REVISION HISTORY

Revisions to Version v1.0

New version/date: Version 2.0/12 Apr 2019 (per Amendment 01)

Change	Rationale	Affected Protocol Section(s)
Clarified, in the text, the number and location of study sites, and the number of subjects.	Document quality	Synopsis (Section 2) – • Sites • Number of Subjects • Sample Size Rationale Section 6 Section 9.3 Section 9.7.2
Clarified, in the text, the Screening Period seizure requirements.	Document quality	Synopsis (Section 2) – • Study Design • Efficacy Assessments Section 9.1.1 Section 9.3.1 Section 9.5.1.2
Clarified, in the text, the length of Titration Period.	Document quality	Synopsis (Section 2) – • Study Design • Duration of Treatment Section 9.1 Section 9.1.2 Section 9.3.3.1
Updated minimum age for study inclusion.	To reflect approved product prescribing information.	Synopsis (Section 2) – • Number of Subjects • Inclusion Criteria Section 7.1 Section 9.1.1 Section 9.3.1 Section 9.4.4
Clarified, in the text, the requirements to support epilepsy diagnosis and analysis of efficacy endpoints.	Document quality	Synopsis (Section 2) – • Inclusion Criteria • Assessments • Safety Analyses Section 9.3.1 Section 9.5.1.1.2
Updated exclusion criteria regarding concomitant therapies and procedures.	Subject safety	Synopsis (Section 2) – • Exclusion Criteria • Concomitant Drug/Therapy Section 9.3.2 Section 9.4.7

Revisions to Version v1.0

New version/date: Version 2.0/12 Apr 2019 (per Amendment 01)

Change	Rationale	Affected Protocol Section(s)
Updated subject treatment during the Follow-Up Period.	To allow option for subject to switch to treatment with commercial perampanel after Maintenance Period completion.	Synopsis (Section 2) – • Study Design Section 9.1.3 Figure 1 Section 9.1.4 Table 4
Clarified, in the text, process for tracking subject dosing.	Document quality	Synopsis (Section 2) – • Study Design Section 9.1.2 Section 9.4.1
Clarified, in the text, restricted concomitant therapies, and use before Visit 1, and clarification of previous AED medication.	Document quality	Synopsis (Section 2) – • Concomitant Drug/Therapy Section 9.4.7
Clarified, in the text, safety assessments based on subject age.	Document quality	Synopsis (Section 2) – • Assessments Section 9.5.1.6.5 Section 9.5.1.6.9 Section 9.7.1.8.3 Table 4
Added fasting laboratory assessments at screening and last treatment visit.	Regulatory authority compliance	Table 3 Table 4
Updated Medical Monitor and Study Director information.	Personnel change	Protocol Signature Page
Grammatical, typographical, and formatting changes were also made.	Document quality	Throughout the Document

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2007-G000-410
Study Protocol Title:	Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Perampanel as Monotherapy or First Adjunctive Therapy in Subjects With Partial Onset Seizures With or Without Secondarily Generalized Seizures or With Primary Generalized Tonic-Clonic Seizures
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 United States
Investigational Product Name:	E2007/Fycompa® (Perampanel)
Indication:	Monotherapy or adjunctive therapy for partial-onset seizures with or without secondarily generalized seizures and primary generalized tonic-clonic seizures in ≥12-year-old epilepsy patients
Phase:	4
IND Number:	068368 EudraCT number 2017-001180-20
Approval Date:	V1.0 23 Mar 2017 (original protocol) V2.0 12 Apr 2019 (Amendment 01)
GCP Statement:	This study is to be performed in full compliance with International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local 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

Multicenter, Open-Label, Study to Evaluate the Efficacy and Safety of Perampanel as Monotherapy or First Adjunctive Therapy in Subjects With Partial Onset Seizures With or Without Secondarily Generalized Seizures or With Primary Generalized Tonic-Clonic Seizures

Investigators

To be determined

Sites

The study will be conducted at up to approximately 25 investigational sites in the US. (revised per Amendment 01)

Study Period and Phase of Development

Approximately 24 months
Phase 4

Objectives

Primary Objective

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

Secondary Objectives

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

Exploratory Objectives

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

Study Design

This is a multi-center, open-label, Phase 4 study. Subjects who meet all of the inclusion and none of

the exclusion criteria will receive perampanel. Baseline seizure counts (frequency) data will be collected by subjects or guardian/legally authorized representative, retrospectively (for history prior to screening) and prospectively as needed (during baseline). The study consists of 4 periods: a Screening Period (to start no earlier than 6 weeks before the 1st dose of study drug), a Titration Period (up to 13 weeks), a Maintenance Period (39 weeks), and a Follow-Up Period (4 weeks). (revised per Amendment 01)

Study subjects will include the following:

- Subjects who have been diagnosed with POS or PGTCS but have not previously received treatment with an antiepileptic drug (AED) or are currently receiving monotherapy treatment (no history of AED polytherapy) and wish to switch to another monotherapy treatment; or
- Subjects who are currently receiving treatment with a single AED administered at a stable dose for at least 8 weeks before Visit 2 (Week 0) and need additional AED treatment; subjects should not have previously received adjunctive AED therapy.

Screening Period

During the Screening Period, informed consent/pediatric assent will be obtained and screening assessments will be conducted. The Screening Visit (Visit 1) will take place no earlier than 6 weeks before the 1st dose of study drug. Seizure data from up to 12 weeks preceding the 1st dose should be collected by the investigator retrospectively and prospectively. Subjects will be eligible for study enrollment after they have experienced either the 2 required unprovoked (or reflex) seizures or the 1 unprovoked (or reflex) seizure with EEG evidence of seizures, and they will not need to complete the full 12-week diary to enter the Titration Period. (revised per Amendment 01)

Titration Period

The Titration Period will begin with Visit 2, which may overlap with the Screening Visit (Visit 1), and will last for up to 13 weeks. (revised per Amendment 01) Subjects will receive perampanel tablets once daily (QD) before bedtime. The initial dose of perampanel 2 mg/day may be up-titrated in increments of 2 mg according to the investigator's judgment, based on individual clinical response and tolerability, as shown in the following dosing schedule:

Dosing Titration Schedule

Category	Week[a]	Perampanel Dose (mg/day)
Required	1	2
	2	2
	3	4
	4	4
		Telephone Visit
Optional Escalation[b]	5	6
	6	6
		Follow-Up Telephone Call[c]
	7	8
	8	8
		Follow-Up Telephone Call[c]
	9	10
	10	10
		Follow-Up Telephone Call[c]
	11	12
	12	12
	13	12

a: Subjects on a concomitant enzyme-inducing antiepileptic drug may be up-titrated at 1-week intervals if needed.
b: Subjects should be titrated to 4 mg. Additional dose escalation is optional depending on subject response and tolerability, following assessment by Telephone Visit or follow-up calls.
c: If needed; investigator should follow-up with subject via telephone call prior to further dose escalation.

Treatment will initially be titrated up to perampanel 4 mg based on clinical response and tolerability. Thereafter, titration will be based on the investigator's judgment; subjects may have further dose increases in increments of 2 mg, per evaluation by the investigator (Telephone Visit 3) prior to further dose escalation. The maximum dose is 12 mg. At least 2 weeks must elapse between dose increases, with the exception of subjects who are taking any concomitant drug that shortens the half-life of perampanel (eg, phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine), in which case the treatment may be up-titrated at 1-week intervals if needed. Sites must enter the perampanel dosing information into the Interactive Response Technology (IRT) system on Weeks 2, 4, 6, 8, 10, and 12 to track subject dosing. Adjustments of the concomitant AED dose level during the Titration Period are not permitted. (revised per Amendment 01)

The perampanel dose can be down-titrated based on tolerability, at the discretion of the investigator. Subjects who cannot tolerate the 4 mg dose by the end of the Titration Period will be discontinued from the study.

Maintenance Period

Subjects will continue to receive the perampanel dose level that was administered at the end of the Titration Period, when they enter the 39-week Maintenance Period. Subjects will come to the study site for Visit 4 (Week 13), Visit 5 (Week 26), Visit 6 (Week 39), Visit 7 (Week 52), and at the Follow-Up Visit (Visit 8). All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments. (revised per Amendment 01)

According to the investigator's clinical judgment, subjects who experience adverse events (AEs) may have their perampanel dose reduced. Conversely, if seizures are not adequately controlled, subjects may have their dose increased up to a maximum of perampanel 12 mg. During the Maintenance Period, subjects whose perampanel dose has been reduced may have the dose increased again, at the discretion of the investigator, as soon as tolerability improves. Subjects who cannot tolerate a dose of 4 mg will discontinue perampanel treatment and be withdrawn from the study. Adjustment of the concomitant AED dose level during the Maintenance Period is permitted; any dose adjustments will be recorded. Subjects who receive perampanel as a 1st adjunctive therapy may also be converted to perampanel monotherapy at the discretion of the investigator.

