Revision History

Revisions to Version v6.0 **New version/date: Version 7.0/31 Oct 2019**		
Change	**Rationale**	**Affected Protocol Section(s)**
Extended the study period	To continue the study until perampanel monotherapy is available in Korea.	Synopsis – Study Period and Phase of Development

Revisions to Version v5.0 **New version/date: Version 6.0/22 Feb 2019**		
Change	**Rationale**	**Affected Protocol Section(s)**
Added "End of Study visit" and related description including procedure, measurement and schedule	Clarification	Synopsis – Study Design Section 9.1 Section 9.1.3 Extension phase Section 9.1.4 Follow-up phase Section 9.5.2 – Table 5

Revisions to Version v4.0 **New version/date: Version 5.0/05 Jul 2018**		
Change	**Rationale**	**Affected Protocol Section(s)**
Added "Analysis at primary endpoint achievement"	To conduct analysis if the primary endpoint is achieved.	Section 9.7.1.6.4

Revisions to Version v3.0 **New version/date: Version 4.0/21 Feb 2018**		
Change	**Rationale**	**Affected Protocol Section(s)**
Added "Study drug compliance" and "Return unused medication" at Visit 2a	To correct an error/missing items in table 4	Section 9.5.2 – Table 4
Revised footnote "e", such that at Visit 4a, if a subject is down-titrated to 6 mg due to intolerability after up-titrated to 8 mg, the subject will enter the Maintenance Period with 6 mg. Removed extra words "and remain seizure free " due to a mistake in writing	To correct an error, to keep a consistency	Section 9.5.2 – Table 4

Revisions to Version v3.0 **New version/date: Version 4.0/21 Feb 2018**		
Change	**Rationale**	**Affected Protocol Section(s)**
Grammatical, typographical, and formatting changes were also made.	Document quality.	Throughout the document

Revisions to Version v2.0 **New version/date: Version 3.0/04 Dec 2017**		
Change	**Rationale**	**Affected Protocol Section(s)**
Correct the name of ICH	To correct typographic error	Title page – GCP statement Investigator signature page
Added the exclusion criteria #24, for subject who is diagnosed with dementia	To clarify that dementia patients are "not eligible" in this study.	Synopsis – Exclusion Criteria Section 9.3.2
Added antidementia drugs in prohibited concomitant therapy	To clarify that concomitant use of antidementia drug is prohibited.	Synopsis – Prohibited concomitant drugs Section 9.4.7.1.1
Expanded the prohibited concomitant therapy to neuromodulation therapy (including vagal nerve stimulation [VNS] and transcranial magnetic stimulation)	To clarify that concomitant neuromodulation therapy without limiting VNS is prohibited.	Synopsis – Prohibited concomitant therapy Section 9.4.7.1.2
Removed "eg." from the text of Urine Drug Test	To correct typographic error	Section 9.5.1.2.3

Revisions to Version v1.0 **New version/date: Version 2.0/05 Jul 2017**		
Change	**Rationale**	**Affected Protocol Section(s)**
Correct the name of ICH	To correct typographic error	Title page – GCP statement List of abbreviations and definitions of terms Section 5.1 Section 5.2 Investigator signature page
Revised the text for subject discontinuation at extension phase, such that if subjects need to take	To clarify the description of the subject	Section 9.1.3

Revisions to Version v1.0 New version/date: Version 2.0/05 Jul 2017		
Change	**Rationale**	**Affected Protocol Section(s)**
other antiepileptic drugs (AEDs) or withdraw perampanel because of insufficient efficacy or tolerability issue of perampanel by the investigator's judgement, they will discontinue the study	discontinuation at extension phase	
Revised the exclusion criteria #9, such that evidence of clinically significant active hepatic disease	To correct miss description on the exclusion criteria #9 assuming add-on therapy with concomitant enzyme-inducer drug(s).	Section 9.3.2
Revised the exclusion criteria #15, such that subjects who have used intermittent rescue medication on 2 or more occasions within 4 weeks before the pretreatment phase	To clarify the exclusion criteria for previous use of intermitted rescue medication (not limited to benzodiazepines)	Section 9.3.2
Added the text "and return unused medication" in footnote "c" for when a taper is provided after discontinuation in follow-up phase	To correct an error/missing items in table 3	Section 9.5.2 – Table 3
Added the text "in case of the local laboratory analysis, the measurement of bicarbonate and magnesium are not mandatory at visit 1, and after that should be conducted as scheduled" in footnote "i"	To correct an error/missing items in table 3	Section 9.5.2 – Table 3
Added the footnote "p" that if a taper is decided based on the judgment of the investigator, dispensing the study drug should be needed at early discontinuation visit	To correct an error/missing items in table 3	Section 9.5.2 – Table 3
Added early transition visit with required procedures/assessments	To correct an error/missing items in table 4	Section 9.5.2 – Table 4
Added the footnote "k" that the visit for transition from the 8 mg treatment phase to the extension phase before completion of the 8 mg treatment phase at early transition visit	To correct an error/missing items in table 4	Section 9.5.2 – Table 4

Revisions to Version v1.0 **New version/date: Version 2.0/05 Jul 2017**		
Change	**Rationale**	**Affected Protocol Section(s)**
Added the footnote "j" that if a taper is decided based on the judgment of the investigator, dispensing the study drug should be needed at early discontinuation visit	To correct an error/missing items in table 4	Section 9.5.2 – Table 4
Added the text "return unused medication" in footnote "c" for when a taper is provided after discontinuation in follow-up phase	To correct an error/missing items in table 4	Section 9.5.2 – Table 4
Added the footnote "a" on follow-up phase to indicate that visit to be done within ±7 days of the schedule	To correct an error/missing items in table 5	Section 9.5.2 – Table 5
Added the footnote "g" that if a taper is decided based on the judgment of the investigator, dispensing the study drug should be needed, for early discontinuation visit	To correct an error/missing items in table 5	Section 9.5.2 – Table 5
Added the text "Return unused medication is needed." in the foot note "b"	To correct an error/missing items in table 5	Section 9.5.2 – Table 5
Added "Dispense subject diary" at early discontinuation visit	To correct an error/missing items in table 5	Section 9.5.2 – Table 5
Revised the text for adverse events, such that 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.	To correct typographic error	Section 9.7.1.8.2 – Adverse events
Removed extra text, such that descriptive statistics for ECG parameters and changes from baseline will be presented by visit	To correct an error/missing items in table 5	Section 9.7.1.8.5 – Electrocardiograms

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2007-J000-342
Study Protocol Title:	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)
Sponsor:	Eisai Co., Ltd. 4-6-10 Koishikawa, Bunkyo-Ku, Tokyo 112 8088 JP
Investigational Product Name:	E2007/Fycompa® (perampanel)
Indication:	Partial onset seizures
Phase:	3
Approval Date:	V1.0 03 Apr 2017 (original protocol) V2.0 05 Jul 2017 (revised protocol) V3.0 04 Dec 2017 (revised protocol) V4.0 21 Feb 2018 (revised protocol) V5.0 05 Jul 2018 (revised protocol) V6.0 22 Feb 2019 (revised protocol) V7.0 31 Oct 2019 (revised protocol)
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2007

Name of Active Ingredient: Perampanel

Study Protocol Title

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)

Sites

Japan and South Korea

Study Period and Phase of Development

Study Period: April 2017 to November 2020

Phase: Phase 3

Objectives

Primary Objective:

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

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

Exploratory Objectives:

- 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)

Study Design

This study will consist of 3 phases: Pretreatment Phase, Treatment Phase (Titration Period, Maintenance Period) and Extension 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 Titration Period and the Maintenance Period of 4 mg, and the Titration Period and the Maintenance Period of 8 mg, if subjects require higher dose.

[4 mg Titration and Maintenance Period]

In the 4 mg Titration Period (6 weeks), subjects will initiate 2 mg QD of perampanel for 2 weeks and then will be up-titrated to 4 mg QD and will continue for 4 weeks. If subjects have no safety issues at the end of the Titration Period, they will start the 4 mg Maintenance Period for 26 weeks.

If subjects experience seizures during the 4 mg Maintenance Period, the investigator will end the 4 mg Maintenance Period and judge the transition to the 8 mg Titration Period based on the subject's tolerability and safety. If subjects could not continue 4 mg dosing due to intolerable adverse event during the 4 mg Maintenance Period, they will discontinue the study.

During the 2 weeks of Weeks 3 and 4 in the 4 mg Titration Period, if subjects are suspected to have tolerability issues for 4 mg dosing due to occurrence of adverse events, 2 mg QD can be administered in accordance with the investigators' discretion. In that case, subjects will visit the investigational site via unscheduled visit within 4 weeks after starting study treatment and will be up-titrated to 4 mg QD (for subjects who has continued 4 mg QD, occurrence of AEs will be confirmed via telephone). All subjects will continue 4 mg QD during the 2 weeks of Weeks 5 and 6. If subjects could not continue 4 mg QD due to intolerable adverse event, they will discontinue the study.

[8 mg Titration and Maintenance Period]

In the 8 mg Titration Period (4 weeks), subjects will be administered 6 mg QD of perampanel for 2 weeks and then will be up-titrated to 8 mg QD and will continue for 2 weeks. If subjects have no safety issues at the end of the Titration Period, they will start the 8 mg Maintenance Period for 26 weeks.

If subjects don't tolerate 8 mg administration of perampanel, they will be able to down-titrate to 6 mg in accordance with the investigators' discretion. After the down-titration, subjects could continue the study with 6 mg QD.

