STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E2007-G000-410
Study Protocol Title:	Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Perampanel as Monotherapy or First Adjunctive Therapy in Subjects With Partial Onset Seizures With or Without Secondarily Generalized Seizures or With Primary Generalized Tonic-Clonic Seizures
Date:	May 17, 2021
Version:	Final Version 1.0

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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
AED	antiepileptic drug
ATC	anatomical therapeutic class
BDI-II	Beck depression inventory-II
BP	blood pressure
CI	confidence interval
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
DMC	Data Monitoring Committee
EOT	end of treatment
FAS	Full Analysis Set
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
PGTCS	primary generalized tonic-clonic Seizures
POS	partial-onset seizures
PSQI	Pittsburgh Sleep Quality Index
PT	preferred term
QOLIE-31	Quality of Life in Epilepsy Inventory-31
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Safety Analysis Set
SD	Standard deviation
SGS	Secondarily Generalized Seizures
SOC	system organ class
TEAE	treatment-emergent adverse event
TLG	tables, listings, and graphs
WHO DD	World Health Organization drug dictionary

3 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for the Eisai Protocol E2007-G000-410.

3.1 Study Objectives

3.1.1 Primary Objective

To assess the retention rate of perampanel when given as monotherapy or 1st adjunctive therapy in subjects with partial-onset seizures (POS) or primary generalized tonic-clonic seizures (PGTCS).

3.1.2 Secondary Objectives

- To evaluate the efficacy of perampanel when given as monotherapy or 1st adjunctive therapy in subjects with POS or PGTCS as measured by seizure freedom
- To assess the proportion of subjects with POS or PGTCS that are able to convert from 1st adjunctive therapy to perampanel monotherapy
- To assess the safety of perampanel as initial monotherapy or 1st adjunctive therapy in subjects with POS or PGTCS
- To assess dosing and titration of perampanel when administered as initial monotherapy or 1st adjunctive therapy in subjects with POS or PGTCS

3.1.3 Exploratory Objectives

- To evaluate the efficacy of perampanel in subjects with POS or PGTCS as measured by responder rates (50% and 75%, in subjects who have sufficient baseline seizure frequency data available)
- To evaluate the efficacy of perampanel in subjects with POS or PGTCS as measured by median percent reduction in seizure frequency (in subjects who have sufficient baseline seizure frequency data available)
- To assess cognition, including the impact of depression, in subjects with POS or PGTCS administered perampanel as monotherapy or as 1st adjunctive therapy.
- To assess subjective sleep quality in subjects with POS or PGTCS administered perampanel as monotherapy or as 1st adjunctive therapy
- To assess quality of life in subjects with POS or PGTCS administered perampanel as monotherapy or as 1st adjunctive therapy