Number of Subjects

Approximately 125 male or female subjects ≥4 years of age who have a diagnosis of epilepsy with POS, with or without secondarily generalized seizures (SGS) or PGTCS, will be enrolled in this study. (revised per Amendment 01)

Inclusion Criteria

1. Subjects will be male or female and no younger than 4 years of age and be able to swallow perampanel tablets. (revised per Amendment 01)
2. Subjects must have a diagnosis of epilepsy with POS (with or without SGS) or with PGTCS. Either of the following must have occurred to support an epilepsy diagnosis: (revised per Amendment 01)
   a. At least 2 unprovoked (or reflex) seizures occurring greater than 24 hours apart

b. 1 unprovoked (or reflex) seizure with EEG evidence of seizures

3. Subjects who receive perampanel as a 1st adjunctive therapy must currently have been treated with stable doses of monotherapy with an AED for 8 weeks prior to Visit 2 (Week 0), have not previously received adjunctive AED treatment, and must, in the investigator's judgement, be in need of initial adjunctive therapy after failure to control seizures with AED monotherapy, at the optimal dose and duration. (revised per Amendment 01)
4. Subjects who receive perampanel as monotherapy, who were newly diagnosed (treatment naïve) following the defined diagnosis of epilepsy. (revised per Amendment 01)
5. Subjects who are currently receiving monotherapy treatment may receive perampanel as monotherapy if, in the investigator's judgment, the subject may benefit from a change in monotherapy treatment. Subjects must not have previously received adjunctive AED treatment.
6. If antidepressants or antianxiety drugs are used, subjects must be on a stable dose regimen of these drugs during the 8 weeks before Visit 2 (Week 0).

Exclusion Criteria

1. Subjects should not have previously received or currently be receiving perampanel.
2. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG or hCG); a separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the 1st dose of study drug.
3. Females of childbearing potential who:

   - Within 28 days before study entry, 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
     - An oral contraceptive (with additional barrier method if using contraceptive containing levogesterol); 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

   For sites outside of the EU, 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).
4. Presence of or previous history of Lennox-Gastaut syndrome
5. Presence of non-motor simple partial seizures only

6. A history of status epilepticus within 1 year before Screening Visit (Visit 1)
7. Subjects on antipsychotics or who have psychotic disorder(s) or unstable recurrent affective disorder(s) with a history of attempted suicide within 1 year before Screening Visit (Visit 1)
8. Presence of a progressive central nervous system (CNS) disease, including degenerative CNS diseases and progressive tumors
9. Concomitant use of barbiturates (except for seizure control indication and premedication for EEG) and benzodiazepines (except for seizure control indication) within 8 weeks prior to Visit 2 (Week 0)
10. Use of intermittent rescue benzodiazepines (ie, 1-2 doses over a 24-hour period is considered a 1-time rescue) 2 or more times in the 8 week period prior to Visit 2 (Week 0)
11. Severe renal insufficiency (defined by estimated glomerular filtration rate of <30 mL/min) or subjects who receive hemodialysis
12. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal disease, hepatic disease) that in the opinion of the investigator(s) could affect the subject's safety or study conduct

    NOTE: Stable elevation of liver enzymes, alanine aminotransferase and aspartate aminotransferase due to concomitant medication(s), will be allowed if they are less than 3 times the upper limits of normal.
13. Hypersensitivity to perampanel or any excipients
14. Subjects with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
15. Subjects who are participating in other interventional clinical trial
16. Subject who are judged to have inadequate cognitive ability for participation in the study (intelligence quotient [IQ] <80 or investigator judgment)
17. Any suicidal ideation with intent with or without a plan, at the time of or within 6 months of screening, as indicated by answering "Yes" to questions 4 and 5 on the Suicidal Ideation section of the Columbia-Suicide Severity Rating Scale (C-SSRS)
18. Any lifetime suicidal behavior based on the C-SSRS
19. Concomitant use of any form of cannabidiol (CBD) (revised per Amendment 01)
20. Planned brain surgery during study participation (revised per Amendment 01)

Study Treatment

Test drug: E2007 (perampanel) oral tablet(s) (2, 4, 6, 8, 10, and/or 12 mg), QD before bedtime

Comparator Drug (if applicable): Not applicable

Duration of Treatment

Titration Period: up to 13 weeks (revised per Amendment 01)

Maintenance Period: 39 weeks

Concomitant Drug/Therapy

- Concomitant AEDs for subjects who receive perampanel as a 1st adjunctive therapy
  - Only 1 AED can be used.
  - A concomitant AED must be used at a stable dose administered between 8 weeks prior to Visit 2 (Week 0) and the end of Titration Period. The dose and administration of the AED

may be modified during the Maintenance Period based on the investigator's judgment.

- Concomitant medication

  The following concomitant drugs are prohibited throughout the study period (up to the Follow-Up Period or early discontinuation visit): (revised per Amendment 01)

  - Cytochrome P450(CYP)3A4-inducing drugs and food below as follows (from 30 days before Visit 1): Rifampicin, troglitazone, barbiturates except for use as AED, modafinil, efavirenz, nevirapine, glucocorticoid except for topical use, pioglitazone, rifabutin, and food containing St. John's Wort (*Hypericum perforatum)*. (revised per Amendment 01)
  - Antipsychotics
  - Other investigational drugs (revised per Amendment 01)
  - CBD products (revised per Amendment 01)

  Restricted concomitant drugs:

  - Any changes in the dosing regimen of antidepressant or antianxiety drugs during the study must be recorded.
  - Barbiturates (except for seizure control indication and premedication for EEG) and benzodiazepines (except for seizure control indication) within 8 weeks prior to Visit 2 (Week 0)

- Concomitant therapy (revised per Amendment 01)

  Prohibited concomitant therapy

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

  - Investigational device

  Restricted concomitant therapy:

  - Vagus nerve stimulation is allowed, but stimulator parameters cannot be changed for 8 weeks prior to Visit 2 (Week 0) or thereafter during the study.
  - A ketogenic diet will be allowed as long as the subject has been on this diet for 8 weeks prior to Visit 2 (Week 0). Additionally, a ketogenic diet cannot be newly added or discontinued during the study.

  Clarification of previous AED medication:

  - Subjects may switch monotherapies provided the time to complete the conversion is less than 30 days.
  - Subjects on short-term monotherapy (<2 weeks) may be eligible for the study provided they stop the initial therapy at the time of perampanel dosing.

Assessments

Efficacy Assessments

Exposure data will be utilized to assess the primary endpoint. Baseline seizure count (frequency) data will be collected retrospectively and prospectively from the subject or their guardian/legally authorized representative for up to 12 weeks before Visit 2 (Week 0). Subjects will be eligible for study enrollment after they have experienced the 2 unprovoked (or reflex) seizures occurring greater than 24 hours apart, or 1 unprovoked (or reflex) seizure with EEG evidence of seizures, and will not need to complete the full 12 week diary to enter the Titration Period. (revised per Amendment 01) The incidence of seizures during treatment will be assessed by prospective reference to seizure diaries or other information collected retrospectively. Diaries will be reviewed at each study visit, as listed in the Schedule of Procedures/Assessments. Seizure frequency from prospective diary entries or principal investigator verification will be used to assess efficacy endpoints as appropriate.

(revised per Amendment 01)

Pharmacokinetic Assessments

Not applicable.

Pharmacodynamic Assessments

Not applicable.

Pharmacogenomic Assessments

Whole blood samples for preparation of genomic DNA may be obtained at baseline from subjects for additional exploratory analyses.

Safety Assessments

Safety will be assessed by monitoring and recording of all of AEs and serious adverse events (SAEs), discontinuation from treatment, prior and concomitant medication usage, periodic measurement of weight, and assessments of cognitive functioning and monitoring of suicidal thoughts or depressive symptoms. The C-SSRS will be administered at specified intervals.

Cognition will be assessed in patients 6 years of age and older using the EpiTrack® assessment tool. The EpiTrack (second edition with recently extended and revised norms) is a screening tool dedicated to the tracking of adverse cognitive effects of antiepileptic medication (Lutz and Helmstaedter, 2005). Studies have demonstrated the usefulness of the EpiTrack with regard to cognitive monitoring of the impact of pharmacological treatments (Lutz and Helmstaedter, 2005; Helmstaedter and Witt, 2008; Helmstaedter and Witt, 2010; Helmstaedter and Witt, 2013; Witt, et al., 2014). The test includes 6 subtests: response inhibition, visuo-motor speed, mental flexibility, visual motor planning, verbal fluency, and working memory. Based on the subtest results, an age-corrected total score is calculated. Higher scores reflect better performance with a maximum score of 49 points. The interval for mild impairment is 29 to 31 points, and the cutoff for significant impairment is 28 or fewer points. Practice corrected reliable change indices indicate a significant change with a gain of more than 3 points and a loss of more than 2 points. The EpiTrack Junior will be administered for subjects ages ≥6 to 16 years old. (revised per Amendment 01)

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

The Pittsburgh Sleep Quality Index (PSQI) is a retrospective sleep quality instrument with 19 items (Buysse, et al., 1989). It measures subjects' perspectives on sleep parameters (length of sleep, sleep disturbances), sleep quality, and impact on daily functioning. The PSQI will be administered to patients 12 years of age and older.

