16.1.9   Documentation of Statistical Methods

STATISTICAL ANALYSIS PLAN
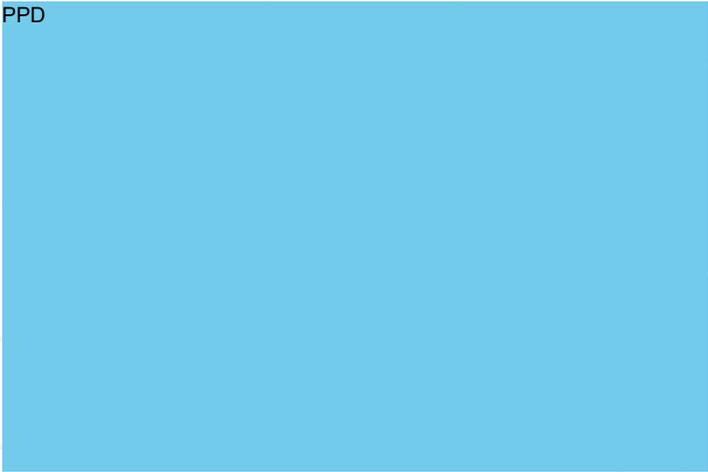
Study Number: **Protocol** E2007-J000-342

Study Title: **Protocol** A multicenter, uncontrolled, open-label study and extension study for verification of efficacy and safety for perampanel monotherapy in untreated patients with partial onset seizures (including secondarily generalized seizures)

Date: 15 Apr 2019

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1   TABLE OF CONTENTS

2   LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
β-hCG	beta-human chorionic gonadotropin
BMI	Body mass index
BUN	blood urea nitrogen
CoA	certificate(s) of analysis
CI	confidence interval
CNS	central nervous system
CPK	creatine phosphokinase
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CT	computed tomography
CYP	cytochrome P450
EAID	enzyme inducing antiepileptic drug
ECG	electrocardiogram
EEG	electroencephalogram
EIAED	enzyme inducing antiepileptic drug
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels
EU	European Union
GABA	gamma-aminobutylic acid
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
ILAE	International League Against Epilepsy
IRB	institutional review board
ITT	intent-to-treat
IUPAC	International Union of Pure and Applied Chemistry

Abbreviation	Term
IUS	intrauterine hormone-releasing system
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LLT	lowest level term
LNH	low/normal/high
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MRI	magnetic resonance imaging
POS	partial onset seizure
PT	preferred term
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
ULN	upper limit of normal
VNS	vagal nerve stimulation
WHO DD	World Health Organization Drug Dictionary

3   INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and statistical methods in detail that will be used to analyze and report results Eisai Protocol E2007-J000-342.

If the primary endpoint is successfully achieved, statistical analysis of the Treatment Phase will be performed when all subjects end the 4 mg Maintenance Period. At that time, the subjects who are continuing the 8 mg Treatment Phase will be regarded as non-seizure free, and their data until the latest visit will be analyzed. In addition, subsequent data after that will be regarded as data of the Extension Phase.

3.1   Study Objectives

3.1.1   Primary Objective

To evaluate the seizure-free rate of the 26-week Maintenance Period in untreated patients with partial onset seizures (POS)

3.1.2   Secondary Objectives

・ To evaluate the seizure-free rate of the 52-week treatment in untreated patients with POS

・ To confirm time to first seizure onset and time to withdrawal from the study from the first date of the Maintenance Period in untreated patients with POS

・ To evaluate the safety and tolerability of perampanel monotherapy in untreated patients with POS

3.1.3   Exploratory Objective

・ To investigate the seizure free-rate of the 26-week Maintenance Period by seizure type in untreated patients with POS

・ To investigate the percent change in seizure frequency from baseline during the Maintenance Period and Extension Phase in untreated patients.

・ To investigate the pharmacokinetics of perampanel as monotherapy

・ To evaluate the impact of perampanel over time (End of Treatment – Baseline) on overall health-related quality of life as measured by the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L)

3.2   Overall Study Design and Plan

This study is a multicenter, uncontrolled, open-label, single-arm study in untreated patients with partial onset seizures (including secondarily generalized seizures). This study consists of a Pretreatment Phase, a Treatment Phase (a Titration Period, a Maintenance Period), an Extension Phase, and a Follow-up Phase.

Pretreatment Phase

During the Pretreatment Phase (maximally 4 weeks), patients will be screened and be

assessed for their eligibility to participate in the study.

Treatment Phase

The Treatment Phase consists of the 4 mg Treatment Phase (the Titration Period [6 weeks] and the Maintenance Period [26 weeks]) and the 8 mg Treatment Phase (the Titration Period [4 weeks] and the Maintenance Period [26 weeks]) if subjects require higher dose.

Extension Phase

When subjects complete the Treatment Phase and agree to continue receiving the perampanel monotherapy, they could enter the Extension Phase. Subjects will continue to receive perampanel until 3 or less months from the date of approval of perampanel monotherapy in each country unless subjects experience tolerability issues such as occurrence of adverse events or need to take other antiepileptic drugs (AEDs) because of insufficient efficacy of perampanel.

Follow-up Phase

Subjects who will finish or discontinue the study will conduct the follow-up visit 4 weeks after withdrawal of perampanel.