3.2 Overall Study Design and Plan

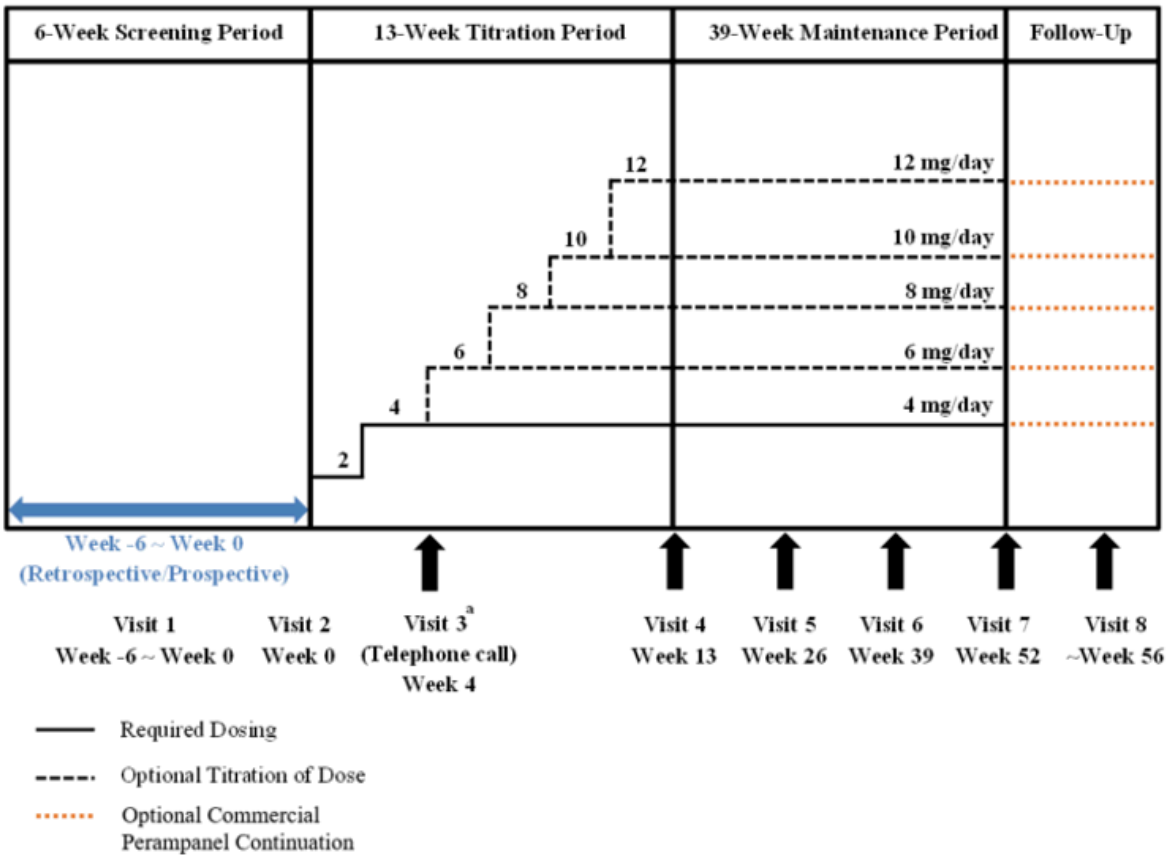
This is a multi-center, open-label, Phase 4 study. Subjects who met all of the inclusion and none of the exclusion criteria will receive perampanel. Baseline seizure counts (frequency) data will be collected by subjects or guardian/legally authorized representative, retrospectively (for history prior to screening) and prospectively as needed (during baseline). The study consists of 4 periods: a Screening Period (to start no earlier than 6 weeks before the 1st dose of study drug), a Titration Period (13 weeks), a Maintenance Period (39 weeks), and a Follow-up Period (4 weeks). The study duration for each subject is expected to be approximately 1 year in total.

Study subjects includes the following:

- Subjects who have been diagnosed with POS or PGTCS but have not previously received treatment with an antiepileptic drug (AED) or are receiving monotherapy treatment (no history of AED polytherapy) and wish to switch to another monotherapy treatment; or

- Subjects who are receiving treatment with a single AED administered at a stable dose for at least 8 weeks before Visit 2 (Week 0) and needs additional AED treatment; subjects should not have previously received adjunctive AED therapy.

An overview of the study design is presented below.



4 DETERMINATION OF SAMPLE SIZE

The efficacy of perampanel as monotherapy and 1st adjunctive therapy for POS and PGTCS is to be evaluated. The primary endpoint is retention rate. The study is planned to enroll approximately 125 subjects. This sample size is considered adequate for an open-label Phase 4 study where there is no statistical hypothesis to be tested.

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 of seizure-related efficacy endpoints will be produced by seizure type (POS, secondarily generalized seizures [SGS], and PGTCS) and overall. Summaries of retention rate and safety data will be produced by seizure type (POS, SGS, and PGTCS) and overall.

5.1 Study Endpoints

5.1.1 Primary Endpoint

The primary endpoint is retention rate, defined as the proportion of subjects remaining on perampanel at the specified time points: 3, 6, 9, and 12 months after initiation of treatment.