The Quality of Life in Epilepsy Inventory-31 (QOLIE-31) is a survey of health-related quality of life for adults (18 years or older) with epilepsy.

An assessment of suicidality will be performed using the C-SSRS, which is a series of questions about suicidal thoughts and behaviors. The C-SSRS will be administered to patients 6 years of age and older. Subjects under 6 years of age will be clinically monitored for suicidality. (revised per Amendment 01)

Bioanalytical Methods

Not applicable.

Statistical Methods

All summaries of efficacy will be produced by seizure type (POS and PGTCS). Summaries of safety data will be produced by seizure type (POS and PGTCS) and overall.

Study Endpoints
Primary Endpoint:

- Retention rate, defined as the proportion of subjects remaining on perampanel at the specified time points: 3, 6, 9, and 12 months after initiation of treatment.

Secondary Endpoints

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

Exploratory Endpoints:

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

Analysis Sets

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

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

Efficacy Analyses

The SAS will be used to summarize retention rate and all safety data. The FAS will be used to summarize seizure data.

The retention rate, defined as the proportion of patients remaining on perampanel treatment at 3, 6, 9, and 12 months after initiation of treatment, will be summarized. The number and percentage of subjects remaining on treatment at each time point and 95% CIs will be summarized.

Analyses of exploratory efficacy endpoints will be performed in the subset of the FAS with sufficient baseline seizure frequency. All seizure-related summaries will be produced by seizure

type (POS, SGS, and PGTCS).

This is a study without a control arm. Therefore, formal hypothetical inferences are not necessary, and only descriptive statistics will be performed, as shown below.

For percent change in seizure frequency endpoints:

- Mean, standard deviation, median (95% CIs), minimum, and maximum will be provided.

For responder rate endpoints:

- Number of responders
- Responder rate and its 95% CI

The details for the analyses will be described in the statistical analysis plan.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetic Analyses

Not applicable.

Pharmacodynamic Analyses

Not applicable.

Pharmacogenomic Analyses

Variation in exposure of perampanel, baseline levels, and changes in clinical measurements (eg, efficacy or other safety parameters such as labs), or occurrence of AEs may be evaluated by testing for association of genetic variants with these measurements or traits. Details of any pharmacogenomic analyses will be described and reported separately.

Safety Analyses

For AEs, drug-related AEs, SAEs and AEs leading to discontinuation, the frequency and percent will be provided. All AEs will be categorized by system organ class (SOC) and preferred term (PT) assigned to the event using Medical Dictionary for Regulatory Activities (MedDRA) terms. Suicidality will be assessed using the C-SSRS and summaries will include the incidence of suicidal behavior and suicidal ideation. Cognitive function in subjects 6 years of age and older will be evaluated using EpiTrack; the EpiTrack Junior will be administered for subjects ages ≥6 to 16 years old. (revised per Amendment 01). Summaries of the proportion of subjects with no/mild/clear cognitive impairment and shifts between these categories from baseline to end of treatment will be produced. The BDI-II will be used to assess depression.

Vital signs and body weight will be summarized.

A laboratory value that is considered abnormal and clinically significant may meet the criteria to qualify as an AE. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event electronic Case Report Form (eCRF).

Other Analyses

Duration of treatment and summaries of maximum and last dose will be produced.

Interim Analyses

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

Sample Size Rationale

The efficacy of perampanel as monotherapy and 1st adjunctive therapy for POS and PGTCS is to be evaluated. The primary endpoint is retention rate. The study is to enroll approximately 125 subjects. This sample size is considered adequate for an open-label Phase 4 study where there

is no statistical hypothesis to be tested. (revised per Amendment 01)

3 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
AED	antiepileptic drug
BDI-II	Beck Depression Inventory-II
CBD	cannabidiol
CNS	central nervous system
CRA	Clinical Research Associate
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
eCRF	electronic Case Report Form
FAS	full analysis set
hCG	human chorionic gonadotropin
ICF	informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IQ	intelligence quotient
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator's Study File
MedDRA	Medical Dictionary for Regulatory Activities
PGTCS	primary generalized tonic-clonic seizures
PI	principal investigator
POS	partial-onset seizures
PSQI	Pittsburgh Sleep Quality Index
PT	preferred term
QD	once daily
QOLIE-31	Quality of Life in Epilepsy Inventory-31
SAE	serious adverse event
SAS	safety analysis set
SGS	secondarily generalized seizures
SOC	system organ class
TEAE	treatment-emergent adverse event

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 on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 (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 (PI) 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 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 investigators or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC 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.

At the end of the study, the sponsor should notify the IRB/IEC within the period, according to requirement of each IRB/IEC.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC within the period, according to requirement of each IRB/IEC, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures 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 (2008)

- ICH E6 Guideline for GCP of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH (CPMP/ICH/135/95)

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject and/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 and/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 at Visit 1 before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

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, kept on file and archived by the investigator in the Investigator's Study File (ISF).

The subject and/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 Inc. at up to approximately 25 investigational sites in the US. (revised per Amendment 01)

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the Contract Research Organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

7 INTRODUCTION

7.1 Planned Indication

Perampanel (E2007; Fycompa®) is a potent, orally active, noncompetitive, and highly selective α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist. Perampanel tablets were approved for marketing as an adjunctive therapy for the treatment of partial-onset seizures (POS) with or without secondarily generalized seizures (SGS) in subjects aged 12 years and older in the EU in July 2012, in the US in October 2012, and in other countries subsequently. Perampanel was also approved for marketing as an adjunctive therapy for the treatment of primary generalized tonic-clonic seizures (PGTCS) in subjects with epilepsy aged 12 years and older in the EU and the US in June 2015, and in other countries subsequently. Perampanel was approved for treatment of POS with or without SGS in patients with epilepsy 4 years of age and older in September 2018. (revised per Amendment 01)

7.2 Study Rationale

Currently, there is little information from clinical studies regarding the use of perampanel as monotherapy; however, in clinical practice, doctors routinely prescribe antiepileptic drugs (AEDs) approved for adjunctive use as monotherapy or withdraw other drugs to monotherapy as per clinical response. In a meeting between Eisai and the European Medicines Agency, the usefulness of information about withdrawal of previous AEDs in the context of combination therapy with perampanel was acknowledged. In particular, observational studies were recognized as an option to collect real-world clinical data to add to the Summary of Product Characteristics for perampanel. Moreover, according to the "Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders" (CHMP/EWP/566/98 Rev.2/Corr) from the European Medicines Agency, the availability of data regarding clinical use of perampanel as adjunctive therapy or monotherapy would be informative for patient management and useful to include in the Summary of Product Characteristics.

Early adjunctive therapy is a frequent modality of use, for which there is limited information for perampanel, since the adjunctive therapy registration studies use late adjunctive therapy in a treatment-resistant patient population.

8 STUDY OBJECTIVES

8.1 Primary Objective:

- To assess the retention rate of perampanel when given as monotherapy or 1st adjunctive therapy in subjects with POS or PGTCS

8.2 Secondary Objectives:

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

8.3 Exploratory Objectives:

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

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multi-center, open-label, Phase 4 study. Subjects who meet all of the inclusion and none of the exclusion criteria will receive perampanel. Baseline seizure counts (frequency) data will be collected by subjects or guardian/legally authorized representative, retrospectively (for history prior to screening) and prospectively as needed (during baseline). The study consists of 4 periods: a Screening Period (to start no earlier than 6 weeks before

the 1st dose of study drug), a Titration Period (up to 13 weeks), a Maintenance Period (39 weeks), and a Follow-up Period (4 weeks). The study duration for each subject is expected to be approximately 1 year in total. (revised per Amendment 01)

Study subjects will include the following:

- Subjects who have been diagnosed with POS or PGTCS but have not previously received treatment with an AED or are currently receiving monotherapy treatment (no history of AED polytherapy) and wish to switch to another monotherapy treatment; or
- Subjects who are currently receiving treatment with a single AED administered at a stable dose for at least 8 weeks before Visit 2 (Week 0) and need additional AED treatment; subjects should not have previously received adjunctive AED therapy

9.1.1 Screening Period (Week -6 ~ Week 0)

The Screening Visit (Visit 1) will take place no earlier than 6 weeks before the 1st dose of study drug. Seizure data from up to 12 weeks preceding 1st dose will be collected by the investigator, including retrospective data collection as needed. Subjects will be eligible for study enrollment after they have experienced either the 2 required unprovoked (or reflex) seizures or the 1 unprovoked (or reflex) seizure with EEG evidence of seizures, and they will not need to complete the full 12 week diary to enter the Titration Period. (revised per Amendment 01) Subjects without the required seizure data will fail screening, but may be rescreened 1 time. During the Screening Period, informed consent will be obtained and screening assessments will be conducted.

