1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2007-M065-412
Study Protocol Title:	Multicenter, open-label trial, evaluating the efficacy and safety of perampanel added to monotherapy in patients with partial onset seizures with or without secondary generalized seizures
Sponsor:	Eisai Korea Inc. 10F Revessant, 6, Bongeunsa-ro 86-gil, Gangnam-gu, Seoul, 06163, Korea
Investigational Product Name:	E2007/Fycompa® (Perampanel)
Indication:	Adjunctive therapy for partial-onset seizures in ≥12 years old epilepsy patients with or without secondarily generalized seizures
Phase:	4
Approval Date:	V1.0 19 Jan 2016 (original protocol) V2.0 29 Mar 2016 (Amendment 01) V2.1 11 Apr 2016 (Amendment 02)
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No. E2007
Name of Active Ingredient: Perampanel
Study Protocol Title Multicenter, open-label trial, evaluating the efficacy and safety of perampanel added to monotherapy in patients with partial onset seizures with or without secondary generalized seizures
Investigators Samsung Medical Center : Seung-Bong Hong Konkuk University Medical Center : Dong-Wook Kim Korea University Guro Hospital : Jee-Hyun Kim Seoul National University Bundang Hospital : Sung-Ho Park Samsung Medical Center : Dae-Won Seo Seoul National University Hospital : Sang-Gun Lee Seoul National University Hospital : Ki-Young Jeong Asan Medical Center : Sang-Ahm Lee Yonsei University Severance Hospital : Kyung Huh Yeungnam University Medical Center : Se-Jin Lee Inje University Haeundae Paik Hospital : Sung- Eun Kim Chonnam National University Hospital : Myoung-Gyu Kim Chungnam National University Hospital : Jae-Moon Kim
Sites Samsung Medical Center / 81, Irwon-ro, Gangnam-gu, Seoul, Korea Konkuk University Medical Center Korea / 120-1, Neungdong-ro, Gwangjin-gu, Seoul, Korea Korea University Guro Hospital / 148, Gurodong-ro, Guro-gu, Seoul, Korea Seoul National University Bundang Hospital / 82, Gumi-ro, 173, Beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do, Korea Samsung Medical Center / 81, Irwon-ro, Gangnam-gu, Seoul, Korea Seoul National University Hospital / 101, Daehak-ro, Jongno-gu, Seoul, Korea Seoul National University Hospital / 101, Daehak-ro, Jongno-gu, Seoul, Korea Asan Medical Center / 88, Olympic-ro, 43-gil, Songpa-gu, Seoul, Korea Yonsei University Severance Hospital / 50-1, Yonsei-ro, Seodaemun-gu, Seoul, Korea Yeungnam University Medical Center / 170, Hyeonchung-ro, Nam-gu, Daegu, Korea Inje University Haeundae Paik Hospital / 875, Haeun-daero, Haeundae-gu, Busan, Korea Chonnam National University Hospital / 42, Jebong-ro, Dong-gu, Gwangju, Korea Chungnam National University / 282 Munhwa-ro, Jung-gu, Daejeon, Korea
Study Period and Phase of Development

From January 2016 to April 2017, Phase 4

Objectives

Primary Objective

- To evaluate the efficacy of perampanel added to monotherapy for partial onset seizures with or without secondarily generalized seizures (total seizures) as measured by 50% responder rate

Secondary Objectives (major)

- To evaluate the safety of perampanel added to monotherapy for partial onset seizures with or without secondarily generalized seizures
- To evaluate efficacy of perampanel added to monotherapy for secondarily generalized tonic clonic seizure in partial onset seizures

Study Design

This is a multi-center, open-label, single-arm, phase 4 study. Subjects who meet all of the inclusion and none of the exclusion criteria will be received perampanel.

Baseline seizure counts (frequency) data is collected by subjects or guardian/legally authorized representative, retrospectively. The study consists of 2 periods; titration period (12 weeks) and maintenance period (24 weeks).

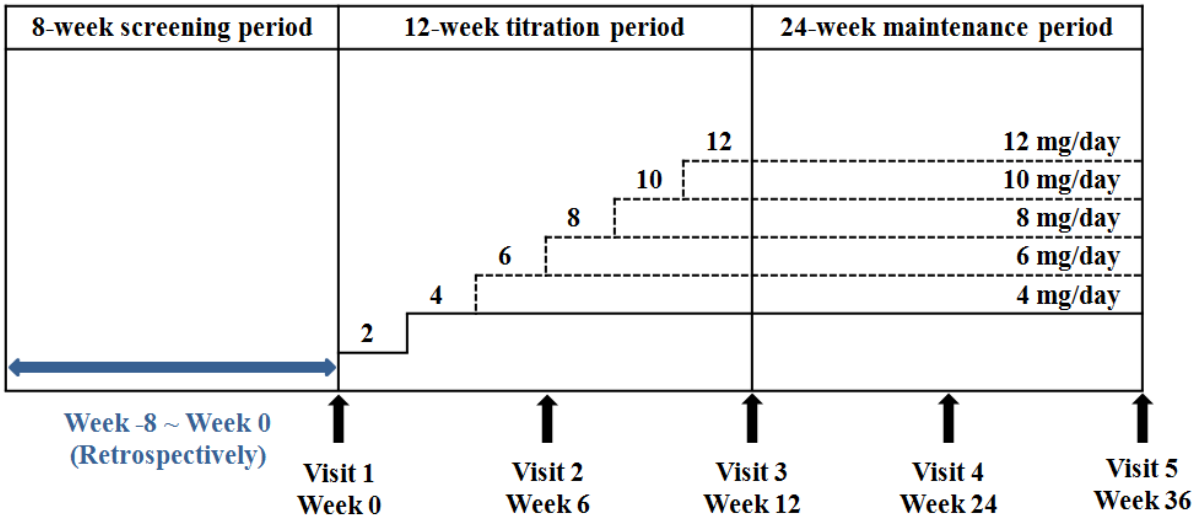
[Titration Period]

Subjects will begin receiving perampanel 2 mg/day and be up-titrated no less than 2-week intervals in increments of 2 mg up to 12 mg according to the investigator's judgment. Subjects experiencing intolerable adverse events (AEs) may remain on the same dose or have their dose reduced to the previously tolerated dose. Subjects who cannot tolerate the 4 mg dose will be discontinued from the study. Subjects who are taking any concomitant drug that shortens the half-life of perampanel (phenytoin, carbamazepine, oxcarbazepine, etc.) can be up-titrated by 2 mg no less than 1-week intervals, if needed. Adjustment of the concomitant anti-epileptic drug (AED) dose level during this period is not permitted.

