STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E2007-G000-338
Study Protocol Title:	A Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial With an Open-Label Extension Phase of Perampanel as Adjunctive Treatment in Subjects at Least 2 years of Age With Inadequately Controlled Seizures Associated With Lennox-Gastaut Syndrome
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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
AED	antiepileptic drug
ALT	alanine amino transferase
ANCOVA	analysis of covariance
AST	aspartate amino transferase
ATC	anatomical therapeutic class
BMI	body mass index
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form
C-SSRS	Columbia Suicide Severity Rating Scale
ECG	electrocardiogram
FAS	full analysis set
LGS	Lennox-Gastaut Syndrome
LN	lower limit of normal
LLT	lower level term
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NGM	Neuroscience and General Medicine
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	preferred term
PP	per protocol
SAE	serious adverse event

SAP	statistical analysis plan
SI	Système International
SOC	system organ class
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal 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 Study of Eisai Protocol E2007-G000-338. The statistical methods used in the Extension Phase will be described in a separate SAP.

3.1 STUDY OBJECTIVES

3.1.1 Primary Objective

The primary objective of the study is to demonstrate that perampanel given as adjunctive anti-epileptic treatment is superior compared to placebo in reducing the incidence of drop seizures during 18 weeks of treatment in subjects with inadequately controlled seizures associated with Lennox-Gastaut Syndrome (LGS)

3.1.2 Secondary Objectives

1. To demonstrate that perampanel given as adjunctive anti-epileptic treatment is superior to placebo in reducing the incidence of all seizures during 18 weeks of treatment in subjects with inadequately controlled seizures associated with LGS

2. To demonstrate that perampanel given as adjunctive anti-epileptic treatment is superior to placebo in the 50%, 75%, and 100% responder rates for drop seizures during 12 weeks of the Maintenance Period in subjects with inadequately controlled seizures associated with LGS

3. To demonstrate that perampanel given as adjunctive anti-epileptic treatment is superior to placebo in the 50%, 75%, and 100% responder rates for total seizures during 12 weeks of the Maintenance Period in subjects with inadequately controlled seizures associated with LGS

4. To demonstrate that perampanel given as adjunctive anti-epileptic treatment is superior to placebo in reducing the incidence of non-drop seizures during 18 weeks of treatment in subjects with inadequately controlled seizures associated with LGS

5. To evaluate the 50%, 75%, and 100% responder rates in non-drop seizure frequency in the Maintenance Period

6. To evaluate physicians' global evaluation of subjects' overall changes in symptoms

7. To evaluate the safety of perampanel relative to placebo as adjunctive therapy in subjects with inadequately controlled seizures associated with LGS during both the Core Study and the Extension Phase

8. To evaluate the pharmacokinetics and the pharmacokinetic/pharmacodynamic (PK/PD) relationships of perampanel as adjunctive therapy in subjects with inadequately controlled seizures associated with LGS

3.1.3 Exploratory Objectives

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3.2 OVERALL STUDY DESIGN AND PLAN

This was to be a multicenter, double-blind, randomized, placebo-controlled, parallel-group study of perampanel as adjunctive therapy in subjects with inadequately controlled seizures associated with LGS. The study was to consist of 3 phases: Prerandomization, Randomization, and Extension. The Core Study was to consist of the Prerandomization and Randomization Phases.

The Prerandomization Phase was to consist of a 4- to 8-week Screening/Baseline Period during which subjects were to be assessed for overall eligibility to participate in the study, including seizure activity; Baseline seizure count was to be assessed using all diary data before randomization.
Following successful completion of this period, subjects were to be randomized to receive perampanel or placebo in a 1:1 ratio.

The Randomization Phase was to consist of 3 periods: Titration (6 weeks), Maintenance (12 weeks), and Follow-up (4 weeks). As required by some regulatory agencies, the following estimates were provided:

- The study was to begin approximately Jan 2017 and was to end approximately Jan 2020 (revised per Amendment 01)
- The maximum estimate period for each subject on the study was anticipated to be approximately 82 weeks.

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

4 DETERMINATION OF SAMPLE SIZE

Randomization of 71 subjects to each treatment arm was to provide a sample with adequate power for the primary endpoint and the key secondary endpoints.

Primary endpoint percent change from baseline in drop seizures:

Placebo rates in drop seizures in the rufinamide and clobazam clinical trials were +1.4%, and -12.1%, respectively. In the active treatment arm, rufinamide had a median decrease of 42.5% in drop seizures and clobazam had mean decreases of 41.2%, 49.4%, and 68.3% for the low, medium, and high doses, respectively. A standard deviation of ~63% was observed for both rufinamide and for the medium dose of clobazam for drop seizures. It is assumed that comparable results will be seen in this trial for the placebo and perampanel treatment arms for drop seizures.

A sample size of 71 subjects in each treatment arm in the Full Analysis Set (FAS) will have 94% power to detect a treatment difference in median percentage seizure frequency change in drop seizures per 28 days of 40% (common SD of 63%) between placebo and perampanel based on a Wilcoxon rank-sum test at the 0.05 two-sided significance level.

50% responder rate in drop seizures:

A sample size of 71 subjects per treatment arm will have 97% power to detect a 30% difference in responder rate proportions between placebo (assuming a placebo response rate of 20%) and perampanel treatment groups at the 0.05 two-sided significance level in drop seizures per 28 days using a two-group chi-square test.

Percent change in seizure frequency for total seizures:

Decreases in total seizures for placebo, and low, medium, and high doses in the clobazam trial were approximately 9%, 35%, 45%, and 65% respectively; common standard deviations ranged from 63% to 83%. It is assumed that comparable results will be seen in this trial for the placebo and perampanel treatment arms for total seizures.

A sample size of 71 subjects in each treatment arm in the FAS will have 80% power to detect a treatment difference in median percentage seizure frequency change in total -seizures per 28 days of 36% (SD=73%) between placebo and perampanel based on a Wilcoxon rank-sum test at the 0.05 two-sided significance level.