Before or at the Screening Visit (Visit 1), informed consent will be obtained after the study has been fully explained to each subject and before any baseline procedures or assessments are conducted. Procedures to be followed when obtaining informed consent are detailed in Section 5.3.

Investigators will confirm the inclusion/exclusion criteria and will conduct the planned evaluations. Subjects should be no younger than 4 years of age and able to swallow perampanel tablets. They must have been diagnosed with epilepsy, consisting of POS with or without SGS or PGTCS. (revised per Amendment 01) Additionally, they must need monotherapy or they must need 1st adjunctive therapy with perampanel after failure to control seizures on monotherapy with another AED at the optimal dose and duration for that AED.

Screening results must be recorded on the appropriate electronic Case Report Form (eCRF) to indicate whether or not the subject is eligible to participate in the study and to provide reasons for screen failure if applicable. In addition, medical history, prior concomitant medications and prior concomitant AED of subjects will be obtained. Subjects who complete Visit 2 (Week 0) and meet all of the inclusion/exclusion criteria (Section 9.3.1 and Section 9.3.2) will be enrolled and will begin the Titration Period.

9.1.2 Titration Period

The Titration Period will begin with Visit 2, which may overlap with the Screening Visit (Visit 1), and will last for up to 13 weeks. (revised per Amendment 01) Subjects will receive perampanel tablets once daily (QD) before bedtime. The initial dose of perampanel 2 mg/day may be up-titrated in increments of 2 mg according to the investigator's judgment, based on individual clinical response and tolerability, as shown in the following dosing schedule (Table 1):

Table 1 Dosing Titration Schedule

Category	Week[a]	Perampanel Dose (mg/day)
Required	1	2
	2	2
	3	4
	4	4
		Telephone Visit
Optional Escalation[b]	5	6
	6	6
		Follow-Up Telephone Call[c]
	7	8
	8	8
		Follow-Up Telephone Call[c]
	9	10
	10	10
		Follow-Up Telephone Call[c]
	11	12
	12	12
	13	12

a: Subjects on a concomitant enzyme-inducing antiepileptic drug may be up-titrated at 1-week intervals if needed.

b: Subjects should be titrated to 4 mg. Additional dose escalation is optional depending on subject response and tolerability, following assessment by Telephone Visit or follow-up calls.

c: If needed; investigator should follow up with subject via telephone call prior to further dose escalation.

Treatment will initially be titrated up to perampanel 4 mg based on clinical response and tolerability. Thereafter, titration will be based on the investigator's judgment; subjects may have further dose increases in increments of 2 mg, per evaluation by the investigator (Telephone Visit 3) prior to further dose escalation. The maximum dose is 12 mg. At least 2 weeks must elapse between dose increases, with the exception of subjects who are taking any concomitant drug that shortens the half-life of perampanel (eg, phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine), in which case the treatment may be up-titrated at 1-week intervals if needed. Sites must enter the perampanel dosing information

into the Interactive Response Technology (IRT) system on Weeks 2, 4, 6, 8, 10, and 12 to track subject dosing. Adjustments of the concomitant AED dose level during the Titration Period are not permitted. (revised per Amendment 01)

The perampanel dose can be down-titrated based on tolerability, at the discretion of the investigator. Subjects who cannot tolerate the 4 mg dose by the end of the Titration Period will be discontinued from the study.

9.1.3 Maintenance Period

Maintenance Period

Subjects will continue to receive the perampanel dose level that was administered at the end of the Titration Period, when they enter the 39-week Maintenance Period. Subjects will come to the study site for Visit 4 (Week 13), Visit 5 (Week 26), Visit 6 (Week 39), Visit 7 (Week 52), and at the Follow-Up Visit (Visit 8). All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments. (revised per Amendment 01)

According to the investigator's clinical judgment, subjects who experience AEs may have their perampanel dose reduced. Conversely, if seizures are not adequately controlled, subjects may have their dose increased up to a maximum of perampanel 12 mg. During the Maintenance Period, subjects whose perampanel dose has been reduced may have the dose increased again, at the discretion of the investigator, as soon as tolerability improves. Subjects who cannot tolerate a dose of 4 mg will discontinue perampanel treatment and be withdrawn from the study. Adjustment of the concomitant AED dose level during the Maintenance Period is permitted. Subjects who receive perampanel as a 1st adjunctive therapy may also be converted to perampanel monotherapy at the discretion of the investigator. All adjustments to concomitant AED dose levels must be reported in the eCRF.

The overall study design is depicted in Figure 1.

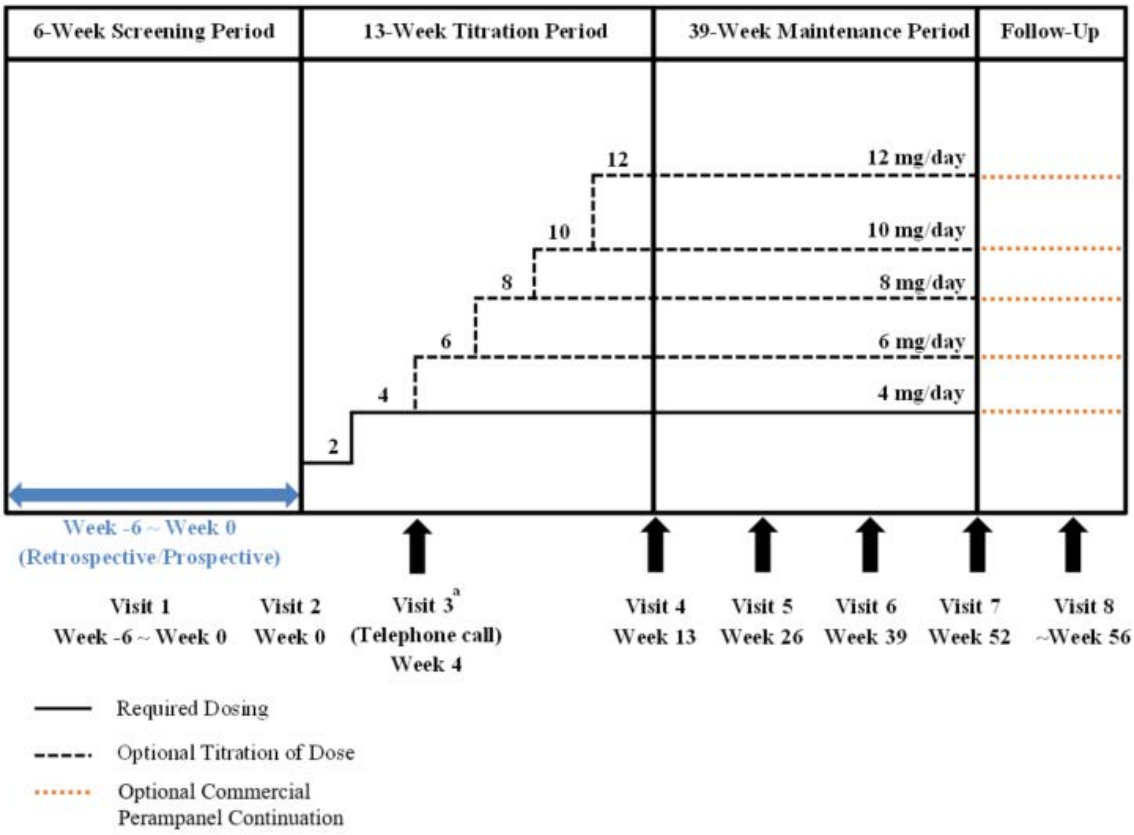

Figure 1 Study Design

a: Follow-up phone calls to Visit 3 will be performed biweekly, as necessary, for dose adjustment according to the discretion of the investigator. Dose adjustments and rationale, as well as any adverse events will be recorded in the electronic case report form.

9.1.4 Follow-Up Period (4 weeks)

The Follow-Up Period will begin at the end of the Maintenance Period. Subjects may continue to receive commercial perampanel during the Follow-Up Period. (revised per Amendment 01) At the end of the Follow-Up Period, a Follow-Up Visit will take place. Subjects who are withdrawn from the study for any reason will also undergo a Follow-Up Visit.

The end of the study will be the date of the last study visit for the last subject. However, if there are AEs that are present and not resolved at the last scheduled visit, these AEs should be followed to stabilization or resolution.

9.2 Discussion of Study Design

9.2.1 Rationale for Subject Population

Perampanel has been extensively evaluated in multiple Phase 3 studies, predominantly in a refractory patient population. The Phase 3 study protocols specified that subjects should have failed therapy with at least 2 AEDs and currently be administered 1 to 3 concomitant AEDs. The current study aims to obtain data in earlier-onset subject groups who require initial AED therapy either with monotherapy or a 1st adjunctive therapy. These data will complement the extensive data that are already available for perampanel and will support its use in early-onset patients.