[Maintenance Period]

Subjects will enter this period on the last dose they achieved at the end of the titration period and will continue taking this dose level once daily for the remainder of the study. According to the investigator's clinical judgment, subjects experiencing intolerable AEs can have their dose reduced and having failure to control seizure can have their dose increased up to 12 mg. During the Maintenance Period, subjects whose dose has been reduced can have the dose increased again, as soon as the tolerability improves. Subjects who cannot tolerate 4 mg dose will be discontinued from the study. Adjustment of the concomitant AED dose level during this period is not permitted.

In the case of tapering, withdrawal will be performed four weeks after last dose of perampanel.
Subjects will visit the study institution at Visit 1 (Week 0), Visit 2 (Week 6), Visit 3 (Week 12), Visit 4 (Week 24) and Visit 5 (Week 36).



Number of Subjects

Male and female subjects ≥ 12 years of age who have a diagnosis of epilepsy with partial-onset seizures with or without secondarily generalized seizures will be included in this study. Approximately 105 subjects will be enrolled.

Inclusion Criteria

1. Male or female and greater than or equal to 12 years of age
2. Have a diagnosis of epilepsy with partial onset seizures with or without secondarily generalized seizures according to the International League Against Epilepsy's Classification of Epileptic Seizures (1981)
3. Need an initial add-on therapy after failure to control seizures with the first or further monotherapy at the optimal dose and duration
4. Despite AED treatment within the last 8 weeks, subjects must have had ≥2 partial onset seizures and the interval between those seizures should be more than 24 hours prior to Visit 1 (Week 0).
5. Are currently being treated with stable doses of monotherapy for 8 weeks prior to Visit 1 (Week 0) [Standard AEDs]; Carbamazepine, phenytoin, zonisamide, phenobarbital, valproate, clobazam, clonazepam, primidone, gabapentin, topiramate, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, felbamate, vigabatrin
6. If antidepressants or antianxiety drugs are used, subjects on stable doses and administrations of antidepressants or antianxiety drugs for 8 weeks prior to Visit 1 (Week 0)

Exclusion Criteria

1. Females who are pregnant (positive β-hCG test) or breastfeeding
2. Presence of previous history of Lennox-Gastaut syndrome
3. Presence of nonmotor simple partial seizures only
4. Presence of primary generalized epilepsies or seizures such as absences and/or myoclonic epilepsies
5. A history of status epilepticus within 12 weeks before Visit 1 (Week 0)
6. 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 Visit 1 (Week 0)
7. Presence of a progressive central nervous system (CNS) disease, including degenerative CNS diseases and progressive tumors
8. Concomitant use of barbiturates (except for seizure control indication and premedication for electroencephalogram (EEG)) and benzodiazepines (except for seizure control indication) within 8 weeks prior to Visit 1 (Week 0)
9. Use of intermittent rescue benzodiazepines (i.e., 1-2 doses over a 24-hr period considered one-time rescue) 2 or more times in 8 weeks period prior to Visit 1 (Week 0)
10. Moderate to severe kidney problems or patients who receive hemodialysis. (Amendment 01)
11. Severe liver problems. (Amendment 01)
12. Hypersensitivity to perampanel or any substances of this drug. (Amendment 01)
13. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption (Amendment 01)
14. Patient who is participating in other intervention clinical trial. (Amendment 01)
15. Patient who judged to be inadequate to participate in the study by investigator

Study Treatment

Test drug: E2007 (perampanel) 2 mg oral tablet(s), once daily before bedtime

Comparator Drug (if applicable): Not applicable

Duration of Treatment

Titration period: 12 weeks

Maintenance period: 24 weeks

Concomitant Drug/Therapy

1. Concomitant antiepilepsy drugs (AED)
   a: Only one AED can be used
   A concomitant AED must be used at the stable dose and administration between 8 weeks prior to Visit 1 (Week 0) and the end of follow-up examination.

2. Concomitant medication
   a: Prohibited concomitant drug
   The following concomitant drugs are prohibited throughout the study period (up to

early discontinuation visit).

- The cytochrome P450 3A4 (CYP3A4)-inducing drugs and food below. If having been treated at enrollment, washout of these drugs is to start at the enrollment.
  [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*)]
- Antipsychotics
- Other trial drugs

b: Restricted concomitant drug
The dosing regimen of the following drugs must not be altered, newly introduced, or discontinued throughout the study (up to early discontinuation visit).
[Antidepressants and antianxiety drugs]

3. Concomitant therapy

a: Prohibited concomitant therapy
The following therapies must not concurrently implemented during the study.

- Brain surgery
- Medical device under clinical trial

b: Restricted concomitant therapy
A vagus nerve stimulation (VNS) is allowed, but stimulator parameters cannot be changed for 8 weeks prior to Visit 1 (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 1 (Week 0). Additionally, a ketogenic diet cannot be newly added or discontinued during the study.

Assessments

Efficacy Assessments

Primary efficacy variable:

50% responder rate in total seizures: 50% responders are defined as subjects who have at least 50% reduction in total seizure frequency during the Maintenance Period relative to the Baseline.

Secondary efficacy variables:

- 75% responder rate in total seizures
- 100% responder rate (seizure free rate) in total seizures
- The percent change in total seizure frequency in the Titration and Maintenance Period relative to the Baseline
- 50% responder rate in secondarily generalized tonic clonic seizures

- 75% responder rate in secondarily generalized tonic clonic seizures
- 100% responder rate (seizure free rate) in secondarily generalized tonic clonic seizures
- The percent change in secondarily generalized tonic clonic seizure frequency in the Titration and Maintenance Period relative to the Baseline

Pharmacokinetic Assessments
Not applicable

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments
Not applicable

Safety Assessments
Safety will be assessed by monitoring of AEs, withdrawal from treatment, clinical laboratory evaluations (hematology), vital signs

Other Assessments
Not applicable

Bioanalytical Methods
Not applicable

Statistical Methods
Study Endpoints
Primary Endpoint
50% responder rate in total seizures: The rate of subjects who have at least 50% reduction in seizure frequency during the Maintenance Period relative to the Baseline

Secondary Endpoints
- 75% responder rate in total seizures
- 100% responder rate (seizure free rate) in total seizures
- The percent change in total seizure frequency in the Titration and Maintenance Period relative to the Baseline
- 50% responder rate in secondarily generalized tonic clonic seizures
- 75% responder rate in secondarily generalized tonic clonic seizures
- 100% responder rate (seizure free rate) in secondarily generalized tonic clonic seizures
- The percent change in secondarily generalized tonic clonic seizure frequency in the Titration and Maintenance Period relative to the Baseline
- Adverse events, Laboratory evaluation, Vital signs.

Exploratory Endpoint
Not applicable

Analysis Sets

The Safety Analysis Set 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 is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose primary efficacy measurement.

The Per Protocol Set is the group of subjects who sufficiently complied with the protocol. Details of the evaluability criteria will be determined before database lock and will be specified in the Statistical Analysis Plan.