50% responder rate in total seizures:

A sample size of 71 subjects per treatment arm (142 total) will have more than 80% power to detect a 22% difference in responder rate proportions between placebo (assuming a placebo response rate of 20%) and perampanel treatment groups at the 0.05 two-sided significance level in total-seizures per 28 days using a two-group chi-square test.

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.

5.1 STUDY ENDPOINTS

5.1.1 Primary Endpoint

The primary efficacy endpoint will be the median percent change in drop seizure frequency per 28 days during double-blind treatment (Titration Period and Maintenance Period) relative to the Prerandomization Phase in the FAS.

5.1.2 Secondary Endpoints

The following key secondary endpoints will be evaluated sequentially using the FAS:

1. Median percent change in total seizure frequency per 28 days during double –blind treatment (Titration Period and Maintenance Period) relative to the Prerandomization Phase.

2. The 50% responder rate in the Maintenance Period of the double-blind treatment relative to the Prerandomization Phase for drop seizures

3. The 50% responder rate in the Maintenance Period of the double-blind treatment relative to the Prerandomization Phase for total seizures.

Other secondary endpoints are:

4. Median percent change in non-drop seizure frequency per 28 days during double-blind treatment (Titration Period and Maintenance Period) relative to the Prerandomization Phase

5. Proportion of subjects with 75%, and 100% responder rates for drop, non -drop, and total seizures in the Maintenance Period relative to the Prerandomization Phase

6. Proportion of subjects with 50% responder rate in the Maintenance Period of the double-blind treatment relative to the Prerandomization Phase for non-drop seizures

7. Physicians' global evaluation of the subject's overall changes in symptoms (using a 7-point Likert scale with 1=very much improved and 7=very much worse) at the end of the double-blind treatment

8. Incidence of adverse events (AEs) and serious adverse events (SAEs), changes in clinical laboratory values, and vital signs

9. Model-derived average perampanel concentrations at steady state (Cav,ss) during the Maintenance Period of the Core Study

5.1.3 Exploratory Endpoints

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5.2 CCI [redacted] CCI [redacted] STUDY SUBJECTS

5.2.1 Definitions of Analysis Sets

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

The **Full Analysis Set (FAS)** is the group of randomized subjects who received at least one dose of study drug and had at least one post-dose seizure measurement.

The **Per Protocol Analysis Set (PP)** is the group of subjects who sufficiently complied with the protocol. Details of the evaluability criteria are given in Section 5.2.3.

The **Pharmacokinetic Analysis Set** is the group of subjects who received perampanel and had at least one quantifiable perampanel concentration during the Maintenance Period of the Core Study and adequately documented dosing history.

The **PK/PD analysis** set is the group of subjects who received perampanel or placebo who had seizure frequency data with documented dosing history. Subjects who received perampanel should have at least one quantifiable perampanel concentration as per the PK analysis set.

The **Intention to Treat Analysis Set (ITT)** is the group of randomized subjects who received at least one dose of study drug.

5.2.2 Subject Disposition

The number of subjects enrolled and the reasons for screen failure will be summarized.

Subject disposition tables will include the number (percentage) of subjects who were:

- Randomized into each treatment group;
- Completed the study;
- Discontinued early from the study, summarized by primary reason for discontinuation.

Subject disposition will be summarized overall and by age group.

5.2.3 Protocol Deviations

The following provide definitions of major protocol deviations; however, exclusions from the PP Analysis Set will be made on a case-by-case basis using these as a guideline and based on reasonable clinical judgment.

- Subject did not meet Inclusion Criterion #4, which was: Subjects must have experienced at least 2 drop seizures per week in the 4-week Baseline Period preceding randomization.

- At any time during the study, subject stopped or interrupted any approved antiepileptic drugs (AED)s he/she was taking upon study entry.
- Subject received incorrect study drug longer than he/she received randomly assigned study drug.
- Subject had <80% study medication compliance
- Subject had <80% diary compliance during the Prerandomization and Randomization Phases.

Other criteria may be identified during the course of the study. Identification of subjects with major protocol deviations will occur before DBL and treatment unblinding.

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the SAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, weight, height and body mass index (BMI); categorical variables include sex, age group (2-<12, 12-<18, 18-<65, ≥65), race and ethnicity.

MEDICAL HISTORY

The number (percentage) of subjects reporting a history of any medical condition, as recorded on the case report form (CRF), will be summarized for the SAS for each treatment group and overall. A subject data listing of medical and surgical history will be provided.

Epilepsy-specific medical history for the SAS will be summarized for each treatment group and by age group using descriptive statistics, including time since diagnosis 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) (Mar 2021). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the FAS by treatment group, Anatomical Therapeutic Chemical (ATC) class (i.e., anatomical class, therapeutic class, pharmacologic 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. All medications will be presented in subject data listings.

The number of baseline AEDs will be summarized by treatment group and by age group and a summary of baseline and concomitant AEDs will be produced by treatment group and by age group. A baseline AED is an AED taken at the date of randomization. Concomitant AEDs are defined as above for concomitant medications.

5.2.6 Treatment Compliance

For subjects taking tablets, percent compliance will be calculated for the Randomization Phase and by visit for the FAS as follows:

$$\text{Compliance} = \frac{\text{Total number of tablets dispensed} - \text{Total number of tablets returned} \times 100}{\text{Planned total number of tablets to be taken}}$$

For subjects taking oral suspension, percent compliance will be calculated for the randomization phase and by visit for the FAS as follows:

$$\text{Compliance} = \frac{\text{Total weight in grams dispensed} - \text{Total weight in grams returned} \times 100}{\text{Planned total volume in mL to be taken} \times \text{suspension density of 1.07 grams per mL}}$$

Where subjects have taken both tablets and oral suspension, overall compliance will be derived by averaging the visit compliance across the Randomization Phase.
Overall compliance with study medication will be summarized using descriptive statistics for each treatment group and by age group. 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

This is a multi-center, international study conducted in three geographic regions, i.e. United States, Europe, and Asia. Data from the centers in the same region and age group will be pooled together for analysis purposes. Each of these strata should have at least 6 subjects. If there are strata with <6 subjects then age-groups will be combined within the region.