9.2.2 Rationale for Efficacy Endpoints

According to "Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders" provided by European Medicines Agency, in an adjunctive study, the primary endpoint should dichotomize the data into responders/non-responders, where responders are subjects who obtained at least a certain pre-defined percentage reduction of seizure frequency (Steinhoff, et al., 2013). Retention rate is commonly used for studies resembling real life, as it represents the result of satisfactory efficacy and safety.

The primary efficacy endpoint is the retention rate of perampanel when given as monotherapy or 1st adjunctive therapy in subjects with POS or PGTCS.

9.2.3 Rationale for Prohibited/Restricted Concomitant Drug/Therapy

For the evaluation of perampanel as 1st adjunctive therapy, 1 concomitant AED is permitted, if it has been administered at a stable dose for 8 weeks before Visit 2 (Week 0). Details of prohibited/restricted concomitant drugs and other therapy are presented in Section 9.4.7.

9.3 Selection of Study Population

Approximately 125 subjects will be entered at up to approximately 25 sites in the US. (revised per Amendment 01) 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.

9.3.1 Inclusion Criteria

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

1. Subjects will be male or female and no younger than 4 years of age and be able to swallow perampanel tablets. (revised per Amendment 01)
2. Subjects must have a diagnosis of epilepsy with POS with or without SGS, or with PGTCS. Either of the following must have occurred to support an epilepsy diagnosis: (revised per Amendment 01)
   a. At least 2 unprovoked (or reflex) seizures occurring greater than 24 hours apart

b. 1 unprovoked (or reflex) seizure with EEG evidence of seizures

3. Subjects who receive perampanel as a 1st adjunctive therapy must currently have been treated with stable doses of monotherapy with an AED for 8 weeks prior to Visit 2 (Week 0), have not previously received adjunctive AED treatment, and must, in the investigator's judgement, be in need of initial adjunctive therapy after failure to control seizures with AED monotherapy, at the optimal dose and duration. (revised per Amendment 01)
4. Subjects who receive perampanel as monotherapy, who were newly diagnosed (treatment naïve), following the defined diagnosis of epilepsy. (revised per Amendment 01)
5. Subjects who are currently receiving monotherapy treatment may receive perampanel as monotherapy if, in the investigator's judgment, the subject may benefit from a change in monotherapy treatment. Subjects must not have previously received adjunctive AED treatment.
6. If antidepressants or antianxiety drugs are used, subjects must be on a stable dose regimen of these drugs during the 8 weeks before Visit 2 (Week 0).

9.3.2 Exclusion Criteria

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

1. Subjects should not have previously received or currently be receiving perampanel.
2. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG] [or human chorionic gonadotropin (hCG)] test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG [or hCG]); a separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the 1st dose of study drug.
3. Females of childbearing potential who:
   - Within 28 days before study entry, 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
     - An oral contraceptive (with additional barrier method if using contraceptive containing levogesterol); 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

   For sites outside of the EU, 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).

4. Presence of or previous history of Lennox-Gastaut syndrome
5. Presence of non-motor simple partial seizures only
6. A history of status epilepticus within 1 year before Screening Visit (Visit 1)
7. Subjects on antipsychotics or who have psychotic disorder(s) or unstable recurrent affective disorder(s) with a history of attempted suicide within 1 year before Screening Visit (Visit 1)
8. Presence of a progressive central nervous system (CNS) disease, including degenerative CNS diseases and progressive tumors
9. Concomitant use of barbiturates (except for seizure control indication and premedication for EEG) and benzodiazepines (except for seizure control indication) within 8 weeks prior to Visit 2 (Week 0)
10. Use of intermittent rescue benzodiazepines (ie, 1-2 doses over a 24-hour period is considered a 1-time rescue) 2 or more times in the 8 week period prior to Visit 2 (Week 0)
11. Severe renal insufficiency (defined by estimated glomerular filtration rate of <30 mL/min) or subjects who receive hemodialysis
12. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal disease, hepatic disease) that in the opinion of the investigator(s) could affect the subject′s safety or study conduct

    NOTE: Stable elevation of liver enzymes, alanine aminotransferase and aspartate aminotransferase due to concomitant medication(s), will be allowed if they are less than 3 times the upper limits of normal.
13. Hypersensitivity to perampanel or any excipients
14. Subjects with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
15. Subjects who are participating in other interventional clinical trial
16. Subject who are judged to have inadequate cognitive ability for participation in the study (intelligence quotient [IQ] <80 or investigator judgment)
17. Any suicidal ideation with intent with or without a plan, at the time of or within 6 months of Screening, as indicated by answering “Yes” to questions 4 and 5 on the Suicidal Ideation section of the Columbia-Suicide Severity Rating Scale (C-SSRS)
18. Any lifetime suicidal behavior based on the C-SSRS
19. Concomitant use of any form of cannabidiol (CBD) (revised per Amendment 01)
20. Planned brain surgery during study participation (revised per Amendment 01)

9.3.3 Removal of Subjects from Therapy or Assessment

9.3.3.1 Scheduled Termination

Subjects will be considered to have completed the Titration Period after up to 13 weeks of titration treatment and completion of the Visit 4 (Week 13) visit procedures. (revised per Amendment 01) Subjects who have completed the Titration Period will enter the Maintenance Period. Subjects will be considered to have completed the Maintenance Period after 39 weeks of maintenance treatment and completion of the Visit 7 (Week 52) visit procedures. Upon completion of the Titration Period, the Maintenance Period, and the Follow-Up Period, and after resolution of any AEs that may be present on the last visit, the subject will be considered to have completed the study.

9.3.3.2 Withdrawals

Subjects who were administered at least 1 dose of study drug but could not participate in the study are classified as 'withdrawals'. 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.

Reasons for withdrawal are as the following:

- Withdrawal of informed consent
- AE(s) requiring discontinuation of study therapy
- Eligibility violation
- Lack of efficacy
- Administration of prohibited medications
- Lost to follow-up
- Unable to continue the study in the investigator's judgment

The investigator will make every reasonable effort to follow up subjects for any AEs. He/she will use all possible ways to communicate (phone call, letters, and visit to home) with the subject. The reason for withdrawal should be documented on the eCRF. Final assessments of withdrawn subjects should be conducted and documented as described in Section 9.6.1. Withdrawn subjects will not be allowed to re-enter the study.

9.4 Treatment

9.4.1 Treatment Administered

Perampanel will be administered to subjects during each study period. Tablets at the assigned dose strength will be taken orally once daily before bedtime. At the beginning of the Titration Period, oral perampanel will start at a dose of 2 mg QD. Doses of perampanel will then be up-titrated in increments of 2 mg/day at no less than 2-week intervals according to the investigator's judgment. At the 4 mg dose (Week 4, telephone call, Visit 3), the investigator will confirm whether further dose escalation is needed based on subject response

and tolerability. The investigator may adjust dosing further or leave the subject at 4 mg. The maximum dose is 12 mg. Subjects who are taking concomitant AEDs that are known cytochrome P450 (CYP) enzyme inducers (eg, phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine) which shorten the half-life of perampanel, can undergo up-titration in 2-mg increments at intervals of at least 1 week.

The study drug will be dispensed to each subject or guardian/legally authorized representative at Visit 2 (Week 0), Visit 4 (Week 13), Visit 5 (Week 26), and Visit 6 (Week 39). Sites must enter the perampanel dosing information into the IRT system on Weeks 2, 4, 6, 8, 10, and 12 to track subject dosing. (revised per Amendment 01)

Tablet(s) cannot be split, broken or crushed prior to administration, and should be administered whole at bedtime.

9.4.2 Identity of Investigational Product

- Perampanel will be supplied by the sponsor.
- Product name/manufacturer: Fycompa/Eisai Inc.
- Formulation/drug appearance is presented in Table 2.
- Storage condition: 20°C to 25°C (68°F to 75°F) with excursions permitted at 15°C to 30°C (59°F to 86°F).

Table 2 Formulation/Drug Appearance

Tablet strength	Description
2 mg	Orange, round, biconvex, film-coated tablets
4 mg	Red, round, biconvex, film-coated tablets
6 mg	Pink, round, biconvex, film-coated tablets
8 mg	Purple, round, biconvex, film-coated tablets
10 mg	Green, round, biconvex, film-coated tablets
12 mg	Blue, round, biconvex, film-coated tablets

9.4.2.1 Chemical Name, Structural Formula of E2007

- Test drug code: E2007
- Generic name: Perampanel
- Chemical name: 2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl)benzonitrile
- Molecular formula: $C_{23}H_{15}N_3O$
- Molecular weight: 349.38 (anhydrous)

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

Test 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. Perampanel (E2007) is a Schedule III Controlled Drug Substance in the United States (US) and will be labeled as such for US sites.