The study design is shown in Figure 1.
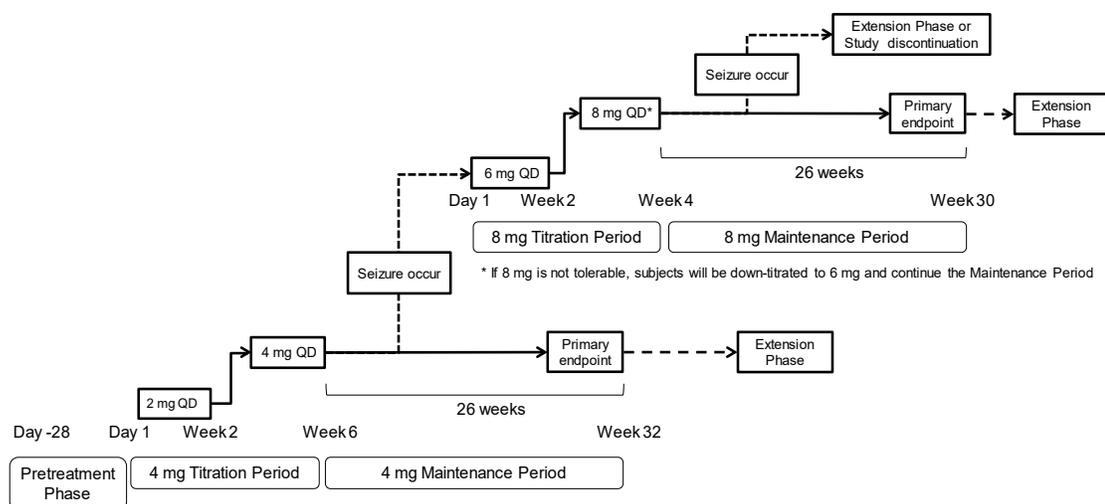
Figure 1 Study Design

4   DETERMINATION OF SAMPLE SIZE

In this study, perampanel will be determined to be efficacious if, in untreated subjects with POS (including secondary generalized seizures), the lower limit of the 95% confidence interval for the seizure-free rate in the 26-week Maintenance Period is above the pre-specified threshold (40%).

Based on the results from research papers of AEDs for mono-therapy (Chadwick, et al., 1999, Arroyo, et al., 2005, Mikkelsen, et al., 1981, Heller, et al., 1995, and Kaneko, et al., 2015), the expected seizure free rate for other AEDs would be assumed 50.0%. According to Glauser, et al. (2013), the relative difference >20% versus the adequate comparator's

efficacy point estimate could be considered non-inferior margin if its 95% lower confidence limit was above this lower acceptable cutoff (Glauser, et. al., 2013).

Under the assumption that the expected seizure free rate of perampanel in the 26-week Maintenance Period would be 60%, sample size of 72 will provide greater than 90% power that the lower limit of the 95% confidence interval for the seizure free rate in the 26-week Maintenance Period is above 40%. Taking into consideration the drop-out rate in the Titration Period (approximately 10%), 80 subjects need to be as the ITT Analysis Set.

If the number of subjects who achieve seizure-free is above the following criteria, this study can declare to confirm the efficacy of perampanel.

Table 1   Seizure free rate and 95% Confidence Interval

Target Number of mITT	Minimum Number of Subjects Who Achieve 26-week Seizure-free to Exceed the Pre-specified Threshold	Seizure-free Rate (95% CI) (%)[a]
71	38	53.5 (41.3, 65.5)
72	38	52.8 (40.7, 64.7)
73	38	52.1 (40.0, 63.9)
74	39	52.7 (40.7, 64.4)
75	39	52.0 (40.2, 63.7)
76	40	52.6 (40.8, 64.2)
77	40	51.9 (40.3, 63.5)
78	41	52.6 (40.9, 64.0)
79	41	51.9 (40.4, 63.3)
80	42	52.5 (41.0, 63.8)
81	42	51.9 (40.5, 63.1)

CI = confidence interval, mITT = modified intent-to-treat.
a: 95%CI is based on Clopper-Pearson method.

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 endpoint is defined as follows.

The seizure free rate in the 26-week Maintenance Period for subjects with POS

The number (percentage) of subjects with POS who achieved seizure-free during the 26-week Maintenance Period of 4 mg and regardless of perampanel dose will be calculated. For subjects who increase the perampanel dose from 4 mg to 8 mg, the seizure-free rate of

the 26-week Maintenance Period of 8 mg will be evaluated to calculate the number (percentage) of subjects who achieved seizure-free regardless of perampanel dose.

5.1.2 Secondary Endpoints

The secondary endpoints are defined as follows.

- The seizure free rate in the 52-week treatment (ie, 26-week Maintenance Period plus 26-week Extension Phase) for subjects with POS
- Time to first seizure onset and time to withdrawal from the study from the first date of the Maintenance Period
- The safety and tolerability of perampanel

5.1.3 Exploratory Endpoints

The exploratory endpoints are defined as follows.

- The seizure free rate in the 26-week Maintenance Period for subjects with POS by types of partial seizure
- The percent change in seizure frequency of POS per 12 weeks in the Maintenance Period and Extension Phase relative to the Pretreatment Phase
- The pharmacokinetics of perampanel as monotherapy
- The effect of perampanel on subjects' quality of life with EQ-5D-5L measurements

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

Safety Analysis Set

The Safety Analysis Set is the group of subjects who sign informed consent, receive at least 1 dose of study drug and have at least 1 postdose safety assessment.

Intent-to-Treat (ITT) Analysis Set

The ITT Analysis Set is the group of subjects who sign informed consent, receive at least 1 dose of study drug and have at least 1 postdose primary efficacy measurement.