For analyses by country, if there are countries with <6 subjects then the countries will be sorted in descending order by the number of subjects in each geographic region. Starting from the smallest, countries will be pooled until the criteria of 6 subjects is fulfilled or there is no country of size <6 left to be pooled in that geographic region. If there is no country of size <6 left to be pooled but the current country is of size <6 then the current country will be pooled with the next country in that geographic region in the order.

5.3.2 Adjustments for Covariates

The Prerandomization Phase seizure frequency per 28 days value will be used as a covariate, and region and age group will be used as a factor in the efficacy models for the primary analysis. Additional covariates may also be explored.

5.3.3 Multiple Comparisons/Multiplicity

If the primary endpoint is statistically significant then the 3 key secondary efficacy endpoints will be tested in a sequential manner.

Median percent change in total seizure frequency per 28 days during double -blind treatment will be tested first. If this test is significant at 0.05 level, then the 50% responder rate in the Maintenance Period for drop seizures will be tested. If this is significant then the 50% responder rate in the Maintenance Period for total seizures will be tested. All tests will be at a 2 -sided 0.05 significance level.

5.3.4 Examination of Subgroups

The following endpoints will be summarised by age (2-<12, 12-<18, 18-<65, ≥65):
Disposition; demography; epilepsy-specific medical history, number of baseline AEDs, baseline AEDs, compliance, percent change in drop, non-drop and total seizure frequency, 50%/75% response and seizure freedom rates in drop, non-drop and total seizures; clinical global impression exposure; treatment-emergent adverse events; change from baseline in laboratory values; treatment-emergent markedly abnormal laboratory values; change from baseline in vital signs; and Columbia Suicide Severity Rating Scale (C-SSRS), for subjects 8 years and over.

5.3.5 Handling of Missing Data, Drop-outs, and Outliers

5.3.5.1 Efficacy

For the last observation carried forward (LOCF) analyses, such as "Maintenance-LOCF" analyses of percent change and 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.

For the ITT analysis, subjects with no post-baseline efficacy data will have their baseline observation carried forward.

Since data is rank transformed prior to analysis, outliers will have no effect on the primary analysis.

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 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 related if there is another 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

5.4.1 Primary Efficacy Analyses

The primary efficacy endpoint will be the percent change from baseline in drop seizure frequency per 28 days during treatment.

A drop seizure is defined as a tonic-atonic or myoclonic with fall.

The null hypothesis and alternative hypothesis are:

H_0: perampanel is not superior to placebo in reducing drop seizure frequency
H_1: perampanel is superior to placebo in reducing drop seizure frequency

The percent change from baseline will be analyzed over the Titration and Maintenance Periods combined in the FAS. Drop seizure frequency per 28 days (as determined from subject diaries) will be calculated as the number of drop seizures divided by the number of days in the interval and multiplied by 28.

Analysis will be conducted using rank analysis of covariance (ANCOVA) with treatment, region (Asia/Pacific, Europe, North America) and age-group (2-<12 years, >=12 years) as factors, and the baseline drop seizure frequency as a covariate (Conover and Inman, 1982).
In this analysis, all drop seizure frequency data will first be rank-transformed for both baseline and endpoint drop seizure frequencies separately. The ANCOVA will then be conducted based on the rank-transformed data. Treatment effect will be tested at a 2-sided 5% level.

Due to an expected irregular distribution of drop seizure frequency, median will be the primary statistic of interest for the primary endpoint. Hodges-Lehmann estimator (Hodges and Lehmann, 1963) and 95% confidence interval (CI) for this estimator will be displayed for understanding the treatment effect size.

The following sensitivity analyses will be conducted for the endpoint of percent change in drop seizure frequency:

- Analysis on the Maintenance with LOCF to impute for missing data, and Titration period in the FAS. In the "Maintenance-LOCF" Analysis for the percent change, if a subject has less than 8 weeks of Maintenance Period, the drop seizure frequency during the last 8 weeks of the Titration and Maintenance Periods combined (or drop seizure frequency during the Titration and Maintenance Periods combined for subjects with less than 8 weeks of Titration and Maintenance Periods combined) will be used to impute for this sensitivity analysis.

  A duration of 8 weeks for the missing data imputation for the percent change is meant to provide more stable estimates for the drop seizure frequency.

- Analysis of the percent change using the PP Analysis Set.

- Analysis of the percent change using the ITT Analysis Set.

- Analysis of subjects in the FAS who complete the entire study period i.e. have last scheduled double-blind visit completed and is marked by the investigator to have completed the study (Completers).

A by visit summary of percentage change will also be produced.

The following graphical displays will be produced: cumulative distribution function of percent change in drop seizure frequency during treatment, plots of median percent change from pre-randomization in drop seizure frequency by major analysis windows, by week during titration and by visit. A bubble plot of the Hodges-Lehmann median difference between perampanel and placebo by country and forest plots of percent change in drop seizure frequency by analysis windows and sub-groups will also be produced.

5.4.2 Secondary Efficacy Analyses

If the primary endpoint is statistically significant then the 3 key secondary efficacy endpoints will proceed in a sequential manner.

Median percent change in total seizure frequency per 28 days during double -blind treatment will be tested first. If this test is significant at 0.05 level, then the 50% responder rate in the Maintenance Period for drop seizures will be tested. If this is significant then the 50% responder rate in the Maintenance Period for total seizures will be tested. All tests will be at a 2 -sided 0.05 significance level.

The same ANCOVA model employed for the primary efficacy variable will be employed to analyze percentage change from baseline in total seizures.