9.4.2.4 Storage Conditions

Perampanel will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the perampanel is maintained within an established temperature range, 20°C to 25°C (68°F to 75°F) with excursions permitted at 15°C to 30°C (59°F to 86°F).

9.4.3 Method of Assigning Subjects to Treatment Group

This is an open-label study. An interactive voice response system will be used to register subjects into this 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 for the Titration Period and Maintenance Period. There is no randomization in this study.

9.4.4 Selection of Doses in the Study

Perampanel is approved for the treatment of POS, with or without SGS, in patients with epilepsy 4 years of age and older, and as adjunctive therapy of PGTCS, in patients with epilepsy 12 years of age and older. (revised per Amendment 01) The initial dose of perampanel will be 2 mg/day and this dose can be escalated by increments of 2 mg/day no more frequently than at weekly intervals, up to 12 mg, a maximum dose, depending on the clinical response and tolerability in subjects.

9.4.5 Selection and Timing of Dose for Each Subject

Subjects will begin receiving perampanel 2 mg/day and be up-titrated in increments of 2 mg to a maximum dose of 12 mg, depending on the clinical response and tolerability in each subject. Subjects will start taking study drug at bedtime at Visit 2 (Week 0).

9.4.6 Blinding

The study will not be blinded.

9.4.7 Prior and Concomitant Drug/Therapy

- Concomitant AED for subjects who receive perampanel as a 1st adjunctive therapy

- Only 1 AED can be used.
- A concomitant AED must be used at the stable dose and administered between 8 weeks before Visit 2 (Week 0) and the end of the Titration Period. The dose and administration of the AED may be modified during the Maintenance Period based on the investigator's judgment.

- Concomitant medication

  The following concomitant drugs are prohibited throughout the study period (up to the Follow-Up Period or early discontinuation visit): (revised per Amendment 01)
  - CYP3A4-inducing drugs and food below as follows (from 30 days before Visit 1): Rifampicin, troglitazone, barbiturates except for use as AED, modafinil, efavirenz, nevirapine, glucocorticoid except for topical use, pioglitazone, rifabutin, and food containing St. John's Wort (*Hypericum perforatum*). (revised per Amendment 01)
  - Antipsychotics
  - Other investigational drugs. (revised per Amendment 01).
  - CBD products (revised per Amendment 01)

  Restricted concomitant drug:
  - Any changes in the dosing regimen of antidepressant or antianxiety drugs during the study must be recorded.
  - Barbiturates (except for seizure control indication and premedication for EEG) and benzodiazepines (except for seizure control indication) within 8 weeks prior to Visit 2 (Week 0)

- Concomitant therapy (revised per Amendment 01)

  Prohibited concomitant therapy

  The following therapies must not be implemented during the study:
  - Investigational device

  Restricted concomitant therapy:
  - Vagus nerve stimulation is allowed, but stimulator parameters cannot be changed for 8 weeks before Visit 2 (Week 0) or thereafter during the study.
  - A ketogenic diet will be allowed as long as the subject has been on this diet for 8 weeks prior to Visit 2 (Week 0). Additionally, a ketogenic diet cannot be newly added or discontinued during the study.

  Clarification of previous AED medication:
  - Subjects may switch monotherapies provided the time to complete the conversion is less than 30 days.
  - Subjects on short-term monotherapy (<2 weeks) may be eligible for the study provided they stop the initial therapy at the time of perampanel dosing.

9.4.8 Treatment Compliance

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

The importance of compliance with the treatment regimen will be emphasized at each visit. The subject must be reminded to return all unused medication from the previous treatment period and report the number of tablet(s) lost to the investigator if tablet(s) are lost. The investigator or designated study site personnel should count the number of tablets returned by the subject and investigate the number of tablet(s) lost from the subject to establish the number of tablets used, and compare this to the number of tablets expected to be used for the period. A record of this reconciliation must be maintained using the accountability forms, and any issues of non-compliance discussed with the subject.

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- An investigator-signed and dated FDA Form FDA 1572, where applicable
- Financial disclosure form(s) for the PI and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the PI including a copy of the PI's current medical license medical registration number on the curriculum vitae
- A signed and dated clinical studies agreement
- A copy of the regulatory authority approval for the country in which the study is being conducted, and the Import License
- For US sites only: A copy of the controlled Substance Registration Certificate (DEA-Form 223), which must be current (ie, not expired) and have the appropriate controlled substance schedule listed for the study drug. Study drug will only be shipped to the exact address found on the DEA-Form 223 registration.

The investigator and 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 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 drug will not be dispensed to any individual who is not enrolled in the study, or to the guardian/legally authorized representative of an adolescent 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, and (d) documentation of returns to the sponsor. 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 (eg, FDA, Medicines and Healthcare products Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator 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 Demographic/Baseline Assessments

9.5.1.1.1 DEMOGRAPHY

Subject demography information will be collected at Screening Visit (Visit 1). Demography information includes date of birth (or age), sex.

9.5.1.1.2 DIAGNOSIS

The subject must have been diagnosed with epilepsy with POS (with or without SGS) or with PGTCS. To support an epilepsy diagnosis, either of the following must have occurred: at least 2 unprovoked (or reflex) seizures occurring greater than 24 hours apart, or 1 unprovoked (or reflex) seizure with EEG evidence of seizures. (revised per Amendment 01) In addition, subjects should be receiving treatment with a single AED, and need additional AED treatment or have not previously received treatment with an AED or are currently receiving monotherapy treatment (no history of AED polytherapy) and wish to switch to another monotherapy treatment.

9.5.1.1.3 SEIZURE TYPE AND FREQUENCY

Seizure type and frequency/interval from the 12 weeks preceding the 1st perampanel dose (Visit 2) will be collected by the investigator, including retrospective data collection as needed.

9.5.1.1.4 MEDICAL HISTORY

Medical and surgical history and current medical conditions will be recorded at the Screening Visit. All pertinent medical and surgical history within 5 years before the Screening Visit must be noted on the appropriate eCRF.

Vital signs including blood pressure, body temperature, respiratory rate and pulse rate will be performed as designated in Section 9.5.1.6.4. Documentation of vital signs will be included in the source documentation at the site. Weight should be recorded at each visit, and height should be recorded at baseline. For subjects <18 years of age, height should also be recorded at the last Follow-Up Visit.

Prior and concomitant medications including drug name, dosage, administration route, within 24 weeks (and as long as available, for AEDs) before the Screening Visit will be recorded.

9.5.1.1.5 CONCOMITANT ANTIEPILEPTIC DRUGS

AED treatment including drug name, dosage, and administration route, will be obtained throughout the study.

9.5.1.2 Efficacy Assessments

Exposure data will be utilized to assess the primary endpoint. Secondary efficacy variables will be based on seizure frequency. Seizure frequency data will be collected in subject diaries by subjects or guardian/legally authorized representative during the study including the Titration Period and the Maintenance Period. Baseline seizure frequency data for up to 12 weeks before Visit 2 (Week 0) will be collected by subjects or guardian/legally authorized representative, retrospectively (for history prior to screening) and prospectively (during baseline). Subjects will be eligible for study enrollment after they have experienced the 2 unprovoked (or reflex) seizures occurring greater than 24 hours apart, or 1 unprovoked (or

reflex) seizure with EEG evidence of seizures, and will not need to complete the full 12-week diary to enter the Titration Period. (revised per Amendment 01) Seizure frequency data in subject diaries will be reviewed with the investigator(s) at Visit 2, 4, 5, 6, and 7. Seizure frequency from diary entries or principal investigator verification will be used to assess efficacy endpoints as appropriate. (revised per Amendment 01)

9.5.1.3 Pharmacokinetic Assessments

Not applicable.

9.5.1.4 Pharmacodynamic Assessments

Not applicable.

9.5.1.5 Pharmacogenomic Assessments

Whole blood samples for preparation of genomic DNA may be obtained at baseline from subjects for additional exploratory analyses.

9.5.1.6 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and serious adverse events (SAEs); discontinuation from treatment, prior and concomitant medication usage, periodic measurement of weight, and assessments of cognitive functioning and monitoring of suicidal thoughts or depressive symptoms. The C-SSRS will be administered at specified intervals.

9.5.1.6.1 ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An AE is any untoward medical occurrence in a subject 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 is 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: A 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, electrocardiography 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 at pretreatment (ie, at 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 observed during the study will be reported on the eCRF. 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. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF. 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 eCRF.

It is the responsibility of the investigator to review the results of the C-SSRS in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE.

All AEs must be followed for 28 days after the subject's last dose, or until resolution, whichever comes first.

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 eCRF. 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 9.5.1.6.2 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 eCRF 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.

9.5.1.6.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

A 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 AE 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.

In addition to the above, 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 1 of the above criteria. All AEs associated with special situations are to be reported on the eCRF 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

9.5.1.6.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 3. Subjects should be in a seated or supine position during blood collection. As depicted in the Schedule of Procedures/Assessments (Table 4), blood for clinical laboratory tests and urine for urinalysis will be collected at Screening. Clinical laboratory evaluations may be performed at other visits, per the investigator's discretion, if required for assessment of an AE.