If subjects experience the occurrence of seizures or could not continue 8 mg (or 6 mg) dosing due to intolerable adverse event during the 8 mg Maintenance Period, they will end the Treatment Phase.

[Extension Phase]

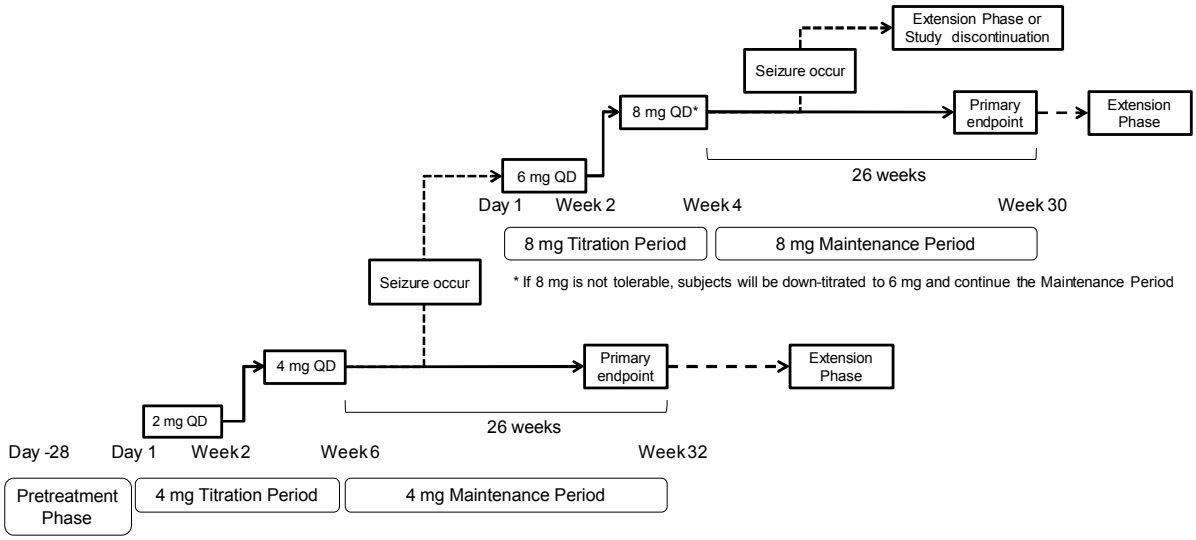
When subjects complete the Treatment Phase and agree to continue receiving the perampanel monotherapy, they could enter the Extension Phase. Subjects who complete the 26-week Maintenance Period will continue the last dose of the Maintenance Period. Subjects who end the Treatment Phase due to insufficient efficacy or safety issue before the completion of the 26-week Maintenance Period will adjust their appropriate dose (within 4 – 8 mg of perampanel) and continue the Extension Phase. Subjects will be allowed to adjust within 2 – 8 mg of perampanel with investigators' consideration for their condition of the seizures and/or tolerability. During whole study period, the maximum dose of perampanel is 8 mg QD. The dose will be increased at intervals of 1 week or more in increments of 2 mg.

If subjects need to take other antiepileptic drugs (AEDs) or withdraw perampanel because of insufficient efficacy or tolerability issue of perampanel by the investigator's judgement, they will discontinue the study.

Once perampanel monotherapy is approved in each country, an End of Study Visit should be conducted promptly, and the subject would have to switch to the commercial product. If a subject does not switch to the commercial product promptly, an End of Study Visit and a Follow-up Visit should be conducted for the subject.

Subjects who will finish or discontinue the study will conduct the follow-up visit 4 weeks after withdrawal of perampanel. Follow-up Visit is not required for subjects who will be switching to the commercial product and attend an End of Study Visit.

The study design is shown below.



Number of Subjects

Eighty subjects with POS who are untreated with any AED(s)

Inclusion Criteria

1. Be considered reliable and willing to be available for the study period and are able to record seizures and report adverse events (AEs) himself/herself or have a caregiver who can record seizures and report AEs for them
2. Male or female aged between 12 and 74 years old
3. Subjects who are newly diagnosed or recurrent epilepsy and have experienced at least 2 unprovoked seizures separated by a minimum of 24 hours in the 1 year prior to the Pretreatment Phase, of which, at least 1 unprovoked seizure (but below 20 seizures) occurred in the 12 weeks prior to the Pretreatment Phase. For subjects with recurrent epilepsy, they must have relapsed at least 2 years after the end of the last AED treatment.
4. Subjects who have excluded the progressive CNS abnormality occurring seizures by CT or MRI conducted within 1 year before the Pretreatment Phase
5. Subjects who have had a diagnosis of epilepsy with partial seizures with or without secondarily generalized seizures according to the International League Against Epilepsy (ILAE) Classification of Epileptic Seizures (1981). Diagnosis should have been established by clinical history and an electroencephalogram (EEG) that is consistent with localization-related epilepsy; normal interictal EEGs will be allowed provided that the subject meets the other diagnosis criterion (ie, clinical history).

Exclusion Criteria

Note: In this protocol, 1 month refers to 28 days (4 weeks).

1. Subjects who present only simple partial seizures without motor signs

2. Subjects who have seizure clusters where individual seizures cannot be counted
3. Subjects who present or have a history of Lennox-Gastaut syndrome
4. Subjects who have a history of status epilepticus within 1 year prior to Day 1 of the Treatment Phase
5. Subjects who have a history of psychogenic non-epileptic seizures within 5 years prior to Day 1 of the Treatment Phase
6. Subjects who have a history of suicidal ideation/attempt within 5 years prior to Day 1 of Treatment Phase
7. Subjects who present clinically problematic psychological or neurological disorder(s)
8. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments
9. Evidence of clinically significant active hepatic disease.
10. A prolonged QTcF interval (>450 ms [2 or 3 times]) as demonstrated by a repeated (3 times) electrocardiogram (ECG)
11. Subjects who have a history of receiving any AEDs (except for AEDs used as rescue treatment), antipsychotics or anti-anxiety drugs within 12 weeks prior to the Pretreatment Phase
12. Subjects who have not used a stable dose of antidepressant in the 12 weeks prior to the Pretreatment Phase, if they treat
13. Subjects who have a history of any type of surgery for brain or central nervous system within 1 year prior to the Pretreatment Phase
14. Subjects who have a history of receiving any AED (including AED used as rescue treatment) for more than 2 weeks in total within 2 years prior to the Pretreatment Phase
15. Subjects who have used intermittent rescue medication on 2 or more occasions within 4 weeks before the Pretreatment Phase (1 to 2 doses over a 24-hour period considered one-time rescue)
16. Subjects who have a history of receiving any AED polytherapy
17. Subjects who experienced treatment with perampanel
18. Subjects who have had non-constant ketogenic diet within 4 weeks before the Pretreatment Phase
19. Subjects who have a history of drug or alcohol dependency or abuse within the last 2 years before the Pretreatment Phase
20. Subjects who have had multiple drug allergies or a severe drug reaction to an AED(s), including dermatological (eg, Stevens-Johnson syndrome), hematological, or organ toxicity reactions
21. Females who are breastfeeding or pregnant in the Pretreatment Phase (as documented by a positive beta-human chorionic gonadotropin [β-hCG] test)
22. Females of childbearing potential who:
    - Within 28 days before the start of the Pretreatment Phase, did not use a highly effective method of contraception, which includes any of the following:
        - total abstinence (if it is their preferred and usual lifestyle)
        - an intrauterine device or intrauterine hormone-releasing system (IUS)
        - a contraceptive implant

- an oral contraceptive (with additional barrier method) (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
- have a vasectomized partner with confirmed azoospermia.

- Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

It is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).

23. Subjects who have participated in a study involving administration of an investigational drug or device within 4 weeks before Visit 1, or within approximately 5 half-lives of the previous investigational compound, whichever is longer.
24. Subject who is diagnosed with dementia

Study Treatment

Test drug

Perampanel is orally administered once a day before bedtime.

Comparator drug

Not applicable.

Duration of Treatment

Pretreatment Phase: maximally 4 weeks

Treatment Phase: maximally 62 weeks (4 mg Titration Period: 6 weeks, 4 mg Maintenance Period: 26 weeks, 8 mg Titration Period: 4 weeks, 8 mg Maintenance Period: 26 weeks)

Extension Phase: 3 or less months from the date of approval of perampanel monotherapy in each country

Concomitant Drug/Therapy

1. Concomitant Medication

(1) Prohibited Concomitant Drug

Throughout the study period, concomitant use of the following drugs is prohibited (till the visit at the time of early discontinuation for discontinued subjects).

- Other AEDs (if emergency care is needed, eg, status epilepticus, uncontrolled seizures, or clusters, occasional use (prn) of other AEDs including diazepam, phenytoin will be permitted as rescue treatment)
- The following drugs or food known to induce CYP3A (not limited to these drugs or food). If one of these drugs was being used at enrollment, washout of the drug will start at this time point. The duration of washout of the drug must be at least 2 weeks.

[carbamazepine, enzalutamide, mitotane, phenytoin, phenobarbital, amobarbital, secobarbital, rifabutin, rifampicin, food containing St. John's Wort (hypericum perforatum), bosentan, efavirenz, etravirine, modafinil, armodafinil, rufinamide, nevirapine, oxcarbazepine, and glucocorticoid (except for topical use)]

- Antipsychotics
- Antianxiety drugs
- Benzodiazepine hypnotic
- Other investigational agents
- Antidementia drugs

(2) Restricted Concomitant Drug

The dosing regimen of the following drugs must not be altered, newly introduced, or discontinued throughout the study. Only for discontinued subjects, this does not apply after the visit at early discontinuation.