50% responder rates will be analyzed using the Cochran-Mantel-Haenszel (CMH) test, adjusting for region (Asia/Pacific, Europe, North America) and age group (2-<12 years, >=12 years). The homogeneity of the odds ratios will be checked across strata. For subjects who discontinue the study with less than 8 weeks of seizure data in the Maintenance Period, the last 8 weeks of data after the first dose (or entire double-blind treatment duration if <8 weeks of data are available) will be used in lieu of Maintenance Period.

Sensitivity analyses of the key secondary endpoints will be performed in the PP and ITT populations.

The primary and key secondary efficacy endpoints will be summarized by age group.
75% responder rate and seizure-freedom rate in drop and total seizures will be analysed by treatment group in the Maintenance-LOCF Period.

Percent change from baseline in non-drop seizures will be analysed similarly to drop and total seizures.

Summaries of the 50%, 75% and seizure freedom rates in non-drop seizures will also be produced. Seizure freedom is defined as being seizure free during the maintenance period and completing the core study.

The other secondary efficacy endpoint of Physicians' global evaluations over time will be analyzed using the CMH test.

5.4.3 Other Efficacy Analyses

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5.5 Pharmacokinetic, Pharmacodynamic, and PHARMACOGENOMIC/PHARMACOGENETIC ANALYSES

Perampanel plasma concentrations were obtained from blood samples drawn at Weeks 7, 13 and 19/ET visit. A listing of perampanel plasma concentrations will be produced. Details of the analysis methods for population pharmacokinetic/pharmacodynamics (PK/PD) modeling will not be described in this statistical analysis plan (SAP) but will be described in a separate analysis plan.

Pharmacogenomics analyses may be performed and will be reported separately. Details of these analyses will be described in a separate analysis plan if appropriate.

5.6 SAFETY ANALYSES

All safety analyses will be performed on the Safety Analysis Set. Safety data, presented by treatment group, will be summarized on an "as treated" basis 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, Study Day 1 for all safety analyses is defined as the date of the first dose of study drug.

Summaries of exposure, TEAEs and treatment-emergent markedly abnormal values (TEMAVs) will be presented by age group.

5.6.1 Extent of Exposure

Duration of Randomization Phase (Titration Period + Maintenance Period) exposure will be calculated as the number of days between the date the subject received the first dose of study drug and the date the subject received the last dose of study drug in the Randomization Phase. The results will be summarized by treatment groups using median, mean, standard deviation, minimum, maximum, and number of subjects with non- missing data.
Exposure to the study medication will also be summarized by categories of cumulative weeks.

The mean, modal, median, maximum and last daily dose over the Titration and Maintenance Periods for each of the randomized treatment arms will be summarized. The mean daily dose for each of the arm will be calculated by taking the average of all the doses taken weighted by the total duration of exposure and rounded to 1 decimal place, ie sum of (days on each dose*dose)/total dose duration of subjects. For subjects ≥12 years, dose will be summarized in mg. For subjects <12 dose will be summarised in mg/kg.

The number of subjects who down-titrated or discontinued at their maximum daily dose will be summarized.

Cumulative extent of exposure and summaries of dose will be presented by age group.

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 24.1 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 emerged during treatment, having been absent at pre-treatment (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.

TEAEs will be summarized by treatment group and by age group. 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). Summaries of treatment-related
TEAEs will be produced.

There will also be summaries of TEAEs by dose at onset and exposure-adjusted event rates.

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

A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent serious adverse events (SAEs) will be summarized by MedDRA SOC and PT for each treatment group~~, overall and by pooled country~~.
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 for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

The number (percentage) of subjects with TEAEs leading to dose adjustment will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to dose adjustment will be provided.

5.6.2.2 Adverse Events of Special Interest

A listing and summary of subjects with AEs related to suicidality, identified by the depression and suicide/self-injury standardized MedDRA query (SMQ) terms, will be provided. TEAEs of special interest listed below will be summarized by SOC and PT for each treatment group.

SMQs will be used to identify relevant terms for the following TEAEs. All of these TEAEs will be summarized by broad and narrow terms, except those related to abuse potential, hostility/aggression and psychosis/psychotic disorder, which will be summarized by both broad and narrow terms and by narrow terms.

- TEAEs suggestive of abuse potential: SMQ of drug abuse, dependence and withdrawal
- TEAEs related to alertness and cognition: SMQ of dementia
- TEAEs related to hostility/aggression: SMQ of hostility/aggression
- TEAEs related to psychosis and psychotic disorder: SMQ of psychosis and psychotic disorders
- TEAEs related to status epilepticus/convulsions: SMQ of convulsions
- TEAEs related to drug related hepatic disorder abnormalities: SMQ of drug-related hepatic disorders
- Cardiac and electrocardiogram (ECG) TEAEs: SMQs of cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrythmias, arrhythmia related investigations, signs and symptoms, cardiac failure, cardiomyopathy, ischaemic heart diseases, and Torsade de pointes/QT prolongation
- Rash: SMQ of severe cutaneous adverse reactions and hypersensitivity

Falls will be summarized for Prerandomization Phase and Follow-up Period, and by actual dose of onset for the Titration Period and Maintenance Period.

Exposure-adjusted rates of falls and AEs in the accident/injury SMQ will be presented.

5.6.3 Laboratory Values

Laboratory results will be summarized using Système International (SI) units, as appropriate. Actual value and change from baseline in all quantitative parameters will be summarized by visit and treatment group for each postbaseline visit and to the end of treatment (defined as the last on-treatment value). Qualitative parameters will be summarized using frequencies at each visit. Whenever normal ranges are available, it will be determined whether the lab value is above (H), below (L) or within (N) the normal 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 be used to compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.
The number of abnormal records and the number of subjects with two consecutive abnormal records will also be summarized.