Efficacy Analyses

The efficacy analysis will be performed in the full analysis set. The per-protocol set will be supportive.

This is a single-arm study having no reference arm. Therefore, formal hypothetical inferences are not necessary and only descriptive statistics will be given.

Primary endpoint

For 50% Responder rate in total seizures:

- Number of 50% responders
- 50% responder rate and its 95% confidence interval (CI) will be provided.

Secondary endpoint

For 75% Responder rate in total seizures:

- Number of 75% responders in total seizures
- 75% responder rate in total seizures and its 95% CI will be provided.

For 100% Responder rate (seizure free) in total seizures:

- Number of 100% responder
- 100% responder rate and its 95% CI will be provided.

For total seizure frequency:

- Mean, standard deviation, median, minimum, maximum and 95% CI will be provided.

For 50% Responder rate in secondarily generalized tonic clonic seizures:

- Number of 50% responders
- 50% responder rate and its 95% CI will be provided.

For 75% Responder rate in secondarily generalized tonic clonic seizures:

- Number of 75% responders in total seizures
- 75% responder rate in total seizures and its 95% CI will be provided.

For 100% responder rate (seizure free) in secondarily generalized tonic clonic seizure:
- Number of 100% responders
- 100% responder rate and its 95% CI will be provided.

For seizure frequency in secondarily generalized tonic clonic seizure:
- Mean, standard deviation, median, minimum, maximum and 95% CI will be provided.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses
Not applicable

Pharmacokinetic Analyses
Not applicable

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses
Not applicable

Safety Analyses
For adverse events, drug-related adverse events, serious adverse events and adverse events leading to discontinuation, the frequency, percent and 95% confidence interval will be provided. All adverse events will be categorized by the body system and preferred term assigned to the event using Medical Dictionary for Regulatory Activities (MedDRA) terms.
Laboratory data, vital signs and body weight will be presented according to their scale. For continuous variable, the mean, standard deviation, median, minimum and maximum will be provided. For categorical variable, the shift table will be provided.

Other Analyses
Not applicable

Interim Analyses
No interim analysis is planned for this study.

Sample Size Rationale
This study will be evaluated for the efficacy of adjunctive perampanel for partial-onset seizures. Primary endpoint is 50% responder rate in total seizures.
There is no statistical hypothesis to be tested in this study and 105 subjects is set to keep 94 subjects for the primary analysis with approximately 10% drop-out rate from the view point of feasibility.
When 94 subjects for the primary analysis is kept and 50% responder rates can be assumed as 35.3% in test group and 19.3% as reference value according to Bernhard J. Steinhoff *et*

al.[1], lower limit of 95% confidence interval of 50% responder rate will be more than 19.3% with more than 90% power.

$$n = \frac{\left(Z_{\alpha/2} + Z_{\beta}\right)^2 \left[p_T(1 - p_T)\right]}{(p_T - p_R)^2}$$
$$= \frac{(1.96 + 1.282)^2 \left[0.353(1 - 0.353)\right]}{(0.353 - 0.193)^2}$$
$$= 93.78 \approx 94$$

$Z_{\alpha/2}$: Type I error (0.05/2)
Z_{β} : Type II error (0.1)
p_T : 50% responder rate in test group
p_R : reference value

Considering a drop-out rate of 10%, total sample size require 105.

[Reference]

Bernhard J. Steinhoff*et al*., Efficacy and safety of adjunctive perampanel for the treatmentof refractory partial seizures: A pooled analysisof three phase III studies, Epilepsia, 54(8):1481–1489, 2013doi: 10.1111/epi.12212

[Schedule of Procedures/Assessments in Study E2007-M065-412]

Period	Screening Period	Titration[a]			Maintenance[b]		Discontinuation	Follow-up[b,c]	Unscheduled[i]
Study Week(s)	**Week -8~0**	**Week 0**	**Week 6**	**Week 12**	**Week 24**	**Week 36**			
Study Day(s)	**Day -56~0**	**Day 0**	**Day 42**	**Day 84**	**Day 168**	**Day 252**			
Visit Number	**(Retrospectively)**	**1**	**2**	**3**	**4**	**5**			
Procedure/Assessment									
Informed consent/assent[d]		X							
Inclusion/exclusion criteria		X							
Demographic data		X							
Seizure type and frequency		X							
Medical history[e]		X							
Concomitant medications		X[f]	X	X	X	X	X	X	X
Concomitant AED		X[g]	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X
Clinical laboratory evaluations		X				X	X	X	
Pregnancy test		X				X	X	X	
Adverse events[h]			X	X	X	X	X	X	X
Dispense the study drug		X	X	X	X		X		
Return the study drug			X	X	X	X	X	X	
Study drug compliance			X	X	X	X	X	X	

[Schedule of Procedures/Assessments in Study E2007-M065-412]

Period	Screening Period	Titration[a]			Maintenance[b]		Discontinuation	Follow-up[b,c]	Unscheduled[i]
Study Week(s)	**Week -8~0**	**Week 0**	**Week 6**	**Week 12**	**Week 24**	**Week 36**			
Study Day(s)	**Day -56~0**	**Day 0**	**Day 42**	**Day 84**	**Day 168**	**Day 252**			
Visit Number	**(Retrospectively)**	**1**	**2**	**3**	**4**	**5**			
Procedure/Assessment									
Dispense subject diary		X	X	X	X		X		
Return and review subject diary			X	X	X	X	X	X	

a: All visits to be done within ±5 days of the schedule.
b: Visit to be done within ±7 days of the schedule.
c: To be completed by subjects who are withdrawn from the study for any reason after Visit 1 (Week 0) and before Visit 5 (Week 36). When a taper is provided after discontinuation, it should be performed 4 weeks after the last dose.
d: Informed consent/assent may be obtained prior to study start; it must be obtained prior to any study related procedures.
e: All pertinent medical and surgical history within 5 years before Visit 1 (Week 0).
f: Prior and concomitant medication(s) within 24 weeks before Visit 1 (Week 0).
g: Prior and concomitant AED.
h: Adverse events will be collected from the time subject starts to receive the study drug form through the last visit. Serious adverse events will be collected for 28 days after the subject's last dose or last visit, whichever is longer.
i: At the unscheduled visit, only the assessments that the investigator(s) judged the necessity based on the subject's condition will be performed.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADR	Adverse Drug Reaction
AE	Adverse Event
AED	Anti-Epilepsy Drug
AMPA	α-Amino-3-Hydroxy-5-Methyl-4-Isoxazole Propionic Acid
ATC	Anatomical Therapeutic Chemical
BP	Blood Pressure
CI	Confidence Interval
CNS	Central Nervous System
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
CYP	Cytochrome P450
ECG	Electrocardiography
ED_{50}	Effective Dose with 50% Reduction
EEG	Electroencephalogram
EMA	European Medicines Agency
f-EPSPs	Excitatory Postsynaptic Field Potentials
EU	European Union
FDA	Food and Drug Administration
GABA	γ-Amino-Butyric Acid
GCP	Good Clinical Practice
HIRA	Health Insurance Review & Assessment Service
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
ILAE	International League Against Epilepsy
IRB	Institutional Review Board
ISF	Investigator's Study File
ITT	Intention-to-Treat
LNH	Low/Normal/High
MedDRA	Medical Dictionary for Regulatory Activities
MES	Maximal Electroshock
MFDS	Ministry of Food and Drug Safety
MRI	Magnetic Resonance Imaging