Modified Intent-to-Treat (mITT) Analysis Set

The mITT Analysis Set is the subset of the ITT Analysis Set who enter the 4 mg Maintenance Period and have at least 1 postdose primary efficacy measurement in the 26-week Maintenance Period.

The number of subjects enrolled, the number (percentage) of subjects included in each analysis set will be presented. Subject data listings will be provided.

5.2.2 Subject Disposition

For the summary table of screening subjects, the number (percentage) of subjects who were enrolled (ie, subjects who signed informed consent), entered the Treatment Phase after screening, failed screening, and the primary reason for screen failures will be presented.

For the summary of the subject disposition, the following items will be presented;

- the number (percentage) of subjects who were treated/not treated

- the number (percentage) of subjects who completed/discontinued the 4 mg Treatment Phase and the primary reason and other reason for the discontinuation

- the number (percentage) of subjects who entered/completed/ongoing/discontinued the 8 mg Treatment Phase and the primary reason and other reason for the discontinuation

- the number (percentage) of subjects who completed/ongoing/discontinued the Treatment Phase and the primary reason and other reason for the discontinuation

- the number (percentage) of subjects who entered/not entered the Extension Phase

- the number (percentage) of subjects who completed/ongoing/discontinued the Extension Phase and the primary reason and other reason for the discontinuation (the percentage will be based on the total subjects who entered the Extension Phase)

Subject data listings will be provided.

5.2.3   Protocol Deviations

Major protocol deviation criteria will be established and subjects with major protocol deviations will be identified and documented before the database lock.

5.2.4   Demographic and Other Baseline Characteristics

This summary table will be generated on the ITT Analysis Set and Safety Analysis Set. (This will be summarized as "ITT / Safety Analysis Set" if the ITT Analysis Set and the Safety Analysis Set are the same.) This summary table will also be generated on the mITT Analysis Set. And this summary table will be performed by country (Japan/ Korea).

Continuous demographic and baseline variables include

- Age
- Height
- Weight
- BMI

Categorical demographic and baseline variables include

- Age group (< 18 years, 18 - < 65 years, 65years ≤)
- Sex
- Race
- Ethnicity
- Country

Epilepsy specific history and characteristics at study entry will also be summarized by:

- History of seizures (newly diagnosed epilepsy, recurrent epilepsy)

- Time since latest diagnosis of epilepsy (months)
- Etiology
- Epileptic syndrome
- Suspected localization of the epileptogenic region
- Seizure type

Subject data listings for demographic and other baseline characteristics will be provided.

MEDICAL HISTORY

A subject data listing of medical history and current medical condition will be provided.

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) drug codes.

Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be 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 the completion or discontinuation of the subject after the subject's last dose. Post-treatment medications will be defined as medications taken on or after the date of study discontinuation.

This summary table will be generated on the ITT Analysis Set and Safety Analysis Set. (This will be summarized as "ITT / Safety Analysis Set" if the ITT Analysis Set and the Safety Analysis Set are the same.)

The number (percentage) of subjects who took prior anti-epileptic medications will be summarized by Anatomical Therapeutic Chemical (ATC) class, and WHO DD preferred term. This analysis will also be performed by both history of seizures (newly diagnosed epilepsy/recurrent epilepsy) and rescue (yes/no).

The number (percentage) of subjects who took prior (except fot anti-epileptic medications) and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) class, and WHO DD preferred term.

The concomitant medications will be summarized for the Treatment Phase and the entire study period (ie, the Treatment Phase or the Extension Phase).

All medications will be presented in subject data listings.

5.2.6   Treatment Compliance

Treatment compliance calculated as follows will be summarized using descriptive statistics for the 26-week Maintenance Period of 4 mg and the 26-week Maintenance Period of the last evaluated dose (ie, 4 or 8mg) on the mITT Analysis Set.

$$\frac{\text{Total days of study drug prescribed - Days of incompliance}}{\text{Total days of study drug prescribed}} \times 100$$

The number (percentage) of subjects in the categories <80%, >= 80% to <= 100%, >100% to <= 120%, and > 120% will also be summarized.

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

No adjustment for covariates will be performed.

5.3.3   Multiple Comparisons/Multiplicity

No statistical comparison is planned in this study.

5.3.4   Examination of Subgroups

Primary efficacy analysis, the key secondary efficacy analysis and analysis of TEAEs by SOC and PT will be performed by the following subgroups: history of seizures (Newly diagnosed epilepsy/Recurrent epilepsy), age group (<18, ≥18 to <65, ≥65), country (Japan/Korea) and sex (Male/Female).

5.3.5   Handling of Missing Data, Dropouts, and Outliers

The details of handling of missing data will be described in section 8.

5.3.6   Other Considerations

Not applicable.

5.4   Efficacy Analyses

All efficacy analyses will be summarized with available data in the clinical database at the data cutoff. The efficacy analysis will be performed based on the mITT Analysis Set, unless otherwise indicated.

5.4.1   Primary Efficacy Analyses

The number (percentage) of subjects with POS who achieved seizure-free during the 26-week Maintenance Period of 4 mg and the exact corresponding 95% confidence interval (CI) will be calculated on the mITT Analysis Set. The primary interest of this study will be to confirm that the exact 95% lower CI is above the pre-specified threshold (ie, 40%). If subjects experience no seizures during the 4 mg Maintenance Period, those will be regarded as seizure-free in this analysis. Otherwise, subjects will be regarded as non-seizure-free.