The incidence of TEMAVs will be summarized over all scheduled and unscheduled visits for the parameters with defined notable ranges given in Section 13.1 of this analysis plan. A phosphate value will be determined to be a TEMAV if the post baseline National Cancer Institute (NCI) common toxicity criteria grade increases from baseline and the post baseline grade is greater than or equal to 3. For all other parameters in Section 13.1, a value will be determined to be a TEMAV if the post baseline NCI grade increases from baseline and the post baseline grade is greater than or equal to 2. The number (percentage) of subjects with TEMAVs will be displayed. Additionally the number of subjects with TEMAVs who were normal at baseline and the number of TEMAVs will also be summarized.

For alanine amino transferase (ALT), aspartate amino transferase (AST) and alkaline phosphatase, the number of subjects with > 3x but ≤ 5x the Upper Limit Normal (ULN) and the number of subjects with > 5x the ULN will be summarized by treatment group by visit. For bilirubin, the number of subjects with serum concentrations > 2x ULN will be summarized by treatment group by visit. 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 at the same visit 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.

Potentially clinically significant (abnormal) changes, defined as an increase in NCI grade to Grade 2 or higher from baseline when the baseline value is normal will be summarized.

5.6.4 Vital Signs

Descriptive statistics for vital signs parameters (diastolic and systolic blood pressure, pulse, respiration rate, temperature, weight, height) and changes from baseline to each post-baseline visit and to the last post-baseline visit will be presented by treatment group

In addition, the criteria described in Table 1 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 by treatment group.

Table 1: Criteria for Clinically Notable[a] Vital Signs

Variable	Criterion Value	Change Relative to Baseline
Systolic BP	> 180 mmHg	Increase of ≥ 20 mmHg
	< 90 mmHg	Decrease of ≥ 20 mmHg

Diastolic BP	>105 mmHg	Increase of ≥ 15 mmHg
	< 50 mmHg	Decrease of ≥ 15 mmHg
Heart Rate	>120 bpm	Increase of ≥ 15 bpm
	< 50 bpm	Decrease of ≥ 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.		

5.6.5 Electrocardiograms

12-lead ECG will be obtained at the Screening Visit only. Since the data are not planned to be included in the database, no ECG summaries will be produced.

5.6.6 Other Safety Analyses

5.6.6.1 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.

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 severity rating (treated as a continuous variable) to assess change in suicidal ideation over time.
Other Analyses

5.7 OTHER ANALYSES

5.7.1 CCI

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CCI

[redacted]

5.7.2 CCI

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[redacted]

5.7.3 CCI

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[redacted]

CCI

5.7.4 CCI

CCI

5.8 EXPLORATORY ANALYSES

CCI

5.9 EXTENSION PHASE ANALYSES

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

6 INTERIM ANALYSES

No interim analyses are planned for this study.

7 CHANGES IN THE PLANNED ANALYSES

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

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

8.1 EFFICACY DATA HANDLING

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.

8.1.1 Pre-randomization/Baseline Efficacy

All diary data prior to first dose date will be used in the computation of Prerandomization 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 non-missing 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 double-blind study drug dose and the last day of double-blind study drug dose, inclusive.
- For non-diary efficacy data: The duration between the day of first double-blind study drug dose and 7 days after the last double-blind study drug dose, inclusive.

For all efficacy analyses, data reported only during the treatment duration will be analyzed.

8.1.3 Handling of Replicate Data

If there is more than 1 diary entry for a date, then the entry with the highest number of drop seizures will be used for that date.

For the CGIC 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 considered to begin at or after the first dose of study drug on Day 1 and ends 14 days after the last dose of double-blind study medication. For AEs, the treatment duration is considered to begin on Day 1 and ends 28 days after the last dose of double-blind study medication.

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, and vital signs 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 the subject signed informed consent to the last visit in the Treatment Phase following the 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 vital sign assessments. Table 3 below gives the mapping of relative day ranges to week for laboratory assessments. 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 earliest assessment of the two (within the allowable window) will be used. .

Table 1: Mapping of Study Day Ranges to Week for Vital Signs and Weight

Windowing Period	Study Day Range (Relative to First Dose)	Week
Pretreatment	Day ≤1[a]	0
Treatment	2 ≤ Day ≤ 20	2
Treatment	21 ≤ Day ≤ 31	4
Treatment	32 ≤ Day ≤ 66	7
Treatment	67 ≤ Day ≤ 104	12
Treatment	105 ≤ Day ≤ 140	18
	Day Relative to 14 Days After Last Dose	
Post-Treatment	Day ≤ 999[c]	4

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: Measurements must have been taken during the treatment duration, ie, within 14 days of the day of last dose, to be included in analyses as on-treatment assessments.

c: Measurements must have been taken more than 14 days after the day of last dose to be included in analyses as Post-treatment assessments. Target day is 28 days after last dose or Post-treatment Week 4.

It should be noted that for the post-treatment duration, the study week window is defined relative to the last dose, rather than to the first dose.

Table 3: Mapping of Study Day Ranges to Week for Laboratory Assessments

Windowing Period	Study Day Range (Relative to First Dose)	Week
Pretreatment	Day ≤1[a]	0
Treatment	2≤ Day ≤ 76	4
Treatment	77≤ Day ≤ 140	18
	Day Relative to 14 Days After Last Dose	
Post-Treatment	Day ≤ 999[c]	4

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: Measurements must have been taken during the treatment duration, ie, within 14 days of the day of last dose, to be included in analyses as on-treatment assessments.

c: Measurements must have been taken more than 14 days after the day of last dose to be included in analyses as Post-treatment assessments. Target day is 28 days after last dose or Post-treatment Week 4.

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.

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.

11 MOCK TABLES, LISTINGS AND GRAPHS

The study table, listing and graph (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

Conover, W. J. and Iman, Ronald L. Analysis of Covariance Using the Rank Transformation. Biometrics, Vol. 38, No. 3, Special Issue: Analysis of Covariance (Sep., 1982), pp. 715- 724.

Hodges, J. L., Jr. and Lehmann, E. L. (1963). Estimates of location based on rank tests, The Annals of Math. Statistics, 34, 598-611.