Abbreviation	Term
NICE	National Institute for Health and Care Excellence
NMDA	*N*-Methyl-D-Aspartic Acid
OLE	Open-Label Evaluation
PK	Pharmacokinetic
POS	Partial-Onset Seizures
PT	Preferred Term
PTZ	Pentylenetetrazole
QD	Once Daily
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TD_{50}	Toxic Dose with 50% Reduction
TEAE	Treatment-Emergent Adverse Event
US	United States
VNS	Vagus Nerve Stimulation

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 Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 (Good Clinical Practice, GCP), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate(s) (CRA[s]), change of telephone number[s]). 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 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 (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Korea Good Clinical Practice (2014)

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 the 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 (the sponsor) at approximately 15 investigational sites in Korea.
The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and C&R research which is the contract research organization (CRO) are listed in the ISF provided to each site.

7 INTRODUCTION

7.1 Epilepsy

Epilepsy is a chronic neurological disorder characterized by recurrent seizures,[2] which are caused by excessive electrical discharges in the brain.[3] According to the Epilepsy Foundation, epilepsy is the fourth most common neurological disorder following migraine, stroke and Alzheimer's disease and affects approximately 50 million people worldwide.[4] The International League Against Epilepsy (ILAE) Commission on Classification and Terminology suggests two diagnostic process steps for clinical practice: 1) seizure type/epilepsy syndrome and 2) the cause of epilepsy.[5] ILAE established Classification of Epileptic Seizures in 1981 and Classification of Epilepsies and Epileptic Syndromes in 1989.[6] ILAE Task Force was appointed in 1997 in attempts to improve or complete the classifications and has published several reports; however, the guidelines have focused on proposing a diagnostic scheme rather than a replacement of the current international classification with refined classification, since the current classification is widely accepted.[6,7] Diagnosis of epilepsy requires electroencephalogram (EEG), computed tomography (CT) and magnetic resonance imaging (MRI) in addition to seizure type and epilepsy syndrome.[8] Syndromic diagnosis is not always feasible due to the complexity of epilepsies; therefore the Classification of Epileptic Seizures is simultaneously referred to supplement the diagnosis of epilepsy.[6] In 1981 Classification of Epileptic Seizures, seizures are classified into two main types, which are generalized seizures and focal seizures. Generalized seizures are further divided into tonic-clonic, absence, clonic, tonic, atonic and myoclonic, and focal seizures (partial-onset seizures, POS) are characterized by features such as aura, motor, autonomic and awareness/responsiveness.[9-11] Brief seizure episodes include involuntary movement of a part of the body (partial) or the whole body (generalized), and other than movement, the abnormal electrical changes may also disturb emotion/sensation, behavior and awareness of surroundings.[11] More specifically, generalized seizures are affected by both sides of the brain, originating from bilaterally distributed networks of the brain whereas POS start from one hemisphere of the brain.[10,11] POS are the most common type of seizures and shown on 60% of epilepsy patients.[12] Partial-onset seizures may arise from brain tumors, injury to brain,

infections in the brain, genetic/nerve disorders and stroke from brain vessels, however, the causes sometimes are unclear.

In South Korea, a nationwide epidemiological study had been conducted collaboratively by Korean Epilepsy Society and the department of Social & Preventive Medicine at Sungkyunkwan University School of Medicine using source data from Health Insurance Review & Assessment Service (HIRA) and medical records from medical institutions. In South Korea, 4.0 people in every 1,000 people have epilepsies (CI: 3.85~4.15), and there are 192,254 patients with epilepsies. Males (4.5) had higher prevalence rate than female (3.5), and children under 10 and elders over 70 showed higher rates than other age ranges. Among epilepsy diagnosis, 78.1% epilepsies were characterized with partial seizures, 8.0% generalized seizures, and 1.1% distinctive constellation.[13]

Although many different pathologic processes influence seizures and epilepsy, imbalance in neuronal excitability, specifically between neuronal inhibition and excitation, is thought to be a governing factor for neurological disorders. Animal experiments on excitatory glutamate receptors demonstrated an induced seizure activity with *N*-methyl-D-aspartic acid (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and kainate agonists and suppressed seizure activity by their antagonists.[14,15] By contrast to the excitatory receptors, inhibitory receptors of γ-amino-butyric acid (GABA) hindered seizure activity with $GABA_A$ receptor agonists such as barbiturates and benzodiazepines.[15] Number of anti-epileptic drugs (AEDs) have been generated, however, one-third of the patients experience nonadherence to current treatments and are at an increased risk of mortality, spinal and head injury from seizures, psychiatric disorders, prejudice, stigma and poor quality of life.[16] Chronic refractory patients with AED discontinuation are majorly influenced by adherence to treatment and poor tolerability on the available medications.[17]

7.2 Current Therapeutic Options

The use of AEDs is generally recommended after a second epileptic seizure according to the current guidelines. Appropriate AED is determined by number of factors such as type of seizure/epilepsy syndrome, individual/carer preferences, the presence of co-morbidity/concomitant drugs, potential drug interactions, childbearing potential, adverse effects and the licensed indications of the drug. Although monotherapy with a single AED as first-line treatment for epilepsy is suggested, adjunctive treatment is often required with one or more concomitant AEDs for the treatment. National Institute for Health and Care Excellence (NICE) guideline instructs the use of combination therapy ('add-on' therapy) only when attempts of monotherapy with a single AED (first-line or alternative first-line) have failed to produce seizure freedom. Discontinuation or withdrawal of AED therapy may be discussed with patients who have been seizure free for at least 2 years. Alternative approaches for refractory epilepsy involve psychological intervention, ketogenic diet or vagus nerve stimulation (VNS).[8]