The definition of seizure-free status will be detailed in the section 8.

SENSITIVITY ANALYSIS

Sensitivity analyses for the primary efficacy analysis will be performed on the ITT Analysis Set.

5.4.2   Secondary Efficacy Analyses

The number (percentage) of subjects with POS who achieved seizure-free during the 26-week Maintenance Period regardless of perampanel dose and the exact corresponding 95% CI will be calculated. To examine if the 95% lower CI exceeds the threshold (ie, 40%) is the key secondary efficacy analysis. The 26-week Maintenance Period mentioned here is the Maintenance Period of the last evaluated dose (ie, 4 or 8mg).

The number (percentage) of subjects with POS who achieved seizure-free during the 52-week treatment of 4 mg (ie, 26-week Maintenance Period of 4 mg and 26-week Extension Phase) and the corresponding 95% CI will be calculated.

The number (percentage) of subjects with POS who achieved seizure-free during the 52-week treatment (ie, 26-week Maintenance Period and 26-week Extension Phase) and the corresponding 95% CI will be calculated. The 26-week Maintenance Period mentioned here is the Maintenance Period of the last evaluated dose.

Median, Q1 and Q3 time to first seizure onset will be estimated by Kaplan-Meier method. The cumulative probability of the event (ie, seizure occurrence) at every 26 weeks will also be calculated. Corresponding 2-sided 95% CIs will also be presented. Kaplan-Meier estimates of the time to event will be plotted over time. The Follow-up Phase will not be included in this analysis. The above analysis will be summarized for the entire study period of 4 mg and the entire study period of the last evaluated dose, respectively.

Time to first seizure onset will be defined as the period from the first dose of study drug in the Maintenance Period of the last evaluated dose to the first seizure onset. The censoring rule for the analysis of time to first seizure onset will be provide in the section 8.

Median, Q1 and Q3 time to withdraw from the study will be estimated by Kaplan-Meier method. The cumulative probability of the event (ie, withdraw from the study) at every 26 weeks will also be calculated. Corresponding 2-sided 95% CIs will also be presented. Kaplan-Meier estimates of the time to event will be plotted over time. The Follow-up Phase will not be the period to be analyzed. The above analysis will be summarized for the entire study period of 4 mg and the entire study period of the last evaluated dose, respectively.

Time to withdraw from the study will be defined as the period from the first dose of study drug in the Maintenance Period of the last evaluated dose to the date of study withdrawal. The censoring rule for the analysis of time to first seizure onset will be provide in the section 8.

5.4.3   Exploratory Efficacy Analyses

The number (percentage) of subjects with POS who achieved seizure-free during the entire study period and the corresponding 95% confidence interval (CI) will be calculated. The above analysis will also be summarized for the period between the Maintenance Period of the last evaluated dose and the date of data cutoff or the date of study discontinuation, whichever comes first.

The number (percentage) of subjects with POS who achieved seizure-free during the 26-week Maintenance Period of 4 mg and the 26-week Maintenance Period of the last

evaluated dose, and each corresponding 95% confidence interval (CI) will be calculated by types of partial seizure (ie, complex partial seizures, complex partial with secondarily generalized seizure, total of the 2 type).

The number (percentage) of subjects with POS who achieved seizure-free during the 52-week treatment of 4 mg (ie, 26-week Maintenance Period of 4 mg and 26-week Extension Phase) and the corresponding 95% CI will be calculated in subjects who had been scheduled to complete 52-week treatment and mITT analysis set. The above analysis will be performed by country, and will also be performed for subjects who completed 26-week maintenance period of 4 mg and did not enter extension phase excluded.

The number (percentage) of subjects with POS who achieved seizure-free during the 52-week treatment (ie, 26-week Maintenance Period and 26-week Extension Phase) and the corresponding 95% CI will be calculated in subjects who had been scheduled to complete 52-Week treatment and mITT analysis set. The 26-week Maintenance Period mentioned here is the Maintenance Period of the last evaluated dose. The above analysis will be performed by country, and will also be performed for subjects who completed 26-week maintenance period of 4 mg and did not enter extension phase excluded.

Median, Q1 and Q3 time to first seizure onset will be estimated by Kaplan-Meier method by country. The cumulative probability of the event (ie, seizure occurrence) at every 26 weeks will be calculated by country. Corresponding 2-sided 95% CIs will also be presented by country. The Follow-up Phase will not be included in this analysis. The above analysis will be summarized for the entire study period of 4 mg and the entire study period of the last evaluated dose, respectively.

Median, Q1 and Q3 time to withdraw from the study will be estimated by Kaplan-Meier method by country. The cumulative probability of the event (ie, withdraw from the study) at every 26 weeks will also be calculated by country. Corresponding 2-sided 95% CIs will also be presented by country. The Follow-up Phase will not be the period to be analyzed. The above analysis will be summarized for the entire study period of 4 mg and the entire study period of the last evaluated dose, respectively.

The number (percentage) of subjects with POS who achieved seizure-free during the 26-week Maintenance Period of 4 mg and the 26-week Maintenance Period of the last evaluated dose, and each corresponding 95% CI will be calculated by Medical History of Simple Partial Seizure Type.

The percent change in seizure frequency of POS per 12 weeks in the Maintenance Period of the last evaluated dose and Extension Phase relative to the baseline will be summarized, respectively. The derivation of seizure frequency will be defined in the section 8.