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
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 x 10^9/L < LLN – 3000/mm^3	< 3.0 – 2.0 x 10^9/L < 3000 – 2000/mm^3	< 2.0 – 1.0 x 10^9/L < 2000 – 1000/mm^3	< 1.0 x 10^9/L < 1000/mm^3
Lymphocytes • 2-6 years old • 7-12 years old • 12 years or older	 NA NA < LLN – 800/mm^3 < LLN – 0.8 x 10^9/L	 NA NA < 800 – 500/mm^3 < 0.8 – 0.5 x 10^9/L	 NA NA < 500 – 200/mm^3 < 0.5 – 0.2 x 10^9/L	 NA NA < 200/mm^3 < 0.2 x 10^9/L
Neutrophils	< LLN – 1.5 x 10^9/L < LLN – 1500/mm^3	< 1.5 – 1.0 x 10^9/L < 1500 – 1000/mm^3	< 1.0 – 0.5 x 10^9/L < 1000 – 500/mm^3	< 0.5 x 10^9/L < 500/mm^3
Platelets	< LLN – 75.0 x 10^9/L < LLN – 75,000/mm^3	< 75.0 – 50.0 x 10^9/L < 75,000 – 50,000/mm^3	< 50.0 – 25.0 x 10^9/L < 50,000 – 25,000/mm^3	< 25.0 x 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 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
ALT, SGPT (serum glutamic pyruvie transaminase)	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
AST, SGOT (serum glutamic oxaloacetic transaminase)	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
Bicarbonate, serum-low	< LLN – 16 mEq/L	< 16 – 11 mEq/L	<11 – 8 mEq/L	< 8 mEq/L
Bilirubin (hyperbilirubinemia)	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 10.0 x ULN	> 10.0 x 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 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 6.0 x ULN	> 6.0 x ULN
GGT (γ-Glutamyl transpeptidase)	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x 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

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
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
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	NA	< 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	NA	> ULN – 10 mg/dL ≤ 0.59 mmol/L with physiologic consequences	> 10 mg/dL > 0.59 mmol/L life-threatening consequences

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

SIGNATURE PAGE

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STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E2007-G000-338 (Extension)
Study Protocol Title:	A Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial With an Open-Label Extension Phase of Perampanel as Adjunctive Treatment in Subjects at Least 2 years of Age With Inadequately Controlled Seizures Associated With Lennox-Gastaut Syndrome
Date:	19 August 2021.
Version:	Final 1.0

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
AED	antiepileptic drug
BMI	body mass index
CRF	case report form
FAS	full analysis set
LGS	Lennox-Gastaut Syndrome
LLT	lower level term
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	preferred term
PP	per protocol
SAE	serious adverse event
SAP	statistical analysis plan
SI	Système International
SOC	system organ class
TEAE	treatment-emergent adverse event
TLG	tables, listings, and graphs

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 Study of Eisai Protocol E2007-G000-338.

3.1 STUDY OBJECTIVES

3.1.1 Primary Objective

The primary objective of the study is to demonstrate that perampanel given as adjunctive anti-epileptic treatment is superior compared to placebo in reducing the incidence of drop seizures during 18 weeks of treatment in subjects with inadequately controlled seizures associated with Lennox-Gastaut Syndrome (LGS)

3.1.2 Secondary Objectives

1. To demonstrate that perampanel given as adjunctive anti-epileptic treatment is superior to placebo in reducing the incidence of all seizures during 18 weeks of treatment in subjects with inadequately controlled seizures associated with LGS

2. To demonstrate that perampanel given as adjunctive anti-epileptic treatment is superior to placebo in the 50%, 75%, and 100% responder rates for drop seizures during 12 weeks of the Maintenance Period in subjects with inadequately controlled seizures associated with LGS

3. To demonstrate that perampanel given as adjunctive anti-epileptic treatment is superior to placebo in the 50%, 75%, and 100% responder rates for total seizures during 12 weeks of the Maintenance Period in subjects with inadequately controlled seizures associated with LGS

4. To demonstrate that perampanel given as adjunctive anti-epileptic treatment is superior to placebo in reducing the incidence of non-drop seizures during 18 weeks of treatment in subjects with inadequately controlled seizures associated with LGS

5. To evaluate the 50%, 75%, and 100% responder rates in non-drop seizure frequency in the Maintenance Period

6. To evaluate physicians' global evaluation of subjects' overall changes in symptoms

7. To evaluate the safety of perampanel relative to placebo as adjunctive therapy in subjects with inadequately controlled seizures associated with LGS during both the Core Study and the Extension Phase

8. To evaluate the pharmacokinetics and the pharmacokinetic/pharmacodynamic (PK/PD) relationships of perampanel as adjunctive therapy in subjects with inadequately controlled seizures associated with LGS

3.1.3 Exploratory Objectives

CCI

[redacted]

3.2 OVERALL STUDY DESIGN AND PLAN

Extension A consisted of 3 periods: 6-week Conversion, 46-week Maintenance, and 4-week Follow-up (except for subjects who planned to enter into Extension B). Extension A was to last approximately 52 weeks overall, or until such time that perampanel was made commercially available or accessible to subjects via an EAP if activated in the country in which they reside, whichever happened sooner.

During the Conversion Period, subjects who received perampanel during the Core Study were to continue receiving perampanel in a blinded manner at the same dose last received during the Core Maintenance Period. Subjects who received placebo during the Core Study were to begin treatment with perampanel in a blinded manner, following the same dosing regimen and titration schedule as that in the Core Study, starting at 2 mg/day and would then be up-titrated to the optimal dose per the investigator's discretion, not to exceed a maximum dose of 8 mg/day.

After the double-blind Conversion Period, subjects could be titrated up to 12 mg/day (except in Japan, where the maximum allowed dose remained at 8 mg/day), at 2-week intervals per the investigator's discretion. Addition, deletion, and dose changes to the concomitant AEDs were allowed during Extension Maintenance Period.

The dosing schedule for Extension A is summarized in Table 7 of the protocol.