AEDs are one of therapeutic class of drugs that are highly concerned with drug interaction due to its pharmacokinetic properties and adverse clinical consequences. A desirable antiepileptic effect is achieved with a certain plasma level of AEDs which is close to the plasma level that may lead to undesirable adverse effects. Loss of seizure control or signs of intoxication may result from subtle changes of the AED plasma concentration. Another major influence of pharmacokinetics of AEDs is on the activity of hepatic drug metabolizing enzymes. A wide variety of metabolization and elimination of other drugs that are affected by the same kind of enzymes may occur as a result of the pharmacokinetic interactions. Some AEDs stimulating hepatic metabolizing enzymes include phenytoin, carbamazepine, primidone and phenobarbital, and inhibitory AEDs are valproic acid, stiripentol and sulthiame.[18] Compared to the first-generation AEDs (phenytoin, phenobarbital, primidone, carbamazepine and valproate), many new AEDs developed since 1989 (second- and third-generation AEDs) are indicated to have less interaction with other drugs and no effect on hepatic enzyme activity. However, avoidance of hepatic metabolism results in eliminated unchanged through the kidneys, leaving susceptibility in metabolic interactions of the drugs which include gastrointestinal absorption, excretion (usually renal) and displacement of protein binding, mostly from plasma albumin binding. 16 new AEDs have been introduced after the first-generation AEDs: eslicarbazepine acetate, gabapentin, lamotrigine, oxcarbazepine, pregabalin, rufinamide, tiagabine, vigabatrin, zonisamide, felbamate, lacosamide, levetiracetam, perampanel, retigabine (ezogabine), stiripentol and topiramate.[19]
The current guidelines for pharmacological treatment of AEDs are generated into two versions in regard to epilepsy syndrome and seizure type.
Carbamazepine, lamotrigine, oxcarbazepine and sodium valproate are instructed as the first-line or alternative AEDs for generalized tonic-clonic seizures (GTC) on the current NICE guideline. GTC is a type of seizure involved with generalized stiffening and rhythmic jerking of the limbs, caused by bilateral malfunction of the brain. Focal seizures, or partial-onset seizures, are recommended to be treated with carbamazepine, lamotrigine, levetiraetam, oxcarbazepine and sodium valproate as the first-line or alternative AEDs. For its add-on therapy, carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate and topiramate are suggested. The guideline is listed with number of other seizure types for pharmacological treatment options such as tonic or atonic seizures, absence seizures and myoclonic seizures.[8]

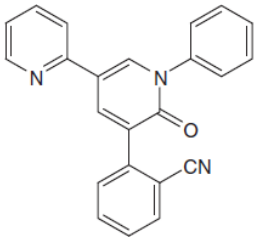
7.3 Perampanel (Fycompa®)

Perampanel is a novel selective, non-competitive AMPA glutamate receptor antagonist.[20] AMPA receptor antagonists have recently been focused for its novel therapeutic target, which can potentially influence an epileptic disorder in pharmacoresistant patients. Perampanel showed a wide range of antiseizure activity in preclinical models and was demonstrated to have consistent pharmacokinetic (PK) data with once-daily regimen. In

randomized clinical trials, perampanel has been shown to be effective and safe as a treatment in the management of seizure frequency for the patients with POS.[20] Currently, perampanel is approved by European Medicines Agency (EMA) and the United States (US) Food and Drug Administration (FDA) in July 2012 and October 2012, respectively. Ministry of Food and Drug Safety (MFDS) in Korea has approved 2, 4, 6, 8, 10 and 12 mg of perampanel (July 2015) for an indication of an adjunctive therapy for partial-onset seizures in ≥12 year old epilepsy patients with or without secondarily generalized seizures. Perampanel is approved for the same indication as in Korea for the European Union (EU) and the United States with an additional indication of an adjunctive therapy for primary generalized tonic-clonic seizures in ≥12 year old patients with epilepsy. In Korea, administration of perampanel is instructed to start with a dose of 2 mg once daily and gradually increase up to the maintenance dose of 4~8 mg with increments of 2 mg based on clinical response and tolerability of patients, and a minimum of 2-week intervals for the increment should be arranged. The dose may be increased to 12 mg when necessary, and patients taking concomitant medication that may reduce perampanel plasma level (phenytoin, carbamazepine and oxcarbazepine) should have 2 mg increment with a minimum of weekly intervals.

7.3.1 Mechanism of Action

Perampanel (2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydro-pyridin-3-yl)benzonitrile) is an orally active, non-competitive and highly selective antagonist of AMPA-type glutamate receptor, a class of ionotropic glutamate receptors on post-synaptic neurons, shown to be effective in various preclinical seizure models.[21] The chemical structure is as below:[20]



Glutamate is diffused to AMPA and NMDA receptors of post-synaptic neurons and induces a major excitatory response by depolarization. Excitotoxicity with elevated levels of glutamate is reported in epilepsy models of human brain tissues and animals.[22-24] Perampanel noncompetitively and allosterically inhibits AMPA receptor activity, reducing excessive excitation and subsequently modulating seizure activity, even in the presence of high concentrations of glutamate. Hyperexcitatory states are also reported to be sustained as an effect of perampanel.[20]

7.3.2 Preclinical Experience with E2007/perampanel (Fycompa®)

7.3.2.1 *in vitro* pharmacology

In preclinical studies, perampanel was shown to have a dose-dependent inhibitory effect on AMPA-induced intracellular calcium concentration ($[Ca^{2+}]_i$) with an the half maximal inhibitory concentration (IC_{50}) of 93 nM in cultured rat cortical neurons. NMDA-induced $[Ca^{2+}]_i$ and the kainate receptor agonist SYM2081, by contrast, were only slightly inhibited by perampanel, reflecting its selective specificity.[21] AMPA-induced Ca^{2+} was inhibited in similar magnitudes even in the presence of 2 μM (low) and 100 μM (high) of AMPA concentrations.[25] Patch clamp recordings with cultured rat hippocampal neurons indicated that perampanel had no effect on AMPA receptor desensitization (reduced response after prolonged exposure to ligands or neurotransmitters).[21] Patch recordings further showed that perampanel induced a rapid desensitization of AMPA receptor currents with 10μM of perampanel, showing nearly a complete block, whereas NMDA receptor currents had no change with 30 μM of perampanel.[25] In the hippocampus, specifically in the stratum radiatum of the CA1 area, perampanel demonstrated IC_{50} of 0.23 μM for inhibition of excitatory postsynaptic field potentials (f-EPSPs), and a complete block of AMPA receptor-mediated f-EPSPs was observed with 3 μM of perampanel, without affecting NMDA- or kainate receptor-mediated f-EPSPs at doses 100-fold higher than 3 μM.[26] Perampanel has similar affinities for AMPA receptors in the open and closed states,[21] non-competitively interacts at the allosteric binding site of the AMPA receptor and is thought to disrupt agonist binding process and channel opening by the interaction, which occurs between S1 and S2 glutamate binding core and channel transmembrane domains.[27-28] No interaction of perampanel with the glutamate binding site of AMPA receptors was supported by functional studies with radiolabelled peramapanel, [^{3}H]perampanel, which demonstrated no displacement of the drug even in the presence of AMPA, glutamate, kainite or NBQX (AMPA receptor antagonist).[25] By contrast, GYKI 52466, an AMPA receptor antagonist, displaced [^{3}H]perampanel, suggesting that GYKI 52466 and perampanel may bind to similar site of the receptor. GYKI 52466, however, is the prototypical non-competitive AMPA antagonist with IC_{50} of 7.8 μM for the inhibition of AMPA receptor-mediated f-EPSPs, requiring 34-fold higher concentration to induce the desired effect compared with perampanel.[25,26]