5.1.2 Secondary Endpoints

- Proportion of subjects who achieve seizure free status for POS, SGS, and PGTCS during the Maintenance Period.
- Proportion of subjects who achieve 3-month seizure-free status for POS, SGS, and PGTCS.
- Proportion of subjects who achieve 6-month seizure-free status for POS, SGS, and PGTCS.
- Proportion of subjects who receive perampanel as a 1st adjunctive therapy who are able to convert to perampanel monotherapy
- Safety and tolerability of perampanel administered as monotherapy or 1st adjunctive therapy in adolescents and adults
- Maximum and last dose during the titration period and the maintenance period

5.1.3 Exploratory Endpoints

- 50% responder rate in total POS, SGS, and PGTCS; 50% responders are defined as subjects who have at least a 50% reduction in seizure frequency relative to baseline (in subjects with sufficient baseline seizure frequency data.
- 75% responder rate in total POS, SGS, and PGTCS; 75% responders are defined as subjects who have at least a 75% reduction in seizure frequency relative to baseline (in subjects with sufficient baseline seizure frequency data)
- Median percent change in total POS, SGS, and PGTCS frequency in the Titration and Maintenance Periods relative to baseline (in subjects with sufficient baseline seizure frequency data)
- Proportion of subjects with no/mild/clear cognitive impairment relative to baseline using the EpiTrack total score
- Change in subjective sleep quality at the end of the Maintenance Period relative to baseline using the PSQI
- Change in quality of life at the end of the Maintenance Period relative to baseline using the QOLIE-31
- Proportion of subjects with Depression relative to baseline using BDI-II scores.

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

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

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

5.2.2 Subject Disposition

The disposition of all subjects will be summarized. Subject disposition tables will include the number (percent) of subjects who will be:

- Included in each analysis population
- Discontinued from the study early, summarized by reason for discontinuation
- Screened and the number (percent) who fail screening will also be summarized

5.2.3 Protocol Deviations

Subjects with major protocol deviations will be listed. These may include:

- Recruitment of a subject who did not satisfy the inclusion/exclusion criteria
- Subjects who took excluded medication
- Overdose of Investigational Products of 120% or above between 2 consecutive visits or Study Medication compliance <80% between two consecutive visits.
- Continuation of treatment with Study Medication after a treatment related withdrawal event
- Unauthorized dose adjustment during Titration Period and Maintenance Period.

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics (e.g., age, sex) for the SAS will be summarized using descriptive statistics. Continuous variables will be summarized using mean, SD, median, minimum, maximum, and categorical variables will be summarized using number and percentages of subjects.

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

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

5.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD). The latest version before database lock will be used for analysis. The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by Anatomical Therapeutic Chemical (ATC) class and WHO DD preferred term (PT). Prior medications are defined as any medications that stopped before the 1st dose of study drug. Concomitant medications are defined as medications that (1) started before the 1st dose of study drug and were continuing at the time of the 1st dose of study drug, or (2) started on or after the date of the 1st dose of study drug up until 28 days after the subject's last dose. All medications will be presented in subject data listings.

5.2.6 Treatment Compliance

Compliance with study medication during the Titration Period and Maintenance Period will be summarized using descriptive statistics. Overall percent compliance will be calculated as follows:

$$\text{Compliance} = \frac{(\text{Study Med issued in grams} - \text{Study Med Returned in grams})}{(\text{Number of Days} \times \text{Prescribed Daily Dose in grams})} \times 100$$

Overall study medication compliance will also be summarized using the categories <80%, 80% to 100%, 100%-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 summaries of seizure-related efficacy endpoints will be produced by seizure type (POS, SGS, and PGTCS) and overall. Summaries of retention rate and safety data will be produced by seizure type (POS, SGS, and PGTCS) and overall. All summaries of retention rate and seizure-related efficacy endpoints will also be produced by sex and age group (<12, 12-<=18, 18–<=65, >65).

5.3.5 Handling of Missing Data, Dropouts, and Outliers

5.3.5.1 Efficacy

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 for handling missing data. For the last observation carried forward (LOCF) analyses, 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.

5.3.5.2 Safety

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

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

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

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 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

This is a study without a control arm. Therefore, only descriptive statistics will be performed. The SAS will be used to summarize retention rate and the FAS will be used to summarize

seizure data.

5.4.1 Primary Efficacy Analyses

The retention rate, defined as the proportion of subjects remaining on perampanel treatment at 3, 6, 9, and 12 months after initiation of treatment, will be summarized. The number and percentage of subjects remaining on treatment at each time point will be summarized using SAS. Corresponding 95% CIs may also be presented if allowed by the data.

5.4.2 Secondary Efficacy Analyses

The FAS will be used to summarize seizure freedom data and conversion data of perampanel as a 1st adjunctive therapy converted to perampanel monotherapy. The number and percentage of subjects who achieved seizure-free status or who converted to perampanel monotherapy will be summarized. 95% CIs may also be calculated if allowed by the data.

