of seizures during this interval divided by the number of days during this interval multiplied by 28.

Data is also collected over the 4-week interval prior to visit 1 for the days when subject experienced seizures. For the secondary analysis of seizure endpoints, baseline seizure frequency per 28 days during the 2-week Pretreatment Phase plus the 4 weeks prior will be used. Baseline seizure frequency for this analysis will be calculated by taking the average of seizure per 28 days from the 2-week Pretreatment Phase and seizures per 28 days from the 4 weeks interval prior to Visit 1. Seizures per 28 days during the 4-week prior interval will be calculated by summing the number of reported seizures during the 4-week (28-day) interval prior to visit 1.

8.1.2 Handling of Missing Efficacy Data, Drop-outs, and Outliers

Only days with valid seizure counts will be used in the calculations of seizures frequency per 28 days. A day is said to have a valid seizure count if either (1) “No” was the answer to the one of questions “Did the subject experience any <seizure category> seizures?” in the Seizures Diary Log or (2) other seizure counts were reported for that day.

In subjects where dose tapering was done before discontinuation, safety data for the entire exposure to study drug will be included in the safety analyses. However, seizure data during tapering will be excluded from the efficacy analyses.

Details on handling efficacy data for early dropouts is provided in section 5.3.5.

8.2 SAFETY DATA HANDLING

8.2.1 Baseline safety Data

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

8.2.2 Visit Windows for Safety Data

For the by-visit summaries of clinical laboratory data, vital signs, ECG, and growth parameters, visit windows will be applied to determine into which study week scheduled, unscheduled, and early discontinuation data were actually recorded, relative the first dose of study drug (Day 1). The aim of using windows for visits is to include the maximum amount of data; hence windows will split at the midpoint between visits. It gives the mapping of relative day ranges to study week, as well as the target day of a given study week. Mappings of relative day ranges to study week will be done for clinical laboratory data, vital signs, ECG data and growth parameter. Tables 1&2 below provide the mapping of relative day ranges to study week for non-AE safety variables. The on-treatment duration for laboratory, vital signs, and ECG data is considered to begin on the day of the first dose of study drug and ends 14 days after the last dose of study drug, inclusive.

Table 1. Visit Windows – Non-EIAED Subjects

Study Period	Study Week	Study Day Range (Relative to First Dose of Study Drug)	Target Day
Pretreatment	Baseline	Day ≤1[a]	≤1
Treatment (Titration)	Week 2	2 ≤ Day ≤ 21	15
Treatment (Titration)	Week 4	22 ≤ Day ≤ 42	29
Treatment (Titration)	Week 8	43 ≤ Day ≤ 70	57
Treatment (Titration)	Week 12	71 ≤ Day ≤ 91	85
Treatment (Maintenance)	Week 14	92 ≤ Day ≤ 105	99
Treatment (Maintenance)	Week 16	106 ≤ Day ≤ 119	113
Treatment (Follow-Up)	Week 99	120 or LD ≤ Day ≤ 999[b]	141

a: All assessments at Visit 2 were to be performed prior to first dose of study drug; results from these assessments will be regarded as Pretreatment values in the analyses.

b: The last non-missing value measured in the treatment duration will be handled as the data of EOT of the core study.

LD = Last Dose (whichever occurs first)

Table 2. Visit Windows – EIAED Subjects

Study Period	Study Week	Study Day Range (Relative to First Dose of Study Drug)	Target Day
Pretreatment	Baseline	Day ≤1[a]	1
Treatment (Titration)	Week 2	2 ≤ Day ≤ 21	15
Treatment (Titration)	Week 4	22 ≤ Day ≤ 42	29
Treatment (Titration)	Week 8	43 ≤ Day ≤ 70	57
Treatment (Titration)	Week 12	71 ≤ Day ≤ 98	85
Treatment (Titration)	Week 16	99 ≤ Day ≤ 119	113
Treatment (Maintenance)	Week 18	120 ≤ Day ≤ 133	127
Treatment (Maintenance)	Week 20	134 ≤ Day ≤ 154	141
Treatment (Follow-Up)	Week 99	155 or LD ≤ Day ≤ 999[b]	169

a: All assessments at Visit 2 were to be performed prior to first dose of study drug; results from these assessments will be regarded as Pretreatment values in the analyses.

b: The last non-missing value measured in the treatment duration will be handled as the data of EOT of the core study.