7.3.2.2 *in vivo* pharmacology

Higher potency of perampanel was observed in mice against audiogenic seizures, maximal electroshock (MES) seizure test, pentylenetetrazole (PTZ) test and 6 Hz seizure test compared to phenytoin (included only in the 6 Hz seizure test), carbamazepine and sodium valproate. Mouse models with tonic-clonic generalized seizures were selected for the audiogenic and MES seizure test and absence/myoclonic seizures for the PTZ test. Activity

of perampanel was presented both in partial and generalized seizures, except in genetic absence epilepsy rats from Strasbourg.[21] Especially, perampanel resulted superior outcomes compared to AEDs of sodium channel blockers in the 6 Hz seizure test and PTZ test since the Na^+ channel blocking AEDs have weak or inactive status in those tests. Amygdala-kindling rat models, displaying a chronic epilepsy model, had increased afterdischarge (discharge of neural impulses) threshold and reduced motor seizure duration with perampanel. Reduced seizure severity and afterdicharge duration were also presented after the drug treatment, suggesting a broad spectrum of perampanel activity in both acute and chronic epilepsy models. Rotarod test was experimented with perampanel for a determination of motor coordination. Toxic dose with 50% reduction (TD_{50}) in motor control of 1.8 mg/kg and 9.14 mg/kg in mice and rats were observed, respectively. Effective dose with 50% reduction (ED_{50}) in seizures from individual seizure tests (audiogenic, PTZ and MES) were used for the protective index of perampanel with the TD_{50}. The protective index, TD_{50}/ED_{50}, resulted in 3.8, 1.9 and 1.1 for audiogenic, PTZ and MES tests, respectively. Despite the low therapeutic window of perampanel as an AMPA receptor antagonist, acute motor toxicity of the antagonists is expected since excitatory neurotransmission is majorly mediated by AMPA receptors throughout the brain. In addition, the low therapeutic window in animal models is not necessarily implied with reduced tolerability in clinical application.[21,25]

7.3.3 Clinical Experience with E2007/perampanel (Fycompa®)

7.3.3.1 Phase I (Pharmacokinetics, PK)

In Phase I clinical studies (study 001 and study 002) in healthy subjects, perampanel was rapidly absorbed and reached maximal plasma concentration in about 1hour. Mean apparent half-life had a range of 52-129 hours in the single-dose study and 66-90 hours in the multiple-dose study. Steady-state plasma concentrations were achieved by day 14 in the multiple-dose study. Sedative effects were dose-dependent and remained similar on day 14 in spite of increased perampanel exposure versus day 1. Data from these studies demonstrated that perampanel possessed favorable pharmacological properties and PK profile of perampanel was consistent with once-daily dosing.

Also, the results in study 017 to determine the absolute bioavailability of perampanel showed that perampanel was readily absorbed and reflected high oral bioavailability.[20]

Perampanel is mainly metabolized by cytochrome P450 3A4 (CYP3A4) and CYP3A5. Thus, concomitant use of strong CYP3A inducers is not recommended. Also, CYP450 inducing AEDs such as carbamazepine, oxcarbazepine and phenytoin may also lead to decreased perampanel exposure and increased perampanel clearance. When related enzyme-inducing AEDs are introduced or withdrawn, patients should be closely monitored.[20,30]

7.3.3.2 Phase II (Dose-escalation studies)

The safety and tolerability of perampanel were examined, and a favorable tolerability and a preliminary evidence of efficacy were shown in randomized, double-blind, placebo-controlled, dose-escalation, parallel-group Phase II studies (study 206 and study 208). Both studies included patients aged 18~70 years with POS with or without secondary generalization, presenting an uncontrolled POS despite treatment of at least three different AEDs within the last 2 years. In study 206 (n=153), patients received placebo or perampanel up to 4 mg/day (once- or twice-daily) during 12 weeks (8 weeks of titration and 4 weeks of maintenance). In study 208 (n=48), patients were given with placebo or perampanel up to a maximum dose of 12 mg/day (once-daily) for 16 weeks (12 weeks of titration and 4 weeks of maintenance).

As a result, in study 206 the highest dose (4 mg/day) was well-tolerated, and the proportion of patients tolerating 4 mg/day was the same in the once-daily (82.4%) and twice-daily (82.4%) perampanel and placebo (82.4%) treatments. Responder rate and seizure frequency were the preliminary efficacy endpoints of the study and showed a favorability of perampanel (4 mg/day) over placebo, however, were statistically insignificant. In study 208, doses of ≥6 mg perampanel once-daily was tolerated by most patients with a Kaplan-Meier analysis. The small numbers of patients for each group inevitably obstructed an assessment of statistical analysis of efficacy endpoints for this dose-escalation study, however, differences between treatment groups were observed for the efficacy endpoints.

Adverse events were not dose-limiting, and most commonly occurred AEs were central nervous system (CNS)-related while most of them were mild or moderate in severity. In study 206, the proportion of patients with at least one AE had similarity in placebo (62.7%) and perampanel (66.7%, once- and twice-daily. combined). The four common treatment-emergent adverse events (TEAEs) in perampanel-treated patients (once-daily, n = 51; twice-daily, n = 51) were dizziness, headache, somnolence and fatigue, and most of AEs had severity of mild or moderate. Patients with once-daily and twice-daily regimens showed no difference in tolerability, and 4 of the five reported serious AEs (SAEs) were treatment related and AEs associated with seizure activity (status epilepticus, convulsive seizure, mental status changes and post-ictal state). In study 208 patients with ≤6 mg (once-daily) and >6 mg (once-daily) were reported with similar distributions of AEs. Dizziness was the most common AE with 42.1% and 42.9% in ≤6 mg and >6 mg patients, respectively. Other common AEs were headache, somnolence, fatigue, diarrhea and rhinitis.[31]

7.3.3.3 Phase III

In multicenter, double-blind, randomized, placebo-controlled three Phase III trials (study 304, 305 and 306), the efficacy and tolerability of adjunctive perampanel have been assessed in

patients aged ≥12 years with an uncontrolled POS despite a treatment of at least two different AEDs within the last 2 years.[1,32,33]