The seizure-free status at 3-month in Maintenance Period, at 6-month in Maintenance Period, and during the entire Maintenance Period will only be counted for subjects who complete the respective period. A subject who dropped out early relative to the respective period would be counted as 'No' for seizure-free status in that period.

A subject is considered converted to perampanel monotherapy during Maintenance Period if the subject had a scheduled visit in Maintenance Period and was not taking any concomitant AED at any time during the scheduled visit. A subject who dropped out early before the conversion would be counted as 'No' for conversion status.

5.4.3 Exploratory Efficacy Analyses

Analyses of exploratory efficacy endpoints will be performed in the subset of the FAS with sufficient baseline seizure frequency i.e. at least 1 seizure during the baseline. All summaries will be produced by seizure type (POS, SGS, and PGTCS).

For percent change in seizure frequency endpoints at each treatment Period [pre-treatment, treatment, (titration plus maintenance), maintenance and maintenance-LOCF], and for each seizure type:

- Mean, standard deviation, median, minimum, and maximum will be provided.

For responder rate endpoints at each time point (3, 6, 9, and 12 months in maintenance period, maintenance and maintenance-LOCF), and for each seizure type:

- Number and percentage of responders will be provided

95% confidence intervals for the percentage change and responder rate may also be calculated if allowed by the data.

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not Applicable

5.6 Safety Analyses

The SAS will be used to summarize all safety variables. Safety data will be summarized using descriptive statistics (e.g., n, mean, standard deviation, median, minimum, maximum for continuous variables; and n [percentage] for categorical variables).

Safety variables include treatment-emergent adverse events (TEAEs), vital signs, EpiTrack, BDI-II, PSQI, QOLIE-31, and C-SSRS scores. 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 extent of exposure to the study drug during the Titration Period and the Maintenance Period will be summarized descriptively. The duration of treatment (Titration Period and Maintenance Period) will be calculated as the number of days between the date the subject receives their first treatment dose and the date the subject receives the last dose of treatment. These values will be used to summarize the extent of exposure to study drug.

The mean daily dose, maximum dose, last dose, and modal dose (mg) for each subject over the Titration period and Maintenance period 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, rounded to 1 decimal place (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). AEs will be coded to the MedDRA (most recent version) lower level term closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also 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

- Reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsened in severity during treatment relative to the pretreatment 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.

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

The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

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

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

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

5.6.3 Vital Signs

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

The number (percentage) of subjects with clinically notable results over all scheduled and unscheduled visits will be summarized using Table 1 below:

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.		

The number of subjects with abnormal results for blood pressure and heart rate will be summarized using the criteria in Table 2 below.

Table 2: Criteria for Abnormal Vital Signs

Variable	Change Relative to Baseline
Systolic BP	Increase of ≥ 20 mmHg
	Decrease of ≥ 20 mmHg
	Increase of ≥ 40 mmHg
	Decrease of ≥ 40 mmHg
Diastolic BP	Increase of ≥ 10 mmHg
	Decrease of ≥ 10 mmHg
	Increase of ≥ 20 mmHg
	Decrease of ≥ 20 mmHg
Pulse	Increase of ≥ 15 bpm
	Decrease of ≥ 15 bpm
	Increase of ≥ 30 bpm
	Decrease of ≥ 30 bpm

5.6.4 Other Safety Analyses

EpiTrack

Cognition will be assessed in subjects 6 years of age and older at Visit 2 (Week 0) and at 3 and 12-month visits (Visits 4 and 7, respectively) using the EpiTrack® assessment tools (Epitrack for subjects aged 16 years and older and EpiTrack Junior for subjects aged 6 to 16 years at Visit 2 [Week 0]?). The EpiTrack includes 6 subtests: response inhibition, visuo-motor speed, mental flexibility, visual motor planning, verbal fluency, and working memory. Based on the subtest results, an age-corrected total score is calculated. "Higher total scores indicate more severe depressive symptoms. The calculation details and performance categories are provided in Section 13.1. Practice corrected reliable change indices indicate a significant change with a gain of more than 3 points and a loss of more than 2 points.

Descriptive statistics for age-corrected total score and changes from baseline will be presented by visit. Summaries of the proportion of subjects with no/mild/clear cognitive impairment and shifts between these categories from baseline to end of treatment will be produced.