- Antidepressants

2. Concomitant Therapy

(1) Prohibited Concomitant Therapy

The following therapies must not concurrently be implemented during the study.

- Brain surgery
- Medical device under clinical trial
- Neuromodulation therapy (including vagal nerve stimulation [VNS] and transcranial magnetic stimulation)

(2) Restricted Concomitant Therapy

The following therapy must not be changed or discontinued during the study. Only for discontinued subjects, this does not apply after the visit at early discontinuation.

- Ketogenic diet

Assessments

1. Efficacy Endpoint

(1) Primary Endpoint

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

(2) Secondary Endpoints

- 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

(3) Exploratory Endpoints

- 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 28 days in the Maintenance Period and Extension Phase relative to the Pretreatment Phase
- Change in EQ-5D-5L measurements in the 26-week Maintenance Period and at Week 26 of the Extension Phase relative to the Pretreatment Phase

2. Safety Assessment

- Adverse events (AEs), prior and concomitant medications, clinical laboratory evaluations (biochemistry, hematology, urinalysis), vital signs, weight, and 12-Lead electrocardiogram (ECG)

3. Pharmacokinetic Assessment

- Plasma concentrations of perampanel

Bioanalytical Methods

The plasma perampanel concentration will be quantified by a validated analytical method.

Statistical Methods

1. Analysis Sets

(1) 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.

(2) 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.

(3) 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.

2. Efficacy Analyses

Primary Efficacy Analysis

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

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 corresponding 95% CI will be calculated on the mITT Analysis Set. To examine if the 95% lower CI exceeds the threshold (ie, 40%) is the key secondary efficacy analysis.

The number (percentage) of subjects in the mITT population 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% confidence interval (CI) will be calculated.

Median time to first seizure onset will be estimated by Kaplan-Meier method. Time to first seizure onset will be defined as the time from the first date of Maintenance Period to the date of first seizure

onset during the Maintenance Period. Subjects who withdraw from the study before first seizure onset will be censored at the time of study discontinuation.

Median time to withdraw from the study will be estimated by Kaplan-Meier method. Time to withdraw from the study will be defined as the time from the first date of Maintenance Period to the date of discontinuation from the study. Subjects who are ongoing at the data cutoff will be censored at the time of data cutoff.

Exploratory Efficacy Analyses

The number (percentage) of subjects with POS who achieved seizure-free during the 26-week Maintenance Period and the corresponding 95% confidence interval (CI) will be calculated by types of partial seizure.

The percent change in seizure frequency of POS per 28 days in the Maintenance Period and Extension Phase relative to the Pretreatment Phase will be summarized.

The change in EQ-5D-5L measurements from baseline to each postbaseline visit will be summarized.

3. Safety Analyses

All safety analyses will be performed based on the Safety Analysis Set.

The AE verbatim descriptions (investigator terms from the CRF) will be coded to system organ class (SOC) and preferred terms (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). The number (percentage) of subjects with treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) will be summarized by MedDRA SOC and PT. The incidence of TEAEs will be summarized by severity (mild, moderate, or severe). The TEAEs will be summarized for the Treatment Phase and the entire study period (ie, the Treatment Phase or the Extension Phase). The changes from baseline will be summarized by visit using descriptive statistics for continuous variables (eg, laboratory values, vital sign, weight, and ECG parameter). Categorical variables will be summarized as number (percentage) of subjects by visit.

4. Pharmacokinetic Analysis

The Safety Analysis Set will be used for pharmacokinetic analysis. Summary statistics of plasma perampanel concentrations will be obtained by visit.

Interim Analyses

No interim analysis is planned for this study.

Sample Size Rationale

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.

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.

3 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

4 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 Council for Harmonisation
IEC	independent ethics committee
ILAE	International League Against Epilepsy

Abbreviation	Term
IRB	institutional review board
ITT	intent-to-treat
IUPAC	International Union of Pure and Applied Chemistry
IUS	intrauterine hormone-releasing system
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LLT	lowest level term
LNH	low/normal/high
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
QT	time from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
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

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Council for Harmonisation (ICH) E6 (Good Clinical Practice [GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in Clinical Research Associate [CRA], change of telephone number). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator, the head of the medical institution, and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Pharmaceuticals for Human Use
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject or guardian/legally authorized representative the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable representative should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF (eg, Pretreatment Phase) before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

If an underage subject is able to understand the study participation, the investigator should explain the nature of the study etc. to the subject with informed assent document prepared separately from the informed consent document and obtain a signature. If a subject is unable to sign the ICF, the investigator should confirm that the subject has orally consented to the subject's participation in the study and record it on the consent form.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject or the subject's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 45 investigational sites in Japan and South Korea.

The name and telephone and fax numbers of the sponsor's responsible medical officer and other contact personnel at the sponsor are listed in the Investigator Study File provided to each site.

7 INTRODUCTION

7.1 Indication

Epilepsy is a common, serious neurological disorder with an overall prevalence of 0.5% to 1%. Epilepsy is characterized by the spontaneous recurrence of seizures and requires long term, often life-long, pharmacological management. There are 2 major types of seizures: generalized and partial (focal) seizures. The most frequent type is partial seizures. Subjects suffering from partial seizures often have poor seizure control. Uncontrolled seizures lead to a wide variety of medical consequences (eg, severe trauma due to seizures, sudden death, depression, intermittent psychotic disorders). In addition, uncontrolled seizures lead to significant lifestyle limitations and social handicaps (eg, loss of driving privileges, difficulties getting and maintaining a job).

The goal of epilepsy treatment is to achieve a long term seizure-free status without adverse effects (Walker, et al., 1996). In the patients with untreated epilepsy, 47% became seizure-free with the first AED, 13% seizure free with the second AED, and only 4% are seizure free with the third AED or multiple AEDs (Kwan, et al., 2000). Monotherapy has been promoted as the ideal in epilepsy treatment because of reduced adverse effects, better compliance, lower cost and avoids drug interactions.

Recent epidemiological studies in the Europe and the United States have consistently shown that, the incidence of the epilepsies in children is decreasing, on the other hand the incidence in elderly is increasing. Partial onset seizures (POS) are the most common type of seizures in elderly-onset. Stroke is the leading cause of POS accounting for up to 30 to 40% of newly diagnosed seizures among the elderly. By the reason that elderly epilepsy patients are more likely to develop seizure recurrence than are younger adults, treatment should be started after a single unprovoked seizure.

7.1.1 Current Therapeutic Options

Current treatment guidelines recommend monotherapy for initial management approach in epilepsy. In the updated guideline of International League Against Epilepsy (ILAE) (Glauser, et al., 2013), carbamazepine, phenytoin, levetiracetam, and zonisamide are recommended as initial monotherapy for adults with partial onset seizures with level A efficacy/effectiveness evidence. In the guideline for Epilepsy Treatment by Japanese Society of Neurology (2014), carbamazepine is considered as first-line treatment, and phenytoin, zonisamide, and valproic acid are is considered as second-line treatment.

7.1.2 E2007/perampanel

E2007 (perampanel; Fycompa®) is a first-in-class noncompetitive and highly selective α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist discovered and developed by Eisai.

Perampanel tablets were approved for marketing as an adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients aged

12 years and older in the European Union (EU) and the United States in 2012, and in more than 50 countries subsequently. Perampanel was also approved for marketing as an adjunctive therapy for the treatment of primary generalized tonic clonic seizures in patients with epilepsy aged 12 years and older in the EU and the United States in Jun 2015. In addition, perampanel was approved in Japan indicated as an adjunctive therapy for partial-onset seizures or tonic-clonic seizures in patients with epilepsy showing inadequate response to other antiepileptic drugs (AEDs).

Depending on mechanism of action, existing AEDs are divided into two groups, one of which decrease neuronal excitation, and the other of which enhance inhibition. Major target sites for AEDs are blockage of voltage-operated sodium channels or calcium channels, regulation of neuronal transmitter release, inhibition of glutamatergic neural transmission, and facilitation gamma-aminobutryic acid (GABA)ergic neurotransmission. Current major AEDs has speculated to have a selective or mixed action on these targets. Perampanel is only available drug showing selective inhibition on AMPA receptor. Therefore, not only adjunctive therapy for refractory epilepsy, perampanel is expected to become novel monotherapy for untreated epilepsy.

7.2 Study Rationale

In general, the clinical development for the novel AED is to confirm the efficacy of the adjunctive therapy in adult patients with refractory epilepsy at first, and after that to confirm the efficacy of monotherapy. To date, a large number of monotherapy studies for AEDs were conducted after acquiring their clinical evidence for the adjunctive therapy and the efficacy of monotherapy has been confirmed as well as adjunctive therapy. In accordance with these historical knowledge, International League Against Epilepsy (ILAE) has recommended that AEDs should be approved for the treatment of specific seizure types, or the treatment of seizures associated with a specific epilepsy syndrome, without regard to use as sole or adjunctive therapy (Mintzer, et al., 2015).

Perampanel has been conducted the clinical trials for the adjunctive therapy in patients with partial onset seizures and primary generalized tonic-clonic seizures and has been confirmed the effectiveness. And also, single-administration of perampanel shows broad effect to various non-clinical seizure model in mice. Based on above evidence, perampanel can be also expected to obtain the sufficient efficacy for use as monotherapy.

From these background, this Phase 3 study to confirm the efficacy and safety of perampanel for use as monotherapy was planned.