The change in EQ-5D-5L measurements from baseline to each postbaseline (ie, the Treatment Phase and the Extension Phase) visit, end of treatment phase (the 26-week Maintenance Period of the last evaluated dose) and end of treatment (the entire study of the last evaluated dose) will be summarized.

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

5.5.1 Pharmacokinetic Analyses

The Safety Analysis Set will be used for individual perampanel plasma concentration listings and summaries of perampanel plasma concentrations. Plasma perampanel concentration data at Early transition visit or Early discontinuation visit will not be included in tables and figures for pharmacokinetic analysis. The plasma perampanel concentration data will be excluded from the plasma concentration analysis if the treatment compliance during site visits at Visit 4, 5, 7, 4a, 5a, or 7a where PK blood sampling will be conducted is inadequate for PK evaluation including following cases but not limited to:

- The dose amount is not constant during the last 3 doses of perampanel before PK blood sampling at Visit 4, 5, 7, 4a, 5a, or 7a.
- The perampanel is not administered on consecutive 3 days just before PK blood sampling at Visit 4, 5, 7, 4a, 5a, or 7a.
- Treatment compliance rate during site visits before PK blood sampling at Visit 4, 5, 7, 4a, 5a, or 7a is <80%.

5.5.1.1 Plasma Concentration Analysis

<Concentration>

Plasma concentrations for perampanel will be summarized using summary statistics (n, mean, SD, median, min and max) at the 4 mg Treatment Phase and at the 8 mg Treatment Phase, respectively, by actual dose of the Treatment Phase for all subjects.

Plasma concentrations for perampanel will be summarized using summary statistics (n, mean, SD, median, min and max) at the 4 mg Treatment Phase and at the 8 mg Treatment Phase, respectively, by actual dose of the Treatment Phase for patients who have at least one plasma perampanel concentration data at the 8 mg Treatment Phase (Titration Period and Maintenance Period).

Plasma concentrations of perampanel will be listed for each subject by actual sampling time.

The relationship between plasma concentrations of perampanel at steady state and seizure free status will be analyzed graphically.

- Individual plasma concentrations of perampanel will be displayed by seizure-free status of the 26-week Maintenance Period at week 6 of the Titration Period of 4 mg (Visit 4) and at week 4 of the Titration Period of 8 mg (Visit 4a).
- Last plasma concentrations of perampanel of 4 mg Treatment Phase and 8 mg Treatment Phase will be displayed individually in subjects who have at least 1 each plasma perampanel concentration data of both the Treatment Phase of 4 mg and 8 mg.

5.5.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable

5.6 Safety Analyses

All safety analysis will be performed based on the Safety Analysis Set. Safety data will be summarized using descriptive statistics (e.g., n, mean, standard deviation, median, minimum, maximum for continuous variables; number [percentage] for categorical variables). The analysis window for summarizing the safety parameters by visit will be defined in the section 8.3. The follow-up Phase will not be included in the by visit summary tables, unless otherwise indicates.

5.6.1 Extent of Exposure

The parameters for extent of exposure defined as follows will be summarized for the period of the entire study (treatment phase or the extension phase). Here "dose" is not actual dose but planned dose. Duration of exposure, last dose and mean daily dose will also be performed for the period of treatment phase.

1. Duration of exposure (weeks)
   - From the date of first study drug dosing to the date of last study drug dosing including the Follow-up Phase
2. Maximum dose
   - From the date of first study drug dosing to the date of last study drug dosing not including the Follow-up Phase
3. Last dose
   - From the date of first study drug dosing to the date of last study drug dosing not including the Follow-up Phase
4. Mean daily dose
   - From the date of first study drug dosing to the date of last study drug dosing not including the Follow-up Phase
5. Number of subject-weeks
   - Summation over all subject's exposure durations

Duration of exposure to the study drug for the period of the entire study will be classified by categories of cumulative weeks (ie, > 6 weeks, > 14 weeks, > 26weeks, > 38 weeks, > 52 weeks, > 64 weeks, > 76 weeks, 12-week interval thereafter). The number (percentage) of subjects in each category will also be summarized.

Subject data listings will be provided.

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 version 19.0 or later). Adverse events will be coded to the MedDRA lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) will also be captured in the database.

A treatment-emergent adverse event (TEAE), defined in "8.3 Safety Data Handling", will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

A subject will be counted only once within a SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT.

An overview table, including the incidence of and the number of subjects with TEAEs, Treatment-related TEAEs, severe adverse event, serious adverse events (SAEs), deaths, and TEAEs that led to treatment discontinuation, dose reduction and interruption will be provided.

All analysis of TEAEs by SOC and PT will also be performed for the Treatment Phase and the entire study period (ie, the Treatment Phase or the Extension Phase). The incidence of below events will be reported as the number (percentage) of subjects with TEAEs by MedDRA SOC and PT.

- TEAEs
- TEAEs by maximum severity
- Serious TEAEs
- Non-serious TEAEs
- Treatment-related TEAEs
- Treatment-related TEAEs by maximum severity
- Treatment-related serious TEAEs
- Treatment-related non-serious TEAEs
- TEAEs leading to discontinuation
- TEAEs leading to dose reduction
- TEAEs leading to interruption

In addition, The analysis of TEAEs by SOC and PT will also be performed by dose. The analysis by period will be summarized every 3 months, but a subject will be counted only the first once within a PT throughout the entire period, even if the subject also experienced TEAE in other later period. The analysis by dose will be summarized using final dose for the Treatment Phase and dose at or prior to AE onset dose for the entire study period.