Beck Depression Inventory-II (BDI-II)

The Beck Depression Inventory-II (BDI-II) is a 21-question multiple-choice self-report inventory and is widely used for measuring the severity of depression. The BDI-II will be administered in subjects 16 years of age and older who are administered the EpiTrack.

There is a four-point scale for each item ranging from 0 to 3. Each of the 21 items corresponding to a symptom of depression is summed to give a single total score for the BDI-II from 0 to 63. Higher total scores indicate more severe depressive symptoms. Descriptive statistics for BDI-II total score and changes from baseline will be presented by visit.

Pittsburgh Sleep Quality Index (PSQI)

Based on 19 items, the PSQI measures several different aspects of sleep, offering seven component scores and one composite score. The component scores consist of subjective sleep quality, sleep latency (i.e., how long it takes to fall asleep), sleep duration, habitual sleep efficiency (i.e., the percentage of time in bed that one is asleep), sleep disturbances, use of sleeping medication, and daytime dysfunction.

Each item is weighted on a 0–3 interval scale. The global PSQI score is then calculated by totaling the seven component scores, providing an overall score ranging from 0 to 21, where lower scores denote a healthier sleep quality. The scoring details of global PSQI score are provided by PSQI website: http://www.psychiatry.pitt.edu/node/8240. Descriptive statistics for individual component and global PSQI scores and changes from baseline will be presented by visit.

Quality of Life in Epilepsy Inventory-31 (QOLIE-31)

The QOLIE-31 contains 7 multi-item scales that tap the following health concepts: emotional well-being, social functioning, energy/fatigue, cognitive functioning, seizure worry, medication effects, and overall quality of life. A QOLIE-31 overall score is obtained using a weighted average of the multi-item scale scores. Scoring details of the QOLIE-31 overall score will be performed as instructed by RAND QOLIE-31 scoring manual website: https://www.rand.org/content/dam/rand/www/external/health/surveys_tools/qolie/qolie31_scoring.pdf. The QOLIE-31 also includes a single item that assesses overall health. QOLIE-31 raw scores are scaled from 0-100 with higher scores reflecting better quality of life. The overall score is calculated by summing the scale scores after weighting with empirically derived weights provided in the manual. Descriptive statistics for QOLIE-31 subscale and overall score and changes from baseline will be presented by visit.

Columbia Suicide Severity Rating Scale (C-SSRS)

Suicidality will be assessed using the C-SSRS and summaries will include the incidence of suicidal behavior and suicidal ideation for subjects 6 years of age and older. Scoring of the C-SSRS will be performed as suggested by the C-SSRS Columbia website: http://www.cssrs.columbia.edu.

The following summaries will be presented for the treatment duration (Titration Period and Maintenance Period).

- Number (percentage) of subjects with any treatment-emergent report of suicidal behavior, suicidal ideation, and suicidality (suicidal behavior and/or ideation) will be displayed. A treatment-emergent report of suicidal behavior, suicidal ideation, or

suicidality is an answer of 'Yes' to any question in the respective category during the treatment duration.

- Shift from baseline to the maximum suicidal ideation severity rating (0=no ideation present to 5=active ideation with plan and intent) in the treatment duration will assess worsening of suicidal ideation. Any score greater than 0 indicates the presence of suicidal ideation while a score of 4 (active suicidal ideation with some intent to act) or 5 (active suicidal ideation with specific plan and intent) can be used to indicate serious suicidal ideation.

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

5.7 Other Analyses

Not applicable.

6 INTERIM ANALYSES

Interim analyses may be conducted at various intervals, depending on the number of accrued subjects.

7 CHANGES IN THE PLANNED ANALYSES

Due to recruitment challenges, enrollment was terminated before reaching the planned sample size. Thus, there will not be enough sample size to calculate the 95% CIs. Analysis of BDI-II scale is added as an exploratory analysis.

There are no other changes to the analysis in this statistical 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

8.1.1 Baseline efficacy

All diary data prior to first dose date plus 6-week prior historical data at the time of enrollment will be used in the computation of baseline seizure frequency per 28 days. All subjects should have at least 6 weeks of diary data prior to baseline (Visit 2).

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 end of treatment (EOT) value is the last non-missing value while on-treatment.