In this study, target population is untreated epilepsy patients with partial onset seizures (POS).

This population is commonly targeted in the clinical study for monotherapy. In the Phase 3 study of lamotrigine monotherapy, not only the untreated newly patients but also the recurrent patients were targeted (Yamamoto, et al., 2014). In this study, patients who had

once achieved end of treatment before 2 years or more but are recurrent thereafter are allowed to enroll.

The primary objective of this study is to evaluate the seizure-free rate of the 26-week Maintenance Period in untreated patients with POS. The primary endpoint is commonly used in studies evaluating the effect of AED monotherapy. According to the guideline of Europe (EMA, 2010), it should be evaluated for more than six months (exclude titration period) when the presence of completion disappearance of seizures (seizure-free) is evaluated.

It is difficult to conduct a placebo controlled study for the AED monotherapy because it has ethical concerns. In this study, the seizure free rate in the 26-week Maintenance Period will be compared with the estimate calculated by other AED monotherapy studies.

Safety data of this study will be compared with the data of adjunctive treatment study of perampanel in patients with POS aged 12 years and older (Study E2007-J000-335 [hereafter referred to as Study 335]). Based on the comparison, safety signals for perampanel monotherapy will be evaluated.

See Section 9.4.4 for selection of doses in the Study.

8 STUDY OBJECTIVES

8.1 Primary Objective

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

8.2 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

8.3 Exploratory Objectives

- 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)

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

Study Design

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. Once perampanel monotherapy is approved in each country, an End of Study Visit should be conducted promptly, and the subject would have to switch to the commercial product. If a subject does not switch to the commercial product promptly, an End of Study Visit and a Follow-up Visit should be conducted for the subject.

Follow-up Phase

Subjects who will finish or discontinue the study will conduct the follow-up visit 4 weeks after withdrawal of perampanel. Follow-up Visit is not required for subjects who will be switching to the commercial product and attend an End of Study Visit.

The study design is shown in Figure 1.

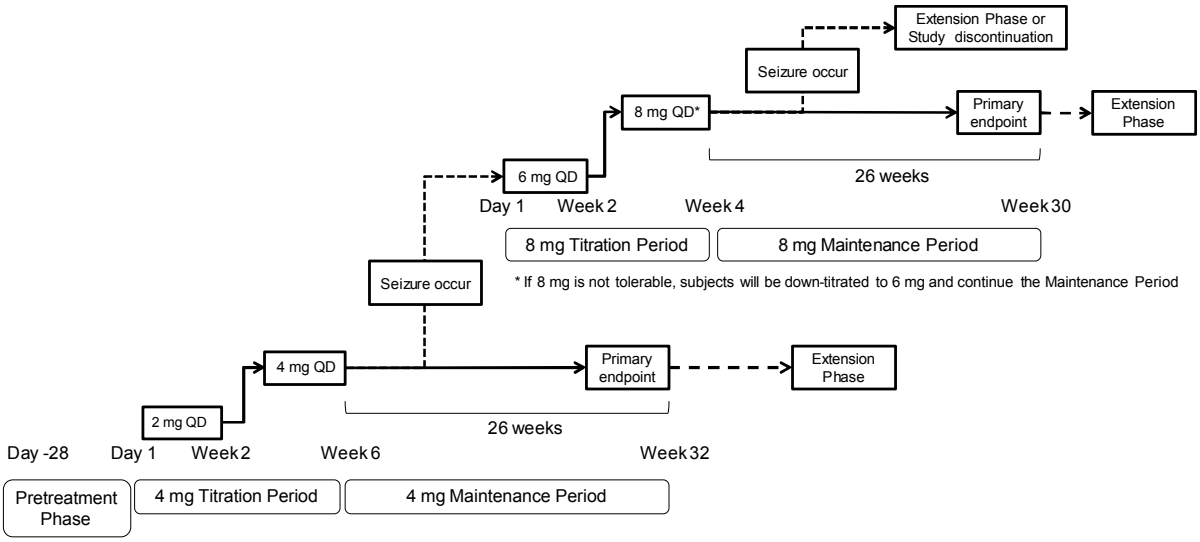


Figure 1 Study Design for Study E2007-J000-342

9.1.1 Pretreatment Phase

During the Pretreatment Phase (maximally 4 weeks), patients will be screened and be assessed for their eligibility to participate in the study. Screening will occur between Day –28 and Day 1 (Day 1 is the date of first dose of perampanel 2 mg). The purpose of the screening at Visit 1 is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3.

Subjects must have a diagnosis of epilepsy with partial seizures with or without secondary generalized seizures according to International League Against Epilepsy (ILAE) Classification of Epileptic Seizures (1981).

Subjects who complete the screening and meet the criteria for inclusion/exclusion (Sections 9.3.1 and 9.3.2) will begin the Treatment Phase.

9.1.2 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.

9.1.2.1 4 mg Titration and Maintenance Period

In the 4 mg Titration Period (6 weeks), subjects will initiate 2 mg QD of perampanel for 2 weeks and then will be up-titrated to 4 mg QD and will continue for 4 weeks. If subjects have no safety issues at the end of the Titration Period, they will start the 4 mg Maintenance Period for 26 weeks.

If subjects experience seizures during the 4 mg Maintenance Period, the investigator will end the 4 mg Maintenance Period and judge the transition to the 8 mg Titration Period based on the subject's tolerability and safety. If subjects could not continue 4 mg dosing due to intolerable adverse event during the 4 mg Maintenance Period, they will discontinue the study.

During the 2 weeks of Weeks 3 and 4 in the 4 mg Titration Period, if subjects are suspected to have tolerability issues for 4 mg dosing due to occurrence of adverse events, 2 mg QD can be administered in accordance with the investigators' discretion. In that case, subjects will visit the investigational site via unscheduled visit within 4 weeks after starting study treatment and will be up-titrated to 4 mg QD (for subjects who has continued 4 mg QD, occurrence of AEs will be confirmed via telephone). All subjects will continue 4 mg QD during the 2 weeks of Weeks 5 and 6. If subjects could not continue 4 mg QD due to intolerable adverse event, they will discontinue the study.

9.1.2.2 8 mg Titration and Maintenance Period

In the 8 mg Titration Period (4 weeks), subjects will be administered 6 mg QD of perampanel for 2 weeks and then will be up-titrated to 8 mg QD and will continue for 2 weeks. If subjects have no safety issues at the end of the Titration Period, they will start the 8 mg Maintenance Period for 26 weeks.

If subjects don't tolerate 8 mg administration of perampanel, they will be able to down-titrate to 6 mg in accordance with the investigators' discretion. After the down-titration, subjects could continue the study with 6 mg QD.

If subjects experience the occurrence of seizures or could not continue 8 mg (or 6 mg) dosing due to intolerable adverse event during the 8 mg Maintenance Period, they will end the Treatment Phase.

9.1.3 Extension Phase

When subjects complete the Treatment Phase and agree to continue receiving the perampanel monotherapy, they could enter the Extension Phase. Subjects who complete the 26-week Maintenance Period will continue the last dose of the Maintenance Period. Subjects who end the Treatment Phase due to insufficient efficacy or safety issue before the completion of the 26-week Maintenance Period will adjust their appropriate dose (within 4 – 8 mg of perampanel) and continue the Extension Phase. Subjects will be allowed to adjust within 2 – 8 mg of perampanel with investigators' consideration for their condition of the seizures and/or tolerability. During whole study period, the maximum dose of perampanel is 8 mg QD. The dose will be increased at intervals of 1 week or more in increments of 2 mg.

If subjects need to take other antiepileptic drugs (AEDs) or withdraw perampanel because of insufficient efficacy or tolerability issue of perampanel by the investigator's judgement, they will discontinue the study.

Once perampanel monotherapy is approved in each country, an End of Study Visit should be conducted promptly, and the subject would have to switch to the commercial product. If a subject does not switch to the commercial product promptly, an End of Study Visit and a Follow-up Visit should be conducted for the subject.

9.1.4 Follow-up Phase

Subjects who will finish or discontinue the study will conduct the follow-up visit 4 weeks after withdrawal of perampanel. When a taper is provided after discontinuation, it should be performed 4 weeks after the last dose at the tapered dose. Follow-up Visit is not required for subjects who will be switching to the commercial product and attend an End of Study Visit.

9.2 Discussion of Study Design, Including Choice of Control Groups

This study is a multicenter, open-label study to evaluate the efficacy, safety and tolerability, and pharmacokinetics of perampanel.

During initial treatment, the dose of monotherapy should be gradually increased to a therapeutic range based on the subject's safety and tolerability (Matsuura, 2009). The interval of titration for each dose was 1 week in the studies of adjunctive therapy, while it is changed to 2 weeks in this study. The point to be considered in medication is the following report (Matsuura, 2009): "When unfavorable side effects such as sleepiness occur in a subject, transient reduction to the dose before titration and re-up-titration to planned dose can make the planned dose administered to the subject." Based on the above report, dose reduction from 4 mg to 2 mg is allowed during the 4 mg Titration Period.

The 26-week Maintenance Period is the duration to evaluate the seizure-free rate as primary objective (see Section 7.2). In addition, the Extension Phase is established to confirm the subsequent seizure-free period for subjects who completed the Maintenance Period; and the subsequent clinical course of non-seizure-free subjects who do not have trouble in daily life, have sufficient therapeutic effect, and desire to continue the study. If subjects need to take other AEDs because of insufficient efficacy of perampanel, they will discontinue the study.

9.3 Selection of Study Population

Approximately 80 subjects will be enrolled at approximately 45 sites in Japan and South Korea. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug. Note that, in this protocol, 1 month refers to 28 days (4 weeks).