Subject data listings of all deaths, SAEs, AEs leading to death, treatment discontinuation, dose reduction and interruption will be provided. All AE regardless of treatment-emergent or not will be included in the subject data listings.

AEs of special Interest

The following categories of TEAEs of special interest will be summarized by PT.

TEAEs related to suicidality

TEAEs suggestive of abuse potential

TEAEs related to alertness and cognition

TEAEs related to psychosis / psychotic disorders

TEAEs related to hostility/aggression

TEAEs related to status epilepticus/convulsions

TEAEs related to drug-related hepatic disorder abnormalities

Cardiac and ECG TEAEs

A Standardized MedDRA Query (SMQ) will be used to identify relevant terms for each category of TEAEs of special interest.

Name of AEI	SMQ to be used	Range
TEAEs related to suicidality	SMQ for depression and suicide/self-injury	Narrow
TEAEs suggestive of abuse potential	SMQ for drug abuse, dependence and withdrawal	Narrow and Broad Narrow
TEAEs related to alertness and cognition	SMQ for dementia	Narrow and Broad
TEAEs related to psychosis/psychotic disorders	SMQ for psychosis and psychotic disorders	Narrow and Broad Narrow
TEAEs related to hostility/aggression	SMQ for hostility/aggression	Narrow and Broad Narrow
TEAEs related to status epilepticus/convulsions	SMQ for convulsions	Narrow and Broad
TEAEs related to drug-related hepatic disorder abnormalities	SMQ for drug-related hepatic disorders-comprehensive search	Narrow and Broad
Cardiac and ECG TEAEs	SMQs for cardiac arrhythmia terms (including bradyarrhythmias and tachyarrhythmias), arrhythmia related investigations, signs and symptoms; cardiac failure; cardiomyopathy; ischaemic heart disease; and Torsade de pointes/QT prolongation	Narrow and Broad

5.6.3   Laboratory Values

Laboratory results will be summarized using Système International (SI) units. For all quantitative parameters, the actual value and the change from baseline to end of treatment will be summarized using summary statistics. Qualitative parameters will be summarized by number and percentage of subjects, and changes from baseline to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value is below (L), within (N), or above (H) the laboratory parameter's reference range. The result of LNH classification will be provided in a subject data listing.

"Sponsor's Grading for Laboratory Values" will be used to identify subjects with Treatment-emergent markedly abnormal laboratory value (TEMAV).   The number

(percentage) of subjects with TEMAV (markedly abnormal high/low) will be summarized for overall study period including the Follow-up Phase. The TEMAV will be defined in the section 8.3. TEMAV will also be summarized for the Treatment Phase and the entire study period.

The baseline and end of treatment values for quantitative data will be displayed using Box plot.

Subject data listings will be provided.

5.6.4   Vital Signs

Summary statistics for vital signs parameters (diastolic and systolic blood pressure, pulse, Respiratory rate, and temperature) and weight, and changes from baseline to end of treatment will be presented.

The baseline and end of treatment values will be displayed using Box plot.

Subject data listings will be provided.

5.6.5   Electrocardiograms

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

Subject data listings will be provided.

5.6.6   Other Safety Analyses

No other safety analyses are planned for this study.

5.7   Other Analyses

No other analyses are planned for this study.

6   INTERIM ANALYSES

No interim analyses are planned for this study.

7   CHANGES IN THE PLANNED ANALYSES

A summary of all major additions, changes and deletions in the planned analyses described in the protocol will be provided in this section.

There was a major addition.

·   Add the descriptuion of statistical analysis and data handling if the primary endpoint is successfully achieved according the protocol amendment (section 3).

There were minor additions, changes and deletions other than the avove.

·   Summarization of "The percent change in seizure frequency of POS per 28 days" has been changed to per 12 weeks from per 28 days bacause considering baseline collection period in the clinical study protocol (section 5.1.3 and 5.4.3).

·   Summarization of "Treatment Compliance" has been added (section 5.2.6).

·   Summarization of "The number (percentage) of subjects with POS who achieved seizure-free during the 52-week treatment of 4 mg (ie, 26-week Maintenance Period of 4 mg and 26-week Extension Phase)" has been added (section 5.4.3).

·   Summarization of "The number (percentage) of subjects with POS who achieved seizure-free during the entire study period and the corresponding 95% confidence interval (CI)" has been added (section 5.4.3).

·   Summarization of "TEAEs by SOC and PT by period, and by dose" has been added (section 5.6.2).

·   Summarization of "TEAEs of special interest" has been added (section 5.6.2).

·   Summarization of "the actual value and the change from baseline to each postbaseline visit by visit" has been changed to "the actual value and the change from baseline to end of treatment will be summarized" (section 5.4.3).

·   Summarization of "shift tables that compare the baseline LNH classification to the LNH classification at each postbaseline visit" has been deleted (section 5.4.3).

·   Summarization of "Summary statistics for vital signs parameters and weight, and changes from baseline will be presented by visit" has been changed to "Summary statistics for vital signs parameters and weight, and changes from baseline to end of treatment will be presented" (section 5.6.4).

·   Summarization of "Shift tables will present changes from baseline in ECG interpretation by visit" has been changed to "Shift tables will present changes from baseline to end of treatment in ECG interpretation" (section 5.6.5).

·   The cases when the plasma perampanel concentration data will be excluded from the calculation of summary statistics have been added (section 5.5.1).