The treatment duration for efficacy variables is defined as follows:

- For diary seizure data: The duration between the date of first dose and the last date of study drug in treatment duration (Titration Period and Maintenance Period), inclusive.
- For non-diary efficacy data: The duration between the date of first dose and 7 days after the last visit of schedule in treatment, inclusive.
- Data reported only during the treatment duration will be analysed.

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 drug.

8.2.2 Treatment Duration for Safety Analyses

For AEs, the treatment duration is considered to begin on Day 1 and ends 28 days after the last dose of treatment.

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 study week the data will be mapped. Scheduled, unscheduled, and early withdrawal visits will be mapped into study weeks. Table 1 below gives the mapping of relative day ranges to week for non-AE safety variables. If a subject did not have a recorded observation falling within a given range of days in order to be assigned to a study 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 not the baseline assessment, then the assessment closest to the scheduled assessment will be used in the summary tables.

Note that if two assessments are equidistant from the scheduled assessment then the last assessment of the two (within the allowable window) will be used.

Table 1: Mapping of Study Day Ranges to Week

Period	Study Week	Study Day Range (Relative to First Dose of Study Drug)	Target Day
Screnning	Baseline	Day ≤1[a]	1
Titration	Week 13	2 ≤ Day ≤ 138	92
Maintenance	Week 26	139 ≤ Day ≤ 229	183
Maintenance	Week 39	230 ≤ Day ≤ 320	274
Maintenance	Week 52	321 ≤ Day ≤ 999[b]	365

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 Study. The Follow-up visit will not be included in this analysis visit.

8.2.3 Handling of Replicate Data

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

For the vital signs, EpiTrack, BDI-II, PSQI, QOLIE-31, and C-SSRS datasets, the measurement noted as the scheduled visit measurement will be used in the analysis. If more than one assessment is present at a scheduled visit, then the nearest assessment for evaluation visit(day) will be used in the summaries of the actual values and changes from baseline. In the event of two assessments being equally close to the scheduled visit day, the last assessment will be used.

8.2.4 Handling of prior/concomitant medication

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

9 PROGRAMMING SPECIFICATIONS

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

10 STATISTICAL SOFTWARE

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

11 MOCK TABLES, LISTINGS, AND GRAPHS

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

12 REFERENCES

1. Pittsburgh Sleep Quality Index (PSQI). University of Pittsburgh. PSQI scoring available from: http://www.psychiatry.pitt.edu/node/8240

2. Quality of Life in Epilepsy Inventory-31 (QOLIE-31). RAND QOLIE-31 scoring manual available from: https://www.rand.org/content/dam/rand/www/external/health/surveys_tools/qolie/qolie31_scoring.pdf.

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

13 APPENDICES

13.1 EpiTrack Age-Corrected Total Score and Performance Category

Dependent on age group points must be added to total score for correction. The result is the age-corrected total EpiTrack score.

EpiTrack Junior

Table 1: Age Correction

6 years	+14 points
7 years	+7 points
8 years	+4 points
9 years	+2 points
10 years	No age Correction
11-14 years	-2 points
15-18 years	- 4 points

Based on the age-corrected total score the Epitrack performance categories are defined as follows:

Table 2: EpiTrack Performance Categories

Good	36 ≤ score points
Average	31 to 35 score points
Mildly impaired	29 to 30 score points
Significantly impaired	≤ 28 score points

EpiTrack (Regular)

Table 1: Age Correction

16 to 20 years	+1 point
21 to 35 years	No correction
36 to 45 years	+1 point
46 to 50 years	+3 points
51 to 65 years	+4 points
66 to 70 years	+6 points
> 70 years	+7 points

Based on the age-corrected total score the Epitrack performance categories are defined as follows:

Table 2: EpiTrack Performance Categories

Excellent	39 ≤ score points
Average	32 to 38 score points
Mildly impaired	29 to 31 score points
Significantly impaired	≤ 28 score points

SIGNATURE PAGE

Author(s):

[electronic signature in eDMS]

PPD

Date

Neuroscience Business Group, Eisai Inc.

Approval:

[electronic signature in eDMS]

PPD

Date

Neuroscience Business Group, Eisai Inc.

[electronic signature in eDMS]

PPD

Date

Neuroscience Business Group, Eisai Inc.