Table 3 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential
Chemistry	
Electrolytes	Chloride, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, calcium, total cholesterol, glucose (fasting), lactate dehydrogenase, phosphorus, total protein, triglycerides, uric acid, lipid profile (fasting).
Urinalysis	glucose, ketones, occult blood, pH, protein, specific gravity, WBCs

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

A laboratory value that is considered abnormal and clinically significant may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.6.1) and the eCRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

9.5.1.6.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

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

9.5.1.6.5 EPITRACK

Cognition will be assessed in subjects 6 years of age and older at Visit 2 (Week 0) and at 3 and 12 month visits (Visits 4 and 7, respectively) using the EpiTrack® assessment tool.

The EpiTrack (second edition with recently extended and revised norms) is a screening tool dedicated to the tracking of adverse cognitive effects of antiepileptic medication (Lutz and Helmstaedter, 2005). Studies have demonstrated the usefulness of the EpiTrack with regard to cognitive monitoring of the impact of pharmacological treatments (Lutz and Helmstaedter, 2005; Helmstaedter and Witt, 2008; Helmstaedter and Witt, 2010; Helmstaedter and Witt, 2013; Witt, et al., 2014). The test includes 6 subtests: response inhibition, visuo-motor speed, mental flexibility, visual motor planning, verbal fluency, and working memory. Based on the subtest results, an age-corrected total score is calculated. Higher scores reflect better performance with a maximum score of 49 points. The interval for mild impairment is 29 to 31 points, and the cutoff for significant impairment is 28 points or less. Practice corrected reliable change indices indicate a significant change with a gain of more than 3 points and a loss of more than 2 points.

The EpiTrack Junior will be administered for subjects ages ≥6 to 16 years old. (revised per Amendment 01)

At the investigator's discretion, a subject may be excluded from the cognition assessments based on their assessment of the subject and the subject's capability to complete the assessment at baseline. If the cognition assessments are not done for a subject, the justification should be recorded in the eCRF.

9.5.1.6.6 BECK DEPRESSION INVENTORY-II

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

At the investigator's discretion, a subject may be excluded from the cognition assessments based on their assessment of the subject and the subject's capability to complete the assessment at baseline. If the cognition assessments are not done for a subject, the justification should be recorded in the eCRF.

9.5.1.6.7 PITTSBURGH SLEEP QUALITY INDEX

The Pittsburgh Sleep Quality Index (PSQI) is a retrospective sleep quality instrument with 19 items (Buysse et al., 1989). It measures subjects' perspectives on sleep parameters (length of sleep, sleep disturbances), sleep quality, and impact on daily functioning. The PSQI will be administered to patients 12 years of age and older.

9.5.1.6.8 QUALITY OF LIFE IN EPILEPSY INVENTORY-31

The Quality of Life in Epilepsy Inventory-31 is a survey of health-related quality of life for adults (18 years or older) with epilepsy.

9.5.1.6.9 COLUMBIA-SUICIDE SEVERITY RATING SCALE

An assessment of suicidality will be performed using the C-SSRS at the visits designated in the Schedule of Procedures/Assessments (Table 4). The C-SSRS will be administered to patients 6 years of age and older. Subjects under 6 years of age will be clinically monitored for suicidality. (revised per Amendment 01)

9.5.1.6.10 PREGNANCY TEST

A urine or serum-hCG pregnancy test will be performed during the Screening Period (Visit 1) and/or at Visit 2 (Week 0), Visit 6 (Week 39) and Follow-Up Visit for premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months.

9.5.1.7 Description of Procedures/Assessments Schedule

The study procedures and assessments are shown in Table 4.

9.5.2 Schedule of Procedures/Assessments

Table 4 Schedule of Procedures/Assessments in Study E2007-G000-410 (revised per Amendment 01)

Period	**Screening[a]**	**Titration[b] (Wk 0 to Wk 12)**				**Maintenance[b]**				**Early Discontinuation**	**Follow-Up[b,c]**	**Unscheduled[d]**
Study Week(s)	**Wk -6 to Wk 0**	**Wk 0**	**Wk 2[e]**	**Wk 4**	**Biweekly[f,g]**	**Wk 13**	**Wk 26**	**Wk 39**	**Wk 52**		**Wk 56**	
Study Day		**1**	**15**	**29**		**92**	**183**	**274**	**365**			
Visit Number	**1**	**2**		**3**		**4**	**5**	**6**	**7**		**8**	
Procedure/ Assessment												
Informed consent/assent[h]	X											
Inclusion/ exclusion criteria	X	X										
Demographic data	X											
Seizure type and frequency	X	X										
Medical history[i]	X											
Documentation of perampanel dose		X		X	X	X	X	X	X	X		
Concomitant medications	X[j]	X				X	X	X	X	X	X	X[d]
Concomitant AED	X[j]	X				X	X	X	X	X	X	X[d]
Vital signs	X	X				X	X	X	X	X	X	X[d]
Cognition assessment (EpiTrack)[k]		X				X			X	X		

Table 4 Schedule of Procedures/Assessments in Study E2007-G000-410 (revised per Amendment 01)

Period	Screening[a]	Titration[b] (Wk 0 to Wk 12)				Maintenance[b]				Early Discontinuation	Follow-Up[b,c]	Unscheduled[d]
Study Week(s)	**Wk -6 to Wk 0**	**Wk 0**	**Wk 2[e]**	**Wk 4**	**Biweekly[f,g]**	**Wk 13**	**Wk 26**	**Wk 39**	**Wk 52**		**Wk 56**	
Study Day		**1**	**15**	**29**		**92**	**183**	**274**	**365**			
Visit Number	**1**	**2**		**3**		**4**	**5**	**6**	**7**		**8**	
Procedure/ Assessment												
Depression assessment (BDI-II)		X				X			X	X		
QOLIE-31		X							X	X		
PSQI		X							X	X		
C-SSRS[l]	X	X				X	X	X	X	X		
Clinical laboratory evaluations[m]	X								X			
Blood sample for pharmacogenomics		X										
Pregnancy test	X	X[n]						X		X	X	
Adverse events	X	X		X	X	X	X	X	X	X	X	X
Dispense study drug		X				X	X	X				
Return study drug						X	X	X	X	X		
Study drug compliance						X	X	X	X	X		
Dispense subject diary	X[o]	X				X	X	X				

Table 4 Schedule of Procedures/Assessments in Study E2007-G000-410 (revised per Amendment 01)

Period	Screening[a]	Titration[b] (Wk 0 to Wk 12)				Maintenance[b]				Early Discontinuation	Follow-Up[b,c]	Unscheduled[d]
Study Week(s)	**Wk -6 to Wk 0**	**Wk 0**	**Wk 2[e]**	**Wk 4**	**Biweekly[f,g]**	**Wk 13**	**Wk 26**	**Wk 39**	**Wk 52**		**Wk 56**	
Study Day		**1**	**15**	**29**		**92**	**183**	**274**	**365**			
Visit Number	**1**	**2**		**3**		**4**	**5**	**6**	**7**		**8**	
Procedure/ Assessment												
Return and review subject diary		X				X	X	X	X	X		

AED = antiepileptic drug, BDI-II = Beck Depression Inventory II, eCRF = electronic Case Report Form, C-SSRS = Columbia-Suicide Severity Rating Scale, PSQI = Pittsburgh Sleep Quality Index, QOLIE-31 = Quality of Life in Epilepsy Inventory-31, Wk = week.

a: Up to 12 weeks of baseline seizure frequency to be determined at screening; any screening assessments may repeated during the Screening Period, at the discretion of the investigator.

b: Visit to be done within ±7 days of the schedule. Subjects may continue to receive commercial perampanel during the Follow-Up Period. (revised per Amendment 01)

c: To be completed by subjects who are withdrawn from the study for any reason after Visit 2 (Week 0) and before Visit 6 (Week 39). (revised per Amendment 01)

d: At the unscheduled visit, only the assessments that the investigator(s) judged necessary based on the subject's condition will be performed

e: At the end of Week 2, the perampanel dose increases from 2 to 4 mg; this is not a visit.

f: Telephone Visit; all dose adjustments and rationale for the adjustments, as well as adverse events will be recorded on the eCRF.

g: Follow-up telephone calls to Visit 3 may occur biweekly, or at a frequency of the investigator's discretion. All dose adjustments and rationale for adjustments, as well as adverse events will be recorded in the eCRF.

h: Informed consent/assent may be obtained prior to study start; it must be obtained prior to any study related procedures.

i: All pertinent medical and surgical history within 5 years before Visit 1 (Week 0).

j: Prior and concomitant medication(s) within 24 weeks (and as long as available for AED[s]) before Visit 2 (Week 0).

k: Subjects 6 years and older. EpiTrack Junior will be administered for subjects aged ≥6 to 16 years old. (revised per Amendment 01)

l: The C-SSRS will be administered to patients 6 years of age and older. Subjects under 6 years of age will be clinically monitored for suicidality. (revised per Amendment 01)

m: Any laboratory value that is considered abnormal and clinically significant will be reported as an adverse event. Clinical laboratory evaluations may be performed at other visits if required for assessment of an adverse event. Blood for laboratory evaluations must be collected in fasting state. (revised per Amendment 01)

n: Required only if a negative screening pregnancy test was obtained more than 72 hours before the 1st dose of study drug.

o: Subjects may also provide retrospective seizure frequency history if available.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of initial adjunctive treatment for POS with or without SGS.