·   "The relationship between plasma concentrations of perampanel at steady state and seizure free status will be analyzed graphically." has been added (section 5.5.1.1).

·   "Plasma perampanel concentration data at Early transition visit or Early discontinuation visit will not be included in tables and figures for pharmacokinetic analysis." has been added (section 5.5.1).

·   "Summarization of plasma concentrations for perampanel at the 4 mg Maintenance Period and at the 8 mg Maintenance Period" has been changed to "Summarization of plasma concentrations for perampanel at the 4 mg Treatment Phase and at the 8 mg Treatment Phase" (section 5.5.1.1).

- Summarization of "seizure-free rate, time to first seizure onset and time to withdraw from study during the 52-week maintenance period of 4 mg and the 52-week maintenance period of the last evaluated dose by country" has been added (section 5.4.3).

- Summarization of "seizure-free rate during the 26-week maintenance period of 4 mg and the 26-week maintenance period of the last evaluated dose by medical history of simple partial seizure type" has been added (section 5.4.3).

8   DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

The data will be handled as follows. The sponsor will determine how to handle all data prior to data base lock.

8.1   General Data Handling

Definition of Baseline data

Baseline is defined as the last non-missing value observed on or prior to the first study drug dispensing date.

Definition of Change from Baseline, Percent Change from Baseline

・Change from baseline = Post-baseline value - Baseline value

・% Change from baseline = (Change from baseline / Baseline value) * 100

For any baseline value of 0, the subject's corresponding percent change from baseline will not be included in the summary statistics table.

Handling of data not within specified periods or within the follow-up period

Data obtained in the Follow-up Phase except for AE, Duration of Exposure and TEMAV will not be included in the summary tables. These data will be presented in the subject data listing.

Definition of End of Treatment

End of treatment phase during the 26-week Maintenance Period of the last evaluated dose is defined as the closest value observed on or post to the disposition date in the 26-week Maintenance Period of the last evaluated dose. If there is no adequate data, the closest value observed prior to the disposition date is selected.

End of treatment during the entire study (treatment phase or extension phase) is defined as the closest value observed on or post to the last disposition date in the entire study. If there is no data, the closest value observed prior to the last disposition date is selected.

8.2   Efficacy Data Handling

Definition of Seizure-Free status

The definition of seizure-free for perampanel 4 mg will be as follows;

The subjects who completed the 4 mg Treatment Phase with no seizures will be treated as Seizure-Free status. The subjects who had any seizures will also be treated as Seizure-Free status only if the seizure(s) appeared after the Day 183 (ie, the target visit date of the 26th week of 4 mg Maintenance Period). Day 1 is the date of first dose of study drug in the 4 mg Maintenance Period. Otherwise, subjects will be regarded as non-Seizure-Free for the evaluation of perampanel 4 mg.

The definition of seizure-free for perampanel total (regardless of doses) will be as follows;

The subjects who completed the Treatment Phase of the last evaluated dose (ie, 4 or 8 mg) with no seizures will be treated as Seizure-Free status. The subjects who had any seizures will also be treated as Seizure-Free status if the seizure(s) appeared after the Day 183 (ie, the target visit date of the 26th week of Maintenance Period for the last evaluated dose). Day 1 here is the date of first dose of study drug in the Maintenance Period of the last evaluated dose. If subjects who were titrated up to 8 mg but down-titrated to 6 mg due to tolerability issue continued the study and completed the Maintenance Period with no seizure, those will also be treated as Seizure-Free status. Otherwise, subjects will be regarded as non-seizure-free.

Handling of seizure frequency

·   **Baseline**

Baseline seizure frequency will be composed of the record based on the interview at visit 1 and the dispensed diary. Baseline seizure frequency will be calculated as the number of seizures per 12 weeks (see below).

$$\frac{\text{Sum of seizures during baseline}}{\text{the number of days (84 days plus the study days during the Pretreatment Phase)}} \times 84$$

Study days during the Pretreatment Phase will be the period between the date of obtaining informed consent and the date of first study drug dosing (ie, the date of study drug dispensing for visit 2).

·   **Post-Baseline (Maintenance Period and Extension Phase)**

Post-baseline seizure frequency will be composed of the dispensed diary. Post-baseline seizure frequency will be calculated as the number of seizures per 12 weeks (see below). The Follow-up Phase will not be included in this analysis.

$$\frac{\text{Sum of seizures during post-baseline}}{\text{the number of study days during post-baseline}} \times 84$$

Study days during the post-baseline of maintenance period will be the period between the date of study drug dispensing for the Maintenance Period of the last evaluated dose and the disposition data in maintenance period of the last evaluated dose. Study days during the post-baseline of extension phase will be the period between the disposition data in maintenance period of the last evaluated dose and the date of data cutoff or the date of study discontinuation, whichever comes first.

the data on seizure expression that obtained during the Titration Period and the Follow-up Phase will be presented only in the subject data listing.

Handling of missing data

• **Seizure frequency**

If subjects have a missing seizure count in any of each seizure type (ie, simple partial with motor signs, simple partial without motor signs, complex partial, and complex partial with secondarily generalized seizure) for each unique diary record, the overall seizure frequency for that record will be handled as missing data. Similarly, if complex partial and/or complex partial with secondarily generalized seizure are missing for each unique diary record, then complex partial seizure plus secondary generalized seizure frequency will be handled as a missing data.

• **EQ-5D-5L**

No imputation will be performed for the missing value.