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Be considered reliable and willing to be available for the study period and are able to record seizures and report adverse events (AEs) himself/herself or have a caregiver who can record seizures and report AEs for them

2. Male or female aged between 12 and 74 years old
3. Subjects who are newly diagnosed or recurrent epilepsy and have experienced at least 2 unprovoked seizures separated by a minimum of 24 hours in the 1 year prior to the Pretreatment Phase, of which, at least 1 unprovoked seizure (but below 20 seizures) occurred in the 12 weeks prior to the Pretreatment Phase. For subjects with recurrent epilepsy, they must have relapsed at least 2 years after the end of the last AED treatment.
4. Subjects who have excluded the progressive CNS abnormality occurring seizures by CT or MRI conducted within 1 year before the Pretreatment Phase
5. Subjects who have had a diagnosis of epilepsy with partial seizures with or without secondarily generalized seizures according to the International League Against Epilepsy (ILAE) Classification of Epileptic Seizures (1981). Diagnosis should have been established by clinical history and an electroencephalogram (EEG) that is consistent with localization-related epilepsy; normal interictal EEGs will be allowed provided that the subject meets the other diagnosis criterion (ie, clinical history).

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Subjects who present only simple partial seizures without motor signs
2. Subjects who have seizure clusters where individual seizures cannot be counted
3. Subjects who present or have a history of Lennox-Gastaut syndrome
4. Subjects who have a history of status epilepticus within 1 year prior to Day 1 of the Treatment Phase
5. Subjects who have a history of psychogenic non-epileptic seizures within 5 years prior to Day 1 of the Treatment Phase
6. Subjects who have a history of suicidal ideation/attempt within 5 years prior to Day 1 of Treatment Phase
7. Subjects who present clinically problematic psychological or neurological disorder(s)
8. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments
9. Evidence of clinically significant active hepatic disease.
10. A prolonged QTcF interval (>450 ms [2 or 3 times]) as demonstrated by a repeated (3 times) electrocardiogram (ECG)
11. Subjects who have a history of receiving any AEDs (except for AEDs used as rescue treatment), antipsychotics or anti-anxiety drugs within 12 weeks prior to the Pretreatment Phase
12. Subjects who have not used a stable dose of antidepressant in the 12 weeks prior to the Pretreatment Phase, if they treat
13. Subjects who have a history of any type of surgery for brain or central nervous system within 1 year prior to the Pretreatment Phase

14. Subjects who have a history of receiving any AED (including AED used as rescue treatment) for more than 2 weeks in total within 2 years prior to the Pretreatment Phase
15. Subjects who have used intermittent rescue medicine on 2 or more occasions within 4 weeks before the Pretreatment Phase (1 to 2 doses over a 24-hour period considered one-time rescue)
16. Subjects who have a history of receiving any AED polytherapy
17. Subjects who experienced treatment with perampanel
18. Subjects who have had non-constant ketogenic diet within 4 weeks before the Pretreatment Phase
19. Subjects who have a history of drug or alcohol dependency or abuse within the last 2 years before the Pretreatment Phase
20. Subjects who have had multiple drug allergies or a severe drug reaction to an AED(s), including dermatological (eg, Stevens-Johnson syndrome), hematological, or organ toxicity reactions
21. Females who are breastfeeding or pregnant in the Pretreatment Phase (as documented by a positive beta-human chorionic gonadotropin [β-hCG] test)
22. Females of childbearing potential who:

- Within 28 days before the start of the Pretreatment Phase, did not use a highly effective method of contraception, which includes any of the following:
    - total abstinence (if it is their preferred and usual lifestyle)
    - an intrauterine device or intrauterine hormone-releasing system (IUS)
    - a contraceptive implant
    - an oral contraceptive (with additional barrier method) (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
    - have a vasectomized partner with confirmed azoospermia.
- Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

It is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).

23. Subjects who have participated in a study involving administration of an investigational drug or device within 4 weeks before Visit 1, or within approximately 5 half-lives of the previous investigational compound, whichever is longer.

24. Subject who is diagnosed with dementia

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

A subject who discontinues study treatment should be followed for subsequent protocol-specified visits and procedures. The primary reason for discontinuation contributing to the subject's discontinuation from study drug(s) should be collected. If subjects need to take other AEDs because of insufficient efficacy of perampanel, they will discontinue the study. The first date when other AEDs are administered will be defined as the final date of perampanel monotherapy, and the subsequent date when the perampanel is completely withdrawn will be defined as the discontinuation date of the study.

9.4 Treatment

9.4.1 Treatment Administered

Treatment Phase

The following treatment will be administered to subjects in the Treatment Phase (Table 1). Perampanel is orally administered once a day before bedtime.

[4 mg Treatment Phase]

In the 4 mg Titration Period (6 weeks), subjects will initiate 2 mg QD of perampanel for 2 weeks and then will be up-titrated to 4 mg QD and will continue for 4 weeks. If subjects have no safety issues at the end of the Titration Period, they will start the 4 mg Maintenance Period for 26 weeks.

If subjects experience seizures during the 4 mg Maintenance Period, the investigator will end the 4 mg Maintenance Period and judge the transition to the 8 mg Titration Period based on the subject's tolerability and safety. If subjects could not continue 4 mg dosing due to intolerable adverse event during the 4 mg Maintenance Period, they will discontinue the study.

During the 2 weeks of Weeks 3 and 4 in the 4 mg Titration Period, if subjects are suspected to have tolerability issues for 4 mg dosing due to occurrence of adverse events, 2 mg QD can be administered in accordance with the investigators' discretion. In that case, subjects will visit the investigational site via unscheduled visit within 4 weeks after starting study treatment and will be up-titrated to 4 mg QD (for subjects who has continued 4 mg QD, occurrence of AEs will be confirmed via telephone). All subjects will continue 4 mg QD during the 2 weeks of Weeks 5 and 6. If subjects could not continue 4 mg QD due to intolerable adverse event, they will discontinue the study.

[8 mg Treatment Phase]

In the 8 mg Titration Period (4 weeks), subjects will be administered 6 mg QD of perampanel for 2 weeks and then will be up titrated to 8 mg QD and will continue for 2 weeks. If subjects have no safety issues at the end of the Titration Period, they will start the 8 mg Maintenance Period for 26 weeks.

If subjects don't tolerate 8 mg administration of perampanel, they will be able to down-titrate to 6 mg in accordance with the investigators' discretion. After the down-titration, subjects could continue the study with 6 mg QD.

If subjects experience the occurrence of seizures or could not continue 8 mg (or 6 mg) dosing due to intolerable adverse event during the 8 mg Maintenance Period, they will end the Treatment Phase.

A taper will be allowed at the investigator's discretion upon early discontinuation of the study.

Table 1 Treatment Administered (Treatment Phase)

Treatment Phase	Week	Day	Dose	Frequency and Number Dispensed
4 mg Titration Period	Weeks 1 – 2	Days 1 – 14	2 mg	QD, 1 × 2 mg tablet before bedtime
	Weeks 3 – 6	Days 15 – 42	4 mg	QD, 2 × 2 mg tablet before bedtime
4 mg Maintenance Period	Weeks 7 – 32	Days 43 – 224	4 mg	QD, 2 × 2 mg tablet before bedtime
8 mg Titration Period	Weeks 1 – 2	Days 1 – 14	6 mg	QD, 3 × 2 mg tablet before bedtime
	Weeks 3 – 4	Days 15 – 28	8 mg	QD, 4 × 2 mg tablet before bedtime
8 mg Maintenance Period	Weeks 5 – 30	Days 29 – 210	8 mg[a]	QD, 4 × 2 mg tablet before bedtime

QD = once daily.

Extension Phase

Subjects who complete the 26-week Maintenance Period will continue the last dose of the Maintenance Period. Subjects who end the Treatment Phase due to insufficient efficacy or safety issue before the completion of the 26-week Maintenance Period will adjust their appropriate dose (within 4 – 8 mg of perampanel) and continue the Extension Phase. Subjects will be allowed to adjust within 2 – 8 mg of perampanel with investigators' consideration for their condition of the seizures and/or tolerability. During whole study period, the maximum dose of perampanel is 8 mg QD. The dose will be increased at intervals of 1 week or more in increments of 2 mg.

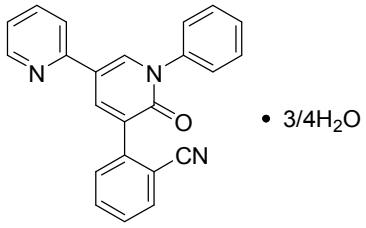
9.4.2 Identity of Investigational Product

Perampanel 2-mg tablets will be provided as orange, 6.6 mm diameter, biconvex film – coated tablets for oral administration. The front side of the tablets will be debossed with

"E274." Each tablet will contain 2 mg of perampanel. The certificate(s) of analysis (CoA) will provide manufacturer information.

9.4.2.1 Chemical Name, Structural Formula of E2007

- Test drug code: E2007
- Generic name: perampanel
- Chemical name (IUPAC): 2-(2-Oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl) benzonitrile hydrate (4:3)
- Molecular formula: $C_{23}H_{15}N_3O \cdot 3/4H_2O$
- Molecular weight: 362.90 (3/4 hydrate), 349.38 (anhydrous)
- Structural formula:



9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

Study drug will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries.

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the pharmacist or its designee) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

This is an open-label, single-arm study. All subjects who provide signed informed consent to participate in this study and satisfy all eligibility requirements (see Section 9.3) will be assigned to receive perampanel. There is no randomization in this study.