In study 306, a total of 706 patients were randomized and received placebo or perampanel (once-daily) with doses titrated from 2 mg to the target doses of 2, 4 or 8 mg of perampanel in 2 mg increments every week for 6-week titration period, followed by a subsequent maintenance period of 13 weeks. 2 mg of perampanel showed no significant difference from placebo; however, 4 mg and 8 mg of perampanel significantly reduced seizure frequency (p=0.003 and p<0.001, respectively). The responder rate was also significantly increased compared to placebo at these doses (p=0.013 and p<0.001, respectively).[33]

In study 304 and 305, higher perampanel doses than those of study 306 were explored: 8 and 12 mg once-daily. Study 304 involved 388 patients in North and South America, and study 305 involved 386 patients worldwide. The identically designed trials (study 304 and 305) both showed significant improvements in seizure frequency in AED-resistant patients with 8 and 12 mg perampanel (304: p=0.026 and p=0.016, respectively; 305: p<0.001 and p=0.01, respectively). When complex partial plus secondary generalized seizures were specifically evaluated, similar improvements in seizure frequency were observed: -33.0% (8 mg) and -33.1% (12 mg) compared with -17.9% (placebo) in study 304. Although statistical significance was absent in responder rates of study 304, when a subsequent sub-analysis was examined, significant differences were observed between placebo and both doses (p<0.05 for both) and -30.5% (8 mg) and -17.6% (12 mg) compared with -9.7% (placebo) in study 304 and 305, respectively.[1,32]

In the Intention-to-treat (ITT) analysis which includes 1,478 patients from 304 (n=387), 305 (n=386) and 306 (n=705) studies, 50% responder rates were higher with 4, 8 and 12 mg than placebo (28.5%, 35.3%, 35.0% and 19.3%, respectively, p<0.05) for all partial seizures. Median percentage changes in seizure frequency for all partial seizures were higher in 4, 8 and 12 mg (-23.3%, -28.8% and -27.2%, respectively) than placebo (-12.8%) with p<0.01. For complex partial seizures with secondarily generalized seizures, significantly (p<0.001) higher median percentage changes in seizure frequency were reported with 4, 8 and 12 mg (-31.2%, -35.6% and -28.6%, respectively) compared to placebo (-13.9%).

In the three clinical trials, perampanel-treated patients achieved a higher seizure-free rate than patients with placebo:[1,32-34]

Seizure-free status					
Study	Placebo	2 mg	4 mg	8 mg	12 mg
304	0.0%	NA	NA	2.2%	1.5%
305	1.5%	NA	NA	2.3%	1.5%
306	1.2%	1.9%	4.4%	4.8%	NA

In study 304, the proportion of patients who experienced at least one AE in 8, 12 mg/day and placebo was over 80% (88.0%, 91.8% and 82.6%, respectively), and most TEAEs were mild or moderate in its severity. The most common TEAEs which had occurred ≥10% in any treatment group include dizziness, somnolence, headache, fall, irritability and ataxia. In study 305, 86.8%, 86.0% and 68.4% of 8 and 12 mg groups and placebo group, respectively, showed at least one TEAE. 7 patients in placebo, 10 in 8 mg and 12 in 12 mg experienced SAEs (5.1%, 7.8% and 9.9%, respectively), and those who had more than one SAE were all related to epilepsy. The common TEAEs with ≥10% occurrence were similar to those of study 304: dizziness, somnolence, fatigue and headache, and most of TEAE severity were mild and moderate.[1,32] In study 306, four most common TEAEs with ≥10% occurrence in any treatment group include dizziness, headache, somnolence and fatigue.[33]

7.3.3.4 Extension study

In study 207, long-term open-label evaluation (OLE) in patients with epilepsy was conducted. Completion of study 206 or 208 was eligibility for the enrollment of patients, and 138 from 180 patients who completed were enrolled for the study 207. The study was designed with 12-week titration period with 2 mg increments of perampanel with 2-week intervals up to a maximum of 12 mg/day and a planned maxium maintenance period of 424 weeks, approximately 8 years. 86.2% of patients (n=119) was exposed to perampanel for more than 6 months and 69.6% with more than a year of treatment. In regard of tolerability and safety, 129 patients had experience at least one TEAE during the lengthy exposures, however, frequencies of the most common TEAEs (dizziness, headache and somnolence) were reduced more than half in the second year, and halved again in the following year. -31.5% of the median percent change in seizure frequency per 28 days during the entire treatment period was observed, and -39.4% was shown for the maintenance period only.[35]

Phase III extension study (study 307) consisting of a 16-week blinded conversion period and a subsequent long-term open-label treatment period was conducted in 1,216 patients from study 304, 305 and 306, increasing the dose from 8 mg/day to 12 mg/day. During more than 3 years of treatment period, stable reductions in seizure frequency was observed. For patients with secondarily generalized seizures, seizure frequency of secondarily generalized seizures was reduced up to 90%. AEs occurred most frequently during titration period, and individual SAEs were rare during long exposure period. Common AEs were dizziness, somnolence and headache, and SAEs included psychiatric symptoms and seizure events. No new major safety concerns were raised during the long exposures of perampanel.[36]

7.3.4 Common Adverse Events

In Phase II (study 206 and 208) and Phase III clinical trials (study 304, 305 and 306) of perampanel in treatment-resistant patients, the most TEAEs were CNS-related and not dose-

dependent. Many AEDs suppress the neuronal hyperexcitability pathologically, and subsequent adverse reactions in the CNS are not unexpected. Most AEDs are known to cause sedation, incoordination, drowsiness, fatigue and nausea, and these AEs are mainly dose-related.[37] The most common adverse drug reactions (ADRs) of perampanel were dizziness, fatigue, somnolence, nausea, irritability and falls. Perampanel treated patients had higher frequency of depression and aggression than patients taking placebo, with particularly at higher doses. The majority of TEAE severities were mild and moderate, with a relatively low incidence of SAEs. Patients taking perampanel had greater rate of side effects in psychiatrics than with placebo, primarily irritability.

7.4 Study Rationale

Perampanel is the first in a new class of highly selective, non-competitive AMPA receptor antagonists for treatment-resistant partial-onset seizures.[20] It was recently approved as an adjunctive treatment for partial seizures with or without secondary generalization, in patients aged ≥ 12 years, in the EU (EMA, 2012), the United States (FDA, 2012) and the Korea (MFDS, 2015).[34] The efficacy and tolerability of adjunctive perampanel has been demonstrated in 3 pivotal studies about patients inadequately controlled despite treatment with 1-3 approved AEDs.[36,39] Overall, 1,480 patients were randomized and treated (safety analysis set) in 3 pivotal studies. Most patients were receiving two or more concomitant AEDs at baseline (one, n=206, 13.9%; two, n=751, 50.7%; three, n=522, 35.3%).[34] In other words, more than 80% of patients were treated with more than 2 concomitant AEDs in these trials, therefore there is limited data to show the efficacy and safety of perampanel as a first add-on therapy to date.