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

4 DETERMINATION OF SAMPLE SIZE

There was no a priori determination of sample size for the extension phase of the study. The number of subjects was determined by the number who completed the Core Study and who chose to enrol into Extension A.

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.

In general, the scope of endpoints and analyses will include the entirety of perampanel exposure (Core and Extension A).

5.1 STUDY ENDPOINTS

5.1.1 Primary Endpoint

The primary efficacy endpoint will be the median percent change in drop seizure frequency per 28 days during double-blind treatment (Titration Period and Maintenance Period) relative to the Prerandomization Phase in the Full Analysis Set (FAS).

5.1.2 Secondary Endpoints

The following key secondary endpoints will be evaluated sequentially using the FAS:

1. Median percent change in total seizure frequency per 28 days during double –blind treatment (Titration Period and Maintenance Period) relative to the Prerandomization Phase.

2. The 50% responder rate in the Maintenance Period of the double-blind treatment relative to the Prerandomization Phase for drop seizures

3. The 50% responder rate in the Maintenance Period of the double-blind treatment relative to the Prerandomization Phase for total seizures.

Other secondary endpoints are:

4. Median percent change in non-drop seizure frequency per 28 days during double-blind treatment (Titration Period and Maintenance Period) relative to the Prerandomization Phase

5. Proportion of subjects with 75%, and 100% responder rates for drop, non -drop, and total seizures in the Maintenance Period relative to the Prerandomization Phase

6. Proportion of subjects with 50% responder rate in the Maintenance Period of the doubleblind treatment relative to the Prerandomization Phase for non-drop seizures

7. Physicians' global evaluation of the subject's overall changes in symptoms (using a 7-point Likert scale with 1=very much improved and 7=very much worse) at the end of the double-blind treatment

8. Incidence of AEs and SAEs, changes in clinical laboratory values, and vital signs

9. Model-derived average perampanel concentrations at steady state (Cav,ss) during the Maintenance Period of the Core Study

5.1.3 Exploratory Endpoints

CCI

[redacted]

5.1.4 Definitions of Analysis Sets

The **Safety Analysis Set (Extension)** is the group of subjects who entered into the Extension and received at least one dose of perampanel and had at least one post-perampanel safety assessment.

The **Full Analysis Set (Extension)** is the group of subjects who entered into the Extension and received at least one dose of perampanel and had at least one post-perampanel seizure measurement.

5.1.5 Subject Disposition

The disposition of all subjects with respect to Extension A and B will be summarized for all enrolled subjects. Subject disposition summaries will present the number (percentage [%]) of subjects who had discontinued or completed, and the primary reason for discontinuation.

5.1.6 Protocol Deviations

Not applicable.

5.1.7 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set (Extension) will be summarized.

Continuous demographic and baseline variables include age, weight, height and body mass index (BMI); categorical variables include sex, age group (2-<12, 12-<18, 18-<65, ≥65), race and ethnicity.

Age is recorded at date of informed consent.

MEDICAL HISTORY

Epilepsy-specific medical history, including time since diagnosis and seizure type will be summarized for the Safety Analysis Set (Extension) using descriptive statistics.

5.1.8 Prior and Concomitant Therapy

The number of baseline AEDs will be summarized and a summary of baseline AEDs will be produced. A baseline AED is an AED taken at the date of randomization to the Core Study.

Other Prior and Concomitant Therapy will be listed.

5.1.9 Treatment Compliance

Investigator assessment of compliance, as recorded on the e-CRF at each visit, will be listed.

5.2 DATA ANALYSIS GENERAL CONSIDERATIONS

5.2.1 Pooling of Centers

There will be no pooling of centers.

5.2.2 Adjustments for Covariates

No models will be fitted to the data hence there will be no adjustments for covariates.

5.2.3 Multiple Comparisons/Multiplicity

As no P-values will be reported, there will be no multiplicity issues.

5.2.4 Examination of Subgroups

All summaries will be presented by the following age groups and overall: 2-<12years, 12-<18 years, 18-<65 and 65 years and above.

5.2.5 Handling of Missing Data, Drop-outs, and Outliers

A conservative principle will be used for an AE with missing date(s) to determine if it is treatment-emergent, that is, if there are missing or partially missing AE start and/or stop dates, and it cannot be determined definitively whether an AE started during the perampanel treatment duration, it will be assumed that the AE was treatment-emergent.

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. A similar principle will be used for a medication with missing date(s). If there are missing or partially missing medication start and/or stop dates, and it cannot be determined definitely whether a medication was taken concomitantly with perampanel, it will be assumed that the medication is concomitant. A detailed algorithm to impute missing dates is given in the programming specifications.

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.

No special handling of missing data is planned for the analysis of any of the other safety variables.

All the listings will display the original missing values.

5.2.6 Other Considerations

A subject who has an AE coded to the same preferred term more than once during perampanel treatment will be counted only once in calculations for that AE. Similarly, if a subject has more than one AE in a 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. Similarly, the AE considered most closely related to open-label treatment will be used in the calculation of incidence of individual AE by relationship.

If no seizure 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.

5.3 EFFICACY ANALYSES

Seizure frequency for a given seizure type (or overall) for any given interval will be based on the number of seizures of that particular type (or overall) recorded over the given interval based only on "days with a valid seizure count," and rescaled to a 28-day window, calculated as the number of seizures over the time interval, multiplied by 28, and divided by the number of "days with a valid seizure count" in the interval. 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 the 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. Although driven by first dose date and not time periods, this means that for subjects randomized to perampanel in the Core Study, baseline will be based on all valid seizure diary data occurring during the Core Study baseline period whereas baseline for subject randomized to placebo in the Core Study will be based on all valid seizure diary data from the Core Study prior to the first dose in the Extension Phase.

The perampanel treatment duration for efficacy analyses consists of (a) the Randomization Phase of the Core Study plus the Extension Phase A for subjects randomized to the perampanel treatment arm during the Core Study, or (b) the Extension Phase A for subjects randomized to placebo treatment during the Core Study.