9.4.4 Selection of Doses in the Study

In this study, if subjects experience seizures during the 4 mg Maintenance Period, they will be titrated to 8 mg. In Japan, perampanel 4 mg has not been approved as the clinical dosage for adjunctive therapy of POS based on the result of Study 335. However, in many other countries including South Korea, perampanel 4 mg is approved as the clinical dosage of adjunctive therapy for POS based on the result of Study E2007-G000-306 (hereafter referred to as Study 306), which was conducted before Study 335 and demonstrated the efficacy by 4 mg. In addition, the efficacy of 4 mg for subjects who did not take enzyme inducing antiepileptic drugs (EIAEDs) was comparable in Study 335 and Study 306; and adjunctive treatment with perampanel 4 mg for the subjects taking EIAEDs was considered effective in improving seizure control. Therefore, perampanel 4 mg as monotherapy has potential to demonstrate the efficacy for POS; and the objective of this study is set to confirmation of the efficacy for perampanel 4 mg. If subjects experience seizures during the 4 mg treatment, the efficacy for perampanel monotherapy will be evaluated with 8 mg dose.

In order to minimize the sample size, the 2 step design, not the two separate arms (4 mg and 8 mg arm) was chosen. In this study, all subjects will be up-titrated to 4 mg firstly. After that, only the subjects who experience seizures during the 4 mg Maintenance Period (26 weeks) will be up-titrated to 8 mg.

9.4.5 Selection and Timing of Dose for Each Subject

Perampanel is orally administered once a day before bedtime.

9.4.6 Blinding

The study will not be blinded.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject during the study (starting at the date of informed consent) will be recorded. For all drugs, the name, route of administration, dose (only for drugs to treat primary disease), treatment start dates, treatment end dates, and reason for use will be recorded on the CRF. Concomitant drugs such as premedications, diagnostic agents, solutions, or fluid transfusions provided for surgery, medical examinations, or administrations will be excepted. For concomitant therapy, the name, treatment start dates (or timing of starting treatment), treatment end dates, and reason for use will be recorded on the CRF. The adverse event or medical condition for which the concomitant medication or therapy was administered will be recorded.

Antidepressant administered within 12 weeks prior to the Pretreatment Phase, available subject's lifetime all AED histories (including AED used as rescue treatment), and rescue benzodiazepines within 4 weeks before the Pretreatment Phase will be recorded on the CRF.

9.4.7.1 Prohibited Concomitant Therapies and Drugs

9.4.7.1.1 PROHIBITED CONCOMITANT DRUG

Throughout the study period, concomitant use of the following drugs is prohibited (till the visit at the time of early discontinuation for discontinued subjects).

- Other AEDs (if emergency care is needed, eg, status epilepticus, uncontrolled seizures, or clusters, occasional use (prn) of other AEDs including diazepam, phenytoin will be permitted as rescue treatment)
- The following drugs or food known to induce CYP3A (not limited to these drugs or food). If one of these drugs was being used at enrollment, washout of the drug will start at this time point. The duration of washout of the drug must be at least 2 weeks.

  [carbamazepine, enzalutamide, mitotane, phenytoin, phenobarbital, amobarbital, secobarbital, rifabutin, rifampicin, food containing St. John's Wort (hypericum perforatum), bosentan, efavirenz, etravirine, modafinil, armodafinil, rufinamide, nevirapine, oxcarbazepine, and glucocorticoid (except for topical use)]
- Antipsychotics
- Antianxiety drugs
- Benzodiazepine hypnotic
- Other investigational agents
- Antidemetia drugs

9.4.7.1.2 PROHIBITED CONCOMITANT THERAPY

The following therapies must not concurrently be implemented during the study.

- Brain surgery
- Medical device under clinical trial
- Neuromodulation therapy (including vagal nerve stimulation [VNS] and Transcranial magnetic stimulation)

9.4.7.2 Restricted Concomitant Drugs and Therapies

9.4.7.2.1 RESTRICTED CONCOMITANT DRUG

The dosing regimen of the following drugs must not be altered, newly introduced, or discontinued throughout the study. Only for discontinued subjects, this does not apply after the visit at early discontinuation.

- Antidepressants

9.4.7.2.2 RESTRICTED CONCOMITANT THERAPY

The following therapy must not be changed or discontinued during the study. Only for discontinued subjects, this does not apply after the visit at early discontinuation.

- Ketogenic diet

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. Clinical research associates (CRAs) will review treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to Good Clinical Practice (GCP) guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) documentation of returns to the sponsor, and (e) certificates of destruction for any destruction of study drugs that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority. As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type

prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at Visit 1. Demography information includes date of birth, sex, race/ethnicity.

9.5.1.2 Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history and current medical conditions will be recorded at Visit 1. All CNS related medical and surgical history within 2 years and current medical conditions must be noted in the Medical History and Current Medical Conditions CRF.

9.5.1.2.2 EPILEPSY MEDICAL HISTORY

In addition to standard medical history, epilepsy history (date of diagnosis, etiology, epileptic syndrome, suspected localization of the epileptogenic region, seizure type, end date of last medication for previous epilepsy if subjects are recurrent epilepsy) will be documented for each subject at Visit 1. The available subject's lifetime all AED histories will be recorded on the CRF. Seizure count and type occurring within 12 weeks before study entry will be recorded based on the interview with each subject at Visit 1.

9.5.1.2.3 URINE DRUG TEST

A urine sample will be collected at Visit 1. This sample will be tested for common drugs of use/abuse: PCP (phencyclidine), benzodiazepines, cocaine, amphetamines, cannabinoids, opioids (as a group), barbiturates, and tricyclic antidepressant.

9.5.1.3 Efficacy Assessments

Efficacy will be assessed by seizure counts and types as recorded on the diary.

Diaries will be dispensed to all subjects and returned from all subjects at each visit as described in Table 3. The diary is to be completed by the subject or the caregiver. All seizure counts and types will be recorded. At each visit the subject or the caregiver will be instructed by the site personnel as to how to complete the diary and reminded that they must return the diary at their next scheduled clinic visit and at the Early Discontinuation and Follow-up Visits (if applicable). To ensure correct seizure classification, the medically qualified investigator should review the diary with the subject or the caregiver at all visits. Subjects or caregivers must be counseled if diary compliance is not satisfactory.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected as specified in Table 3 and Table 4. See the Laboratory Manual for a description of collection, handling, and shipping procedures for pharmacokinetic samples. Pharmacokinetic sampling date and time for plasma concentrations of perampanel, treatment compliance (with or without) and dose of last 3 doses of perampanel, and date and time of last dose of perampanel before pharmacokinetic sampling will be recorded on the CRF.

Plasma perampanel concentrations will be determined by a validated method using liquid chromatography with tandem mass spectrometry (LC-MS/MS).

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

Not applicable.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and serious adverse events (SAEs); regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs, weight, and 12-Lead electrocardiogram (ECG); and performance of physical examinations as detailed in Table 3, Table 4, and Table 5.

9.5.1.5.1 ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug(s) is(are) perampanel.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or

symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)

- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs, regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject signs the study ICF through the last visit. SAEs will be collected for 28 days after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

Abnormal ECG (QTcF) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTcF interval is more than 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

All AEs must be followed for 28 days after the subject's last dose, or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the CRF. The definitions are as follows:

Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of

SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

Events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria (see Sections 9.5.4.2 and 9.5.4.3). All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 2. The Schedule of Procedures/Assessments (Table 3, Table 4, and Table 5) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 2 Clinical Laboratory Tests

Category	Parameters
Hematology	RBC count, hemoglobin, hematocrit, platelets, and WBC count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Chemistry	
Electrolytes	Bicarbonate, chloride, potassium, sodium, calcium, magnesium
Liver function tests	Alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, total bilirubin
Renal function tests	Blood urea nitrogen, creatinine
Other	Glucose, albumin, total cholesterol, triglycerides, phosphorus, lactate dehydrogenase, total protein, uric acid, creatine phosphokinase
Urinalysis	pH, protein, glucose, ketones, occult blood, specific gravity

RBC = red blood cell, WBC = white blood cell.

Clinical laboratory tests during the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection (in principle) unless otherwise instructed. In case of a safety concern or dispensing study drugs on the start day of the Pretreatment Phase, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic blood pressure [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in the Schedule of Procedures/Assessments (Table 3, Table 4, and Table 5) by a validated method. Blood pressure and pulse will be measured after the subject has been resting for 5 minutes. All blood pressure measurements should be performed on the same arm, preferably by the same person. Height (cm) will be measured only at Visit 1.

9.5.1.5.5 PHYSICAL EXAMINATIONS

Physical examinations will be performed at the visits as designated in the Schedule of Procedures/Assessments (Table 3, Table 4, and Table 5). Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

9.5.1.5.6 ELECTROCARDIOGRAMS

Twelve-lead ECGs will be obtained at the visits as designated in the Schedule of Procedures/Assessments (Table 3, Table 4, and Table 5). Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

At Visit 1 and Visit 2 (Day 1), 3 consecutive ECGs separated by 5-10 minutes will be performed in all subjects. At Visit 3 and thereafter, if the QTcF is measured as >450 ms, additional 2 (total of 3) consecutive ECGs separated by 5-10 minutes will be performed to confirm the abnormality.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1). In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

9.5.1.5.7 OTHER SAFETY ASSESSMENTS

Pregnancy Test

A serum β-hCG pregnancy test will be performed for all female subjects at Visit 1. On Visit 2 (Day 1) and thereafter, a urine β-hCG pregnancy test will be performed for women of childbearing potential (ie, premenopausal women or postmenopausal women who have been amenorrheic for less than 12 months).