The safety assessments to be performed in this study, including assessment of AEs and SAEs, discontinuation from treatment, prior and concomitant medication usage, periodic measurement of weight, and assessments of cognitive functioning and monitoring of suicidal thoughts or depressive symptoms, 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 (in US) no later than 1 business day or (in EU) no later than 24 hours from the time at which the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected through the last visit. 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 ISF.

For urgent safety issues call: Designated CRO (C&R Research) contact number.

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 ISF.

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.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor to be filed in the sponsor's Trial Master File.

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 ISF. 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

AEs 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 eCRF 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 eCRF.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators 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

AEs 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.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All suspected unexpected serious adverse reactions will be reported, as required, to the competent authorities of all involved European member states.

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 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: AE(s), lost to follow-up, subject choice, inadequate therapeutic effect, progression of disease, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for discontinuation. Study disposition information will be collected on the Subject Disposition eCRF.

A subject removed from the study for any reason may not be replaced.

9.5.6 Abuse or Diversion of Study Drug

During the study, the investigator will report any concern about abuse or diversion of study drug. AEs associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.4. Abuse is always to be captured as an AE.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the eCRF 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 eCRF must follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs 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 eCRF and external 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. Details of the statistical analyses will be included in a separate statistical analysis plan, which will be finalized before database lock.

9.7.1 Statistical and Analytical Plans

All summaries of seizure-related efficacy endpoints will be produced by seizure type (POS, SGS, and PGTCS). Summaries of retention rate and safety data will be produced by seizure type (POS and PGTCS) and overall.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

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

9.7.1.1.2 SECONDARY ENDPOINTS

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

9.7.1.1.3 EXPLORATORY ENDPOINTS

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

- Change in quality of life at the end of the Maintenance Period relative to baseline using the QOLIE-31

9.7.1.2 Definitions of Analysis Sets

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

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

9.7.1.3 Subject Disposition

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

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

9.7.1.4 Demographic/Baseline Characteristics

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

9.7.1.5 Prior and Concomitant Therapy

The number (percentage) of subjects who took prior and concomitant medications will be summarized on the SAS by Anatomical Therapeutic Chemical class. Prior medication is defined as any medication that stopped before the 1st dose of study drug. Concomitant medication is defined as any medication that (1) started before the 1st dose of study drug and was continuing at the time of the 1st dose of study drug, or (2) started on or after the date of the study drug until the last dose of study drug.

9.7.1.6 Efficacy Analyses

This is a study without a control arm. Therefore, formal hypothetical inferences are not necessary, and only descriptive statistics will be performed, as shown below:

For percent change in seizure frequency endpoints:

- Mean, standard deviation, median (95% CIs), minimum, and maximum will be provided.

For responder rate endpoints:

- Number of responders
- Responder rate and its 95% CI

The details for the analyses will be described in the statistical analysis plan.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

The SAS will be used to summarize retention rate. The retention rate, defined as the proportion of patients remaining on perampanel treatment at 3, 6, 9, and 12 months after initiation of treatment, will be summarized.

The number and percentage of subjects remaining on treatment at each time point and 95% CIs will be summarized.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

The FAS will be used to summarize seizure data.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

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

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Not applicable.

9.7.1.7.2 PHARMACODYNAMIC ANALYSES

Not applicable.

9.7.1.7.3 PHARMACOGENOMIC ANALYSES

Variation in exposure of perampanel, baseline levels and changes in clinical measurements (eg, efficacy or other safety parameters such as labs), or occurrence of AEs may be evaluated by testing for association of genetic variants with these measurements or traits. Details of any pharmacogenomic analyses will be described and reported separately.

9.7.1.8 Safety Analyses

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

include treatment-emergent adverse events (TEAEs) including SAEs and TEAEs resulting in discontinuation of perampanel.

9.7.1.8.1 EXTENT OF EXPOSURE

The extent of exposure to the study drug during the Titration and the Maintenance Period will be summarized descriptively.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA (most recent version) lower level term closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

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

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

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

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

9.7.1.8.3 COGNITION, DEPRESSION, AND SUICIDALITY

Cognitive function in subjects 6 years of age and older will be evaluated using EpiTrack. It will be administered at Visits 2, 4, and 7 (Weeks 0, 13, and 52, respectively). Summaries of the proportion of subjects with no/mild/clear cognitive impairment and shifts between these categories from baseline to end of treatment will be produced. The BDI-II will be used to assess depression. Suicidality will be assessed using the C-SSRS and summaries will include the incidence of suicidal behavior and suicidal ideation. The C-SSRS will be administered to patients 6 years of age and older. Subjects under 6 years of age will be clinically monitored for suicidality. (revised per Amendment 01)

9.7.1.8.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital signs and body weight will be summarized. Descriptive statistics for vital signs parameters, weight and changes from baseline will be presented by visit.

9.7.2 Determination of Sample Size

The efficacy of perampanel as monotherapy and 1st adjunctive therapy for POS and PGTCS is to be evaluated. The primary endpoint is retention rate. There is no statistical hypothesis to be tested in this study.

The study is to enroll approximately 125 subjects. (revised per Amendment 01)

9.7.3 Interim Analysis

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

9.7.4 Other Statistical/Analytical Issues

Not applicable.

10 REFERENCE LIST

Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index (PSQI): A new instrument for psychiatric research and practice. Psychiatry Res. 1989;28(2):193-213.

Helmstaedter C, Witt JA. The effects of levetiracetam on cognition: A non-interventional surveillance study. Epilepsy Behav. 2008;13(4):642-9.

Helmstaedter C, Witt JA. Cognitive outcome of antiepileptic treatment with levetiracetam versus carbamazepine monotherapy: A non-interventional surveillance trial. Epilepsy Behav. 2010;18:74–80.

Helmstaedter C, Witt JA. The longer-term cognitive effects of adjunctive antiepileptic treatment with lacosamide in comparison with lamotrigine and topiramate in a naturalistic outpatient setting. Epilepsy Behav. 2013;26:182–7.

Lutz MT, Helmstaedter C. EpiTrack: Tracking cognitive side effects of medication on attention and executive functions in patients with epilepsy. Epilepsy Behav. 2005;7:708-14.

Steinhoff BJ, Ben-Menachem E, Ryvlin P, Shorvon S, Kramer L, Satlin A, et al. Efficacy and safety of adjunctive perampanel for the treatment of refractory partial seizures: A pooled analysis of three phase III studies. Epilepsia. 2013;54(8):1481–9.

Witt JA, Werhahn KJ, Kramer G, Ruckes C, Trinka E, Helmstaedter C. Cognitive-behavioral screening in elderly patients with new-onset epilepsy before treatment. Acta Neurol Scand. 2014;130:172–7.

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's medical monitor 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, but the health or regulatory authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities 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/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 will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs 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 an interactive voice response system, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, magnetic resonance images, radioactive images, electrocardiographs, rhythm strips, EEG, 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
- eCRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

An eCRF is required and must be completed for each subject by qualified and authorized personnel. All data on the eCRF must reflect the corresponding source document, except when a section of the eCRF itself is used as the source document. Any correction to entries made on the eCRF 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 eCRF. The investigator will report the eCRFs to the sponsor and retain a copy of the eCRFs.

11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, 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, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of the period of 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 standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the PI (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. 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 to the sponsor's CRA or, when approval is given by the sponsor, will destroy supplies and containers at the site.

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

Not applicable.

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E2007-G000-410

Study Protocol Title: Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Perampanel as Monotherapy or First Adjunctive Therapy in Subjects with Partial Onset Seizures With or Without Secondarily Generalized Seizures or With Primary Generalized Tonic-Clonic Seizures

Investigational Product Name: E2007/Fycompa® (Perampanel)

SIGNATURES

Authors:

PPD

Date

Neurology Business Group
Eisai Inc.

PPD

Date

Neurology Business Group
Eisai Ltd.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number: E2007-G000-410

Study Protocol Title: Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Perampanel as Monotherapy or First Adjunctive Therapy in Subjects With Partial Onset Seizures With or Without Secondarily Generalized Seizures or With Primary Generalized Tonic-Clonic Seizures

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 ICH and all applicable local GCP guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date