LD = Last Dose (whichever occurs first)

8.2.3 Handling of Replicate Data

For the clinical laboratory data, vital signs, ECG, growth data analyses, when there are repeated laboratory tests that occur within the same visit windows (Section 8.2.2), the following rules will be used in the by-visit summary tables:

The scheduled visit assessment will be used if there are multiple assessments.

- If there are multiple scheduled visit assessments, the scheduled assessment closest
- to the target day of the visit will be used.

- If there are 2 scheduled assessments within the same visit window that are equally
- close to the target visit data, the earlier assessment will be used.
- If there are 2 scheduled assessments on the same visit, the average will be used for that visit.

If a subject did not have a recorded observation falling within a given range of days in order to be assigned a study week, the subject's data for that study week will be regarded as missing for summarization purposes.

A subject having a TEAE coded to the same PT more than once during the study will be counted only once in the incidence calculations for that TEAE. Similarly, if a subject has more than 1 TEAE in a single SOC, the incidence will be counted only once for that SOC.

For summaries by closest relationship to study drug, if a subject had a single incident of a TEAE with a missing relationship to study drug, the subject will be counted in the 'Missing' category for that PT. If a subject had two or more TEAEs in the same SOC (or with the same PT) with different relationships to study drug, then the event with the closest relationship will be used for that subject. Subjects with missing relationship to study drug for the TEAE are counted under 'Missing' category unless the subject already has another TEAE classified as Related, in which case the subject is counted under 'Related' category.

For summaries by maximum severity, if a subject had a single incident of a TEAE with a missing severity, the subject will be counted in the 'Missing' category for that PT. If a subject had two or more TEAEs in the same SOC (or with the same PT) with different severities, then the event with the maximum severity will be used for that subject. Subjects with missing severity for the TEAE are counted under 'Missing' category unless the subject already had another AE with severe intensity, in which case subject is counted under 'Severe' category.

9 PROGRAMMING SPECIFICATIONS

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

10 STATISTICAL SOFTWARE

All statistical analyses and summaries 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

ILAE guidelines. Proposal for revised clinical and electrographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 1981;22(4):489-501.

2000 Center for Disease Control Growth Charts for the United States. CDC. Available from: http://www.cdc.gov/growthcharts.

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 study protocol, Appendix 1.

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<$3.0 – 2.0\times10^9$/L <3000 – 2000/mm^3	<$2.0 – 1.0\times10^9$/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <$0.8 – 0.5\times10^9$/L	<500 – 200/mm^3 <$0.5 – 0.2\times10^9$/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<$1.5 – 1.0\times10^9$/L <1500 – 1000/mm^3	<$1.0 – 0.5\times10^9$/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<$75.0 – 50.0\times10^9$/L <75,000 – 50,000/mm^3	<$50.0 – 25.0\times10^9$/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L;

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
				life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
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).

13.2 Age and Sex Specific Percentile Calculation for Weight and Height

The following information is from US CDC website: http://www.cdc.gov/growthcharts.
To obtain the z-score (Z) and corresponding percentile for a given measurement (X), use the following equation:

$Z=((X/M)^{L}-1)/LS$ when $L\neq 0$;
or
$Z = \ln(X/M)/S$ when $L=0$;

where X is the physical measurement (e.g. weight, length, or calculated BMI value) and L, M and S are the values from the appropriate table corresponding to the age in months of the child (or length/stature). $(X/M)^{L}$ means raising the quantity (X/M) to the L-th power.

For example, to obtain the weight-for-age z-score of a 9-month-old male who weighs 9.7 kg, we would look up the L, M and S values from the WTAGEINF table found at http://www.cdc.gov/growthcharts/percentile_data_files.htm, which are L=-0.1600954, M=9.476500305, and S=0.11218624. Using the equation above, we calculate that the z-score for this child is 0.207. This z-score corresponds to the 58th percentile.

SIGNATURE PAGE

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