5.3.1 Pre-Perampanel Baseline Analysis

The following analyses will be conducted for drop, non-drop and total seizures using the Full Analysis Set (Extension):

- Median percentage change in seizure frequency per 28 days from baseline over the entire perampanel treatment duration.

- Proportion of subjects with ≥50%, ≥75%, and 100% response for the perampanel treatment duration.

Efficacy endpoints will be summarised in 13-week intervals and overall.

For summaries by 13-week intervals a subject needs at least 1 day of seizure frequency data in a 13-week interval to be included in the summary for the overall perampanel treatment duration. To be counted as seizure-free, they would need to have completed the time interval.

5.4 Pharmacokinetic, Pharmacodynamic, and PHARMACOGENOMIC/PHARMACOGENETIC ANALYSES

Not applicable.

5.5 SAFETY ANALYSES

All safety analyses will be performed on the Safety Analysis Set (Extension). Treatment-emergent adverse events will be summarized. The incidence of on treatment suicidality as measured by the C-SSRS will be summarized. Clinical laboratory parameters and vital signs data will be listed. Study Day 1 for all safety analyses is defined as the date of the first dose of perampanel.

5.5.1 Extent of Exposure

Total perampanel exposure will be calculated as the number of days between the date the subject received the first dose of perampanel (from Core Study or Extension Phase) and the date the subject received the last dose of study drug in Extension Phase (A or B).

The mean, modal, median, maximum and last daily dose over the conversion, extension maintenance (A+B), overall extension and overall perampanel treatment duration will be summarized.. The mean daily dose will be calculated by taking the average of all the doses taken weighted by the total duration of exposure and rounded to 1 decimal place.

5.5.2 Adverse Events

Adverse events will be addressed with respect to the Safety Analysis Set (Extension).

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 16.1 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 emerged during treatment, having been absent at pre-treatment (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.

For subjects randomized to the perampanel treatment group in the Core Study, the first dose date of perampanel is from the Core Study. For subjects randomized to placebo in the Core study, the first dose date of perampanel is from the Extension Phase

TEAEs will be summarized. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by PT and decreasing frequency. A subject will be counted only once within a PT, even if the subject experienced more than one TEAE within a specific PT. Treatment-related TEAEs will also be summarized.

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

A listing of deaths will be produced.

The number (percentage) of subjects with treatment-emergent serious adverse events (SAEs) will be listed and summarized by MedDRA PT and decreasing frequency.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be listed and summarized by MedDRA PT and decreasing frequency

Standardized MedDRA Query (SMQ) will be used to identify relevant terms for the following TEAEs. All of these TEAEs will be summarized by narrow terms.

- TEAEs suggestive of abuse potential: SMQ of drug abuse, dependence and withdrawal
- TEAEs related to alertness and cognition: SMQ of dementia
- TEAEs related to hostility/aggression: SMQ of hostility/aggression
- TEAEs related to psychosis and psychotic disorder: SMQ of psychosis and psychotic disorders
- TEAEs related to status epilepticus/convulsions: SMQ of convulsions
- TEAEs related to drug related hepatic disorder abnormalities: SMQ of dryg-related hepatic disorders
- Cardiac and electrocardiogram (ECG) TEAEs: SMQs of cardiac arrhythmia terms (including bradyarrhythmias and tachyarrhytmias, arrhythmia related investigations, signs and symptoms, cardiac failure, cardiomyopathy, ischaemic heart diseases, and Torsade de pointes/QT prolongation
- Rash: SMQ of severe cutaneous adverse reactions and hypersensitivity

5.5.3 Laboratory Values

Laboratory results will be listed.

5.5.4 Vital Signs

Vital signs data will be listed.

5.5.5 Electrocardiograms

ECG was not obtained during the extension.

5.5.6 Other Safety Analyses

5.5.6.1 C-SSRS

The following summary 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.

5.6 OTHER ANALYSES

Not applicable.

5.6.1 CCI

CCI

5.7 EXPLORATORY ANALYSES

There will be no exploratory analysis.

6 INTERIM ANALYSES

No interim analyses are planned for this study.

7 CHANGES IN THE PLANNED ANALYSES

Limited data summaries are being produced due to the early termination of the study. 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 Baseline Seizure Frequency

For the summaries of overall perampanel treatment duration, all diary data before the first perampanel dose date will be used in the computation of the baseline seizure frequency per 28 days. For subjects assigned to perampanel treatment during the Core Study, baseline will be computed from the Prerandomization Phase of the Core study. For subjects assigned to placebo treatment during the Core Study, baseline would be computed from data during the Core Study plus the Prerandomization Phase of the Core Study.

8.1.2 Treatment Duration for Efficacy Analyses.

The treatment duration for diary seizure data are defined as follows:

- The date of first perampanel dose during the Core Study to the last perampanel dose during the Extension Phase A for subjects assigned to perampanel treatment during the Core Study.

- The date of first to last perampanel dose during Extension Phase A for subjects assigned to placebo treatment during the Core Study.

8.1.3 Seizure Frequency Formulae

The following formula will be used to estimate the "seizure frequency per 28 days" period for each subject, where "Y" is the number of days with valid diary data for that period:

Seizure frequency = Number of seizures of type(s) of interest (captured over Y days) x 28/Y days.

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 perampanel.

8.2.2 Treatment Duration for Safety Analyses

For AEs, the perampanel treatment duration is considered to begin:

- at the first dose of perampanel in the Core Study and ends 28 days after the last dose of perampanel in Extension Phase A for subjects assigned to perampanel treatment during the Core Study
- at the date of first perampanel dose to 28 days after the last dose of perampanel in Extension Phase A for subjects assigned to placebo treatment during the Core Study.

The Post-treatment duration will begin on the day after the permapanel treatment duration during Extension Phase A.

AEs for the subject were collected and reported on the 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.

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.

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.

11 MOCK TABLES, LISTINGS AND GRAPHS

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

SIGNATURE PAGE

Author:

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