If Visit 1 and Visit 2 are the same day and a result of serum pregnancy test can be assessed by the local laboratory during the day, urine pregnancy test at Visit 2 is not required.

9.5.1.6 Other Assessments

EuroQol 5 Dimensions 5 Levels

Quality of life will be assessed using the EQ-5D-5L questionnaires at the visits as designated in the Schedule of Procedures/Assessments (Table 3, Table 4, and Table 5).

Questionnaires should be self-read and self-completed unless the subject has a physical disability that prevents him or her from doing so. In these cases, a caregiver or study coordinator should read and/or record the subject's answers.

9.5.2 Schedule of Procedures/Assessments

Table 3, Table 4, and Table 5 present the schedule of procedures/assessments for the study.

Subjects will continue to receive perampanel until 3 or less months from the date of approval of perampanel monotherapy in each country or the sponsor discontinues the study.

Table 3 Schedule of Procedures/Assessments (Pretreatment Phase to 4 mg Treatment Phase) in Study E2007-J000-342

Phase	Pretreatment Phase[a]		4 mg Treatment Phase								Follow-up Phase[b, c]		
Period			4 mg Titration Period[a]			4 mg Maintenance Period[b]							
Study Week(s) (from Day 1 of Titration Period)	Week –4	–	Week 2	Week 4	Week 6	Week 10	Week 14	Week 20	Week 26	Week 32	4 weeks after the last dose		
Study Day(s) (from Day 1 of Titration Period)	Day –28 to 1	Day 1[m]	Day 15	Day 29	Day 43	Day 71	Day 99	Day 141	Day 183	Day 225	–		
Visit	1	2	3	Phone[n]	4	5	6	7	8	9	–	Unscheduled visit[o]	Early discontinuation visit[p]
Procedure/Assessment													
Informed consent/assent[d]	X												
Inclusion/exclusion criteria	X	X											
Physical examinations	X	X	X		X	X	X	X	X	X	X	X	X
Medical history	X												
Concomitant medications	X[e]	X	X		X	X	X	X	X	X	X	X	X
Adverse events[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug compliance			X		X	X	X	X	X	X			X
Dispense subject diary	X	X	X		X	X	X	X	X	X			X
Return and review subject diary		X	X		X	X	X	X	X	X	X		X
Discontinuation/continuation/titration judgment[g]			X	X	X	X	X	X	X	X			
Vital signs and weight[h]	X	X			X			X		X	X	X	X
Clinical laboratory evaluations[i]	X	X			X			X		X	X	X	X
Study drug plasma concentration					X	X		X					X[j]
Urine drug screen	X												
Urine pregnancy test[k]		X	X		X	X	X	X	X	X	X	X	X
Serum pregnancy test[k]	X												
12-Lead ECG[l]	X	X			X			X		X	X	X	X
EQ-5D-5L	X									X			X
Dispense study drug		X	X		X	X	X	X	X	X			
Return unused medication			X		X	X	X	X	X	X			X

AE = adverse event, β-hCG = beta-human chorionic gonadotropin, ECG = electrocardiogram, EQ-5D-5L = EuroQol 5 Dimensions 5 Levels.

a: Visit to be done within ±3 days of the schedule. Each visit to be specified based on the date of Visit 2.

b: Visit to be done within ±7 days of the schedule. Each visit to be specified based on the date of Visit 2.

c: To be completed by subjects who are withdrawn from the study after Visit 2 and before Visit 9 (for any reason). When a taper is provided after discontinuation, it should be performed 4 weeks after

the last dose at the tapered dose and return unused medication.

d: Informed consent/assent must be obtained prior to any study related procedure.

e: Prior and concomitant medication(s)

f: Adverse events will be collected from the time the subject signs the informed consent/assent form through the last visit. Serious adverse events will be collected for 28 days after the subject's last dose.

g: After Visit 4, if a subject experiences seizures, the investigator will end the 4 mg Maintenance Period and judge the transition to the 8 mg Titration Period based on the subject's tolerability and safety.

h: Height is to be measured only at Visit 1.

i: At Visit 1, confirm the results of the local laboratory analysis, if necessary. In case of the local laboratory analysis, the measurement of bicarbonate and magnesium are not mandatory at Visit 1, and after that should be conducted as scheduled

j: Collect blood samples if subjects are withdrawn from the study before Visit 7.

k: All female subjects will undergo the serum β-hCG pregnancy test at Visit 1. After Visit 2, only potentially pregnant female subjects will undergo the urine β-hCG pregnancy test.

l: At Visits 1 and 2, all subjects will undergo 3 consecutive ECGs at 5- to 10-minute intervals. After Visit 3, only subjects whose QTcF is measured as >450 ms at any Visit will undergo additional 2 consecutive ECGs at 5- to 10-minute intervals (a total of 3 ECGs) to confirm the abnormality.

m: If Visit 1 and Visit 2 are the same day, only duplicate procedures/assessments will be performed once. If Visit 1 and Visit 2 are the same day and a result of serum pregnancy test can be assessed by the local laboratory during the day, urine pregnancy test at Visit 2 is not required.

n: For subjects who continue 4 mg QD, occurrence of AEs will be confirmed via telephone. Subjects who continue 2 mg QD or who are reduced from 4 mg QD to 2 mg QD during the 2 weeks of Weeks 3 and 4 will visit the investigational site via unscheduled visit within 4 weeks after starting study treatment and will be up-titrated to 4 mg QD.

o: At an unscheduled Visit, only the procedures/assessments that the investigators etc. has judged as necessary according to the subject's conditions will be performed.

p: If a taper is decided based on the judgment of the investigator, dispensing the study drug should be needed.

Table 4 Schedule of Procedures/Assessments (8 mg Treatment Phase) in Study E2007-J000-342

Phase	8 mg Treatment Phase								Follow-up Phase[b,c]			
Period	8 mg Titration Period[a]			8 mg Maintenance Period[b]								
Study Week(s) (from Day 1 of 8 mg Titration Period)	–	Week 2	Week 4	Week 8	Week 12	Week 18	Week 24	Week 30	4 weeks after the last dose			
Study Day(s) (from Day 1 of 8 mg Titration Period)	Day 1	Day 15	Day 29	Day 57	Day 85	Day 127	Day 169	Day 211	–			
Visit	2a	3a	4a	5a	6a	7a	8a	9a	–	Early transition visit[k]	Unscheduled visit[i]	Early discontinuation visit[j]
Procedure/Assessment												
Physical examinations	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[d]	X	X	X	X	X	X	X	X	X	X	X	X
Study drug compliance	X	X	X	X	X	X	X	X		X		X
Dispense subject diary	X	X	X	X	X	X	X	X		X		X
Return and review subject diary	X	X	X	X	X	X	X	X	X	X		X
Discontinuation/continuation/titration judgment[e]		X	X	X	X	X	X	X		X		
Vital signs ad weight	X		X			X		X	X	X	X	X
Clinical laboratory evaluations	X		X			X		X	X	X	X	X
Study drug plasma concentration			X	X		X				X[g]		X[g]
Urine pregnancy test[f]	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[h]	X		X			X		X	X	X	X	X
EQ-5D-5L	X							X		X		X
Dispense study drug	X	X	X	X	X	X	X	X		X		
Return unused medication	X	X	X	X	X	X	X	X		X		X

β-hCG = beta-human chorionic gonadotropin, ECG = electrocardiogram, EQ-5D-5L = EuroQol 5 Dimensions 5 Levels.

a: Visit to be done within ±3 days of the schedule. Each visit to be specified based on the date of Visit 2a.

b: Visit to be done within ±7 days of the schedule. Each visit to be specified based on the date of Visit 2a.

c: To be completed by subjects who are withdrawn from the study after Visit 2a and before Visit 9a (for any reason). When a taper is provided after discontinuation, it should be performed 4 weeks after the last dose at the tapered dose and return unused medication.

d: Adverse events will be collected from the time the subject signs the informed consent/assent form through the last visit. Serious adverse events will be collected for 28 days after the subject's last dose.

e: At Visit 4a, if a subject is down-titrated to 6 mg due to intolerability after up-titrated to 8 mg, the subject will enter the Maintenance Period with 6 mg. After Visit 4a, if a subject experiences seizures or could not continue dosing due to intolerable adverse event, the investigator will end the 8 mg Maintenance Period.

f: Only potentially pregnant female subjects will undergo the urine β-hCG pregnancy test.

g: Collect blood samples if subjects are withdrawn from the study before Visit 7a.

h: Only subjects whose QTcF is measured as >450 ms at any Visit will undergo additional 2 consecutive ECGs at 5- to 10-minute intervals (a total of 3 ECGs) to confirm the abnormality.

i: At an unscheduled Visit, only the procedures/assessments that the investigators etc. has judged as necessary according to the subject's conditions will be performed.

j: If a taper is decided based on the judgment of the investigator, dispensing the study drug should be needed.
k: The visit for transition from the 8 mg Treatment Phase to the Extension Phase before completion of the 8 mg Treatment Phase

Table 5 Schedule of Procedures/Assessments (Extension Phase) in Study E2007-J000-342