Censoring rules for time to event analysis

1. The censored rule for the analysis of time to first seizure onset will be provided in the following table. If subjects met multiple censoring criteria, the censoring date will be the earliest date of them.

No.	Situation	Date of Event or Censoring	Outcome
1	Seizure onset	Date of the first seizure onset	Event
2	Withdraw from the study	Date of study withdrawal	Censored
3	Ongoing at the data cutoff (with no seizure)	Date of data cutoff (each subject's final non-missing assessment date)	Censored

2. The censored rule for the analysis of time to study withdrawal will be provided in the following table. If subjects met multiple censoring criteria, the censoring date will be the earliest date of them.

No.	Situation	Date of Event or Censoring	Outcome
1	Withdraw from the study	Date of study withdrawal	Event
2	Ongoing at the data cutoff	Date of data cutoff (each subject's final non-missing assessment date)	Censored

8.3   Safety Data Handling

Definition of derived variables for extent of exposure

The derivation rule will be presented in the section 5.6.1.

Treatment-emergent adverse event

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during time from the first dose of study drug to the last visit or 28 days after the subject's last dose, whichever comes later, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

TEMAV (Treatment-Emergent Markedly Abnormal Value)

A TEMAV is defined as follows:

- For a phosphate, if the post baseline grade increases from baseline and the post baseline grade is greater than or equal to 3 then a value will be determined to be a TEMAV.

- For all other parameters presented in the section 13.1, if the post baseline grade increases from baseline and the post baseline grade is greater than or equal to 2 then a value will be determined to be a TEMAV.

If the grade of baseline value is missing, then, if the grade of post-baseline value is Grade 2 or higher, the laboratory values will be classified into treatment emergent markedly abnormal.

Laboratory values, Vital signs, ECGs

For the end of treatment, the closest value measured on or post to the last disposition date in the Treatment Phase and the entire study period will be imputed using Last Observation Carried Forward (LOCF) method. If there is no adequate data, the closest value observed prior to the disposition date is selected.

Handling of below lower quantification values in laboratory results

In the cases where laboratory result contains below lower quantification (BLQ) value, it will be replaced to the lower limit value of quantification (LLOQ) for summary tables.

8.4   Pharmacokinetic Data Handling

8.4.1   Lower Limit of Quantification of Perampanel Plasma Concentration

The LLOQ of perampanel plasma concentrations is 0.250 ng/mL.

8.4.2   BLQ Handling for Calculation of PK Parameters

Not applicable

8.4.3   BLQ Handling for Developing Concentration-Time Profiles

Not applicable

8.4.4   Handling of Anomalous Concentration Values

The handling of anomalous concentration values will follow the guidance in the Eisai manual 302-104.00-MNL for non compartmental PK analysis (Version Date: 08 Jun 2016).

8.4.5   General Rules for Presentation of Drug Concentrations and PK Parameters

When presenting individual/raw (raw, hereafter) values and summary statistics, the following rule will be applied: for drug concentrations, all summary statistics (mean, median, and standard deviation [SD]) will have 3 significant digits.

Variable	Unit	N	Digit rule	Raw/ Minimum/ Maximum	Mean Median	SD	Geometric Mean	CV (%)
Perampanel concentration	ng/mL	X	Significant digits	3	3	3	-	-

9   PROGRAMMING SPECIFICATIONS

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

10   STATISTICAL SOFTWARE

All statistical analyses will be conducted by the designee, using validated standard programs or double programming. For analyses needed in data review, single programming will be used.

All statistical analyses will be performed using SAS (version 9.2 or later). As necessary, other validated statistical software will also be used.

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

- Arroyo S, Dodson WE, Privitera MD, Glauser TA, Naritoku DK, Dlugos DJ, et al. Randomized dose-controlled study of topiramate as first-line therapy in epilepsy. Acta Neurol Scand. 2005;112:214–22.
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- Heller AJ, Chesterman P, Elwes RD, Crawford P, Chadwick D, Johnson AL, et al. Phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed adult epilepsy: a randomised comparative monotherapy trial. J Neurol Neurosurg Psychiatry. 1995;58:44–50.

- Kaneko S, Chan R, Nakatsu T, Yoshida K. A Phase III, multicenter, randomized, open-label study of levetiracetam monotherapy in Japanese patients with partial onset seizures. J.Jpn.Epil.Soc. 2015;32:519-32.

- Mikkelsen B, Berggreen P, Joensen P, Kristensen O, Køhler O, Mikkelsen BO. Clonazepam (Rivotril®) and Carbamazepine (Tegretol®) in Psychomotor Epilepsy: A Randomized Multicenter Trial. Epilepsia. 1981;22:415–20.

13 APPENDICES

13.1 Sponsor's Grading for Laboratory Values

The following table of Eisai's Grading for Laboratory Values is based on 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	N/A
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	N/A
ALP	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bicarbonate, serum-low	<LLN – 16 mmol/L	11 – 15 mmol/L	8 – 10 mmol/L	<8 mmol/L
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	>ULN – 160 mg/dL >ULN – 8.9 mmol/L	>160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L	>500 mg/dL; >27.8 mmol/L
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
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

Sponsor's Grading for Laboratory Values

	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	N/A	<3.0 – 2.5 mmol/L	<2.5 mmol/L
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	>160 mmol/L
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L
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
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L	N/A	N/A	>10 mg/dL >0.59 mmol/L

ALP = alkaline phosphatase, 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).