Phase	Extension Phase[a]					Follow-up Phase[a]			
Study Week(s) (from start date of Extension Phase)	Week 6	Week 12	Week 18	Week 26	Every 12 weeks thereafter	4 weeks after the last dose [b, i]			
Study Day(s) (start date of Extension Phase)	Day 43	Day 85	Day 127	Day 183	–	–			
Visit	10	11	12	13	14~	–	Unscheduled visit [f]	Early discontinuation visit [g]	End of study visit [h]
Procedure/Assessment									
Physical examinations	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events[c]	X	X	X	X	X	X	X	X	X
Study drug compliance	X	X	X	X	X			X	X
Dispense subject diary	X	X	X	X	X			X	X
Return and review subject diary	X	X	X	X	X	X		X	X
Vital signs ad weight		X		X	X	X	X	X	X
Clinical laboratory evaluations		X		X	X	X	X	X	X
Urine pregnancy test[d]	X	X	X	X	X	X	X	X	X
12-Lead ECG [e]		X		X		X	X	X	X
EQ-5D-5L				X				X	X
Dispense study drug	X	X	X	X	X				
Return unused medication	X	X	X	X	X			X	X

β-hCG = beta-human chorionic gonadotropin, ECG = electrocardiogram, EQ-5D-5L = EuroQol 5 Dimensions 5 Levels.

a: Visit to be done within ±7 days of the schedule. Each visit to be specified based on the start date of the Extension Phase

b: Conduct 4 weeks after complete withdrawal of perampanel, if perampanel is tapered. Return unused medication is needed.

c: Adverse events will be collected from the time the subject signs the informed consent/assent form through the last visit. Serious adverse events will be collected for 28 days after the subject's last dose.

d: Only potentially pregnant female subjects will undergo the urine β-hCG pregnancy test.

e: Only subjects whose QTcF is measured as >450 ms at any Visit will undergo additional 2 consecutive ECGs at 5- to 10-minute intervals (a total of 3 ECGs) to confirm the abnormality.

f: At an unscheduled Visit, only the procedures/assessments that the investigators etc. has judged as necessary according to the subject's conditions will be performed.

g: If a taper is decided based on the judgment of the investigator, dispensing the study drug should be needed.

h: Once perampanel monotherapy is approved in each country, an End of Study Visit should be conducted promptly, and the subject would have to switch to the commercial product.

i: Follow-up Visit is not required for subjects who will be switching to the commercial product and attend an End of study visit.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies evaluating the effect of AEDs.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, vital signs, weight, 12-lead ECG, and assessment of AEs, are standard evaluations to ensure subject safety.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 1 business day from the date the investigator becomes aware of the event.

Serious adverse events, regardless of causality assessment, must be collected for 28 days after the subject's last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in a female subject in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through

breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse

is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.3.2 REPORTING OF STUDY-SPECIFIC EVENTS

Not applicable.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

Not applicable.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 3 and Table 4).

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons. Study disposition information will be collected on the Subject Disposition CRF.

9.5.6 Abuse or Diversion of Study Drug

During the study, the investigator will report any concern about abuse or diversion of study drugs by completing the CRF.

Adverse events associated with abuse or diversion will be appropriately reported as AEs and monitored per Sections 9.5.1.5.1 and 9.5.1.5.2. Abuse is always to be captured as an AE.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released. Statistical analyses will be performed using SAS software or other validated statistical software as required.

9.7.1 Statistical and Analytical Plans

The statistical analyses of the study data are described in this section. Further details of the analytical plan will be provided in a separate statistical analysis plan (SAP), which will be finalized before database lock.

9.7.1.1 Study Endpoints

9.7.1.1.1 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.

9.7.1.1.2 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

9.7.1.1.3 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 28 days 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

9.7.1.2 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.

9.7.1.3 Subject Disposition

The number (percentage) of subjects screened for study entry and screen failures, and the primary reason for screen failures will be summarized. The number (percentage) of treated subjects will be summarized as well as subjects who discontinued from the study treatment and reasons for discontinuation from study treatment.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set will be summarized using descriptive statistics. Continuous demographic and baseline variables include age, height, weight, and body mass index (BMI); categorical variables include sex, age group (<65 years, ≥65 years). This summary table will be generated on the ITT Analysis Set if the Safety Analysis Set and the ITT Analysis Set are not identical. This summary table will also be generated on the mITT Analysis Set.

9.7.1.5 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 number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by Anatomical Therapeutic Chemical (ATC) class (ie, anatomical class, therapeutic class, pharmacologic class, chemical class), and WHO DD preferred term.

This summary table will be generated on the ITT Analysis Set if the Safety Analysis Set and the ITT Analysis Set are not identical.

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. All medications will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

All efficacy analyses will be performed based on the mITT Analysis Set unless otherwise noted.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

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

9.7.1.6.2 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 corresponding 95% CI will be calculated on the mITT Analysis Set. To examine if the 95% lower CI exceeds the threshold (ie, 40%) is the key secondary efficacy analysis.

The number (percentage) of subjects in the mITT population 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% confidence interval (CI) will be calculated.

Median time to first seizure onset will be estimated by Kaplan-Meier method. Time to first seizure onset will be defined as the time from the first date of Maintenance Period to the date of first seizure onset during the Maintenance Period. Subjects who withdraw from the study before first seizure onset will be censored at the time of study discontinuation.

Median time to withdraw from the study will be estimated by Kaplan-Meier method. Time to withdraw from the study will be defined as the time from the first date of Maintenance Period to the date of discontinuation from the study. Subjects who are ongoing at the data cutoff will be censored at the time of data cutoff.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

The number (percentage) of subjects with POS who achieved seizure-free during the 26-week Maintenance Period and the corresponding 95% confidence interval (CI) will be calculated by types of partial seizure.

The percent change in seizure frequency of POS per 28 days in the Maintenance Period and Extension Phase relative to the Pretreatment Phase will be summarized.

The change in EQ-5D-5L measurements from baseline to each postbaseline visit will be summarized.

9.7.1.6.4 ANALYSIS AT PRIMARY ENDPOINT ACHIEVEMENT

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.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

The Safety Analysis Set will be used for pharmacokinetic analysis. Summary statistics of plasma perampanel concentrations will be obtained by visit.

9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Not applicable.

9.7.1.8 Safety Analyses

All safety analyses will be performed based on the Safety Analysis Set. Safety data will be summarized using descriptive statistics (eg, 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, weight, and 12-lead ECG results. Study Day 1 for all safety analyses will be defined as the date of the first dose of study drug.

9.7.1.8.1 EXTENT OF EXPOSURE

Extent of exposure to the study drug (eg, mean daily dose, maximum dose, last dose, duration of exposure) will be summarized using descriptive statistics. The exposure to the study drug will be classified by an appropriate category, and the number (percentage) of subjects will be summarized for the category, if necessary.

9.7.1.8.2 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 19.1 or higher) lower level term (LLT) 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 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.

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. 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 treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study treatment. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

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. A subject data listing of all SAEs will be provided.

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

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

9.7.1.8.3 LABORATORY VALUES

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

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

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

9.7.1.8.4 VITAL SIGNS

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

9.7.1.8.5 ELECTROCARDIOGRAMS

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) by visit.

9.7.1.8.6 OTHER SAFETY ANALYSES

Not applicable.

9.7.1.9 Other Analyses

Not applicable.

9.7.2 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 6 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.

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

10 REFERENCE LIST

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.

Chadwick D, Vigabatrin European Monotherapy Study Group. Safety and efficacy of vigabatrin and carbamazepine in newly diagnosed epilepsy: a multicentre randomised double-blind study. Lancet. 1999;354:13–9.

Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Guerreiro C, Kälviäinen R, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia. 2013;54:551–63.

Guideline for epilepsy treatment 2010 Supplement (2014). Japanese Society of Neurology, 2014.

Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders. EMA, 2010.

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.

Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Eng J Med. 2000;342(5):314–9.

Matsuura M, editor. Clinical question of epilepsy examination 194. Shindan to Chiryo Sha, Inc., 2009.

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.

Mintzer S, French JA, Perucca E, Cramer JA, Messenheimer JA, Blum DE, et al. Is a separate monotherapy indication warranted for antiepileptic drugs?. The Lancet Neurology. 2015;14(12):1229–40.

Walker MC, Sander JW. The impact of new antiepileptic drugs on the prognosis of epilepsy Seizure freedom should be the ultimate goal. Neurology. 1996;46(4):912–4.

Yamamoto T, Hong SB, Shimizu M, Sato K, Numachi Y. Lamotrigine monotherapy in newly diagnosed epilepsy or recurrent epilepsy: A multi-center, open-label study. Epilepsy & Seizure. 2014;7: 5–65.

11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's/contract research organization's (CRO's) CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production

- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each consented subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents. For the following item(s), the data recorded directly on the CRF are to be considered source data:

- Study drug compliance (eg, the reason for any change of dosage)
- Indication for prior/concomitant medication (drug/therapy)
- Discontinuation information (eg, in the case of lost to follow-up due to the subject choice)
- Sampling date and time for the drug concentration; date and time of dosing of study drug
- Sampling date for the clinical laboratory tests
- Comments and other information on AEs (eg, severity, relationship to study drug, outcome)

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. A government regulatory authority may request an inspection during the study or after its completion.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study (upon request). An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form (upon request) to the sponsor.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission

pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/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	life-threatening consequences; urgent intervention indicated
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)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

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).

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E2007-J000-342

Study Protocol Title: 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)

Investigational Product Name: E2007/Fycompa® (perampanel)

SIGNATURES

Authors:

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Eisai Co., Ltd.

Date

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Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2007-J000-342
Study Protocol Title:	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)
Investigational Product Name:	E2007/Fycompa® (perampanel)

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date