Meanwhile probability of seizure freedom decreases significantly with subsequent AED regimens,[40] so it is of interest to assess the first add-on therapy. Further, considering the novel mode of action of perampanel, there is a possibility of synergistic effects on the combination therapy which can only be demonstrated by a study of perampanel as the first adjunctive AED.

Therefore, we try to assess the efficacy and safety of perampanel in patients with partial onset seizure with or without secondary generalized seizure as a first add-on therapy in Korea.

8 STUDY OBJECTIVES

8.1 Primary Objective

To evaluate the efficacy of perampanel added to monotherapy for partial onset seizures with or without secondarily generalized seizures (total seizures) as measured by 50% responder rate.

8.2 Secondary Objectives

1) To evaluate the safety of perampanel added to monotherapy for partial onset seizures with or without secondarily generalized seizures
2) To evaluate efficacy of perampanel added to monotherapy for secondarily generalized tonic clonic seizure in partial onset seizures

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multi-center, open-label, single-arm, phase 4 study. Subjects who meet all of the inclusion and none of the exclusion criteria will be received perampanel.
Baseline seizure counts (frequency) data is collected by subjects or guardian/legally authorized representative, retrospectively. The study consists of 2 periods; titration period (12 weeks) and maintenance period (24 weeks).

Titration Period
Subjects will begin receiving perampanel 2 mg/day and be up-titrated no less than 2-week intervals in increments of 2 mg up to 12 mg according to the investigator's judgment. Subjects experiencing intolerable AEs may remain on the same dose or have their dose reduced to the previously tolerated dose. Subjects who cannot tolerate the 4 mg dose will be discontinued from the study. Subjects who are taking any concomitant drug that shortens the half-life of perampanel (phenytoin, carbamazepine, oxcarbazepine, etc.) can be up-titrated by 2 mg no less than 1-week intervals, if needed. Adjustment of the concomitant AED dose level during this period is not permitted.

Maintenance Period
Subjects will enter this period on the last dose they achieved at the end of the titration period and will continue taking this dose level once daily for the remainder of the study. According to the investigator's clinical judgment, subjects experiencing intolerable AEs can have their dose reduced and having failure to control seizure can have their dose increased up to 12 mg. During the Maintenance Period, subjects whose dose has been reduced can have the dose increased again, as soon as the tolerability improves. Subjects who cannot tolerate 4 mg dose will be discontinued from the study. Adjustment of the concomitant AED dose level during this period is not permitted.

In the case of tapering, withdrawal will be performed four weeks after last dose of perampanel.

Subjects will visit the study institution at Visit 1 (Week 0), Visit 2 (Week 6), Visit 3 (Week 12), Visit 4 (Week 24) and Visit 5 (Week 36).

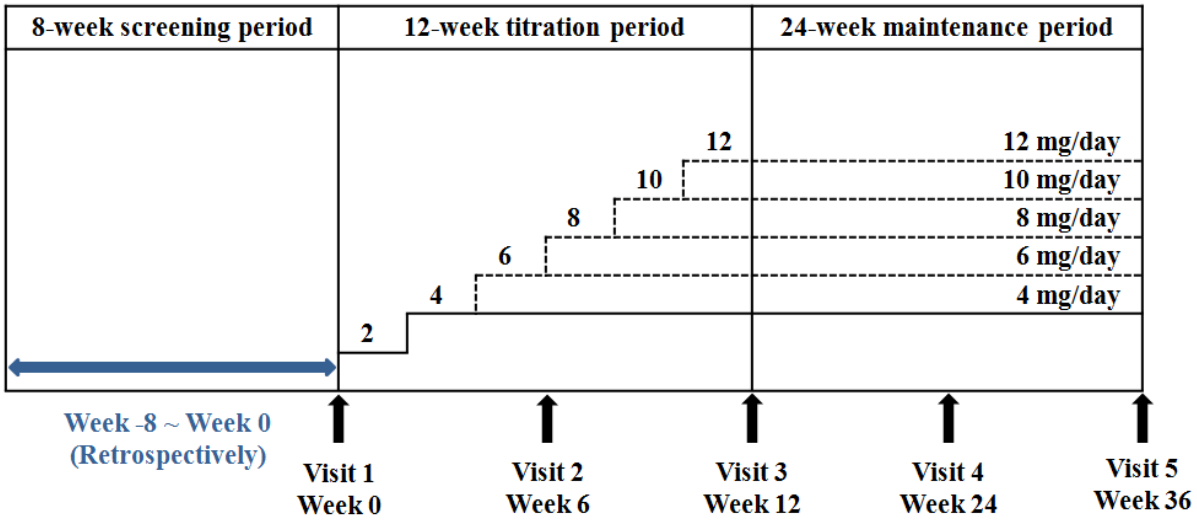


Figure 1 Study Design

9.1.1 Screening Period/Visit 1 (Week -8 ~ Week 0)

Before/At the Visit 1 (Week 0), informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any baseline procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3.

Investigators will confirm the inclusion/exclusion criteria and perform the evaluations to the subjects. Subjects should be greater than or equal to 12 years of age, be/have diagnosed with epilepsy with partial onset seizures with or without secondarily generalized seizures according to ILAE's Classification of Epileptic seizures and need the initially add-on therapy after failure to control seizures with the first or further monotherapy at the optimal dose and duration.

Results of the Screening information must be recorded on the appropriate case report form (CRF) to indicate whether 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 the Visit 1 (Week 0) and meet all of the inclusion/exclusion criteria (Sections 9.3.1 and 9.3.2) will be enrolled and begin the treatment period.

9.1.2 Titration Period (0 ~ 12 weeks)

In the 12-week Titration Period, subjects will begin receiving perampanel 2 mg once daily (QD) before bedtime and can be up-titration no less than 2-week intervals in increments of 2 mg QD up to 12 mg QD according to the investigator's judgment. Subjects experiencing intolerable AEs may remain on the same dose or have their dose reduced to the previously tolerated dose. Subjects who cannot tolerate 4 mg QD dose will be discontinued from the study. Subjects who are taking concomitant drug that shorten the half-life of perampanel (phenytoin, carbamazepine, oxcarbazepine, etc.) can be up-titrated by 2 mg QD no less than 1-week intervals, if needed. Adjustment of the concomitant AED dose level during this period is not permitted.

9.1.3 Maintenance Period (12 ~ 36 weeks)

In the 24-week Maintenance Period, subjects will enter this period on the last dose they achieved at the end of the titration period and will continue taking this dose level once daily for the remainder of the study. According to the investigator's clinical judgment, subjects experiencing intolerable AEs can have their dose reduced and having failure to control seizure can have their dose increased up to 12 mg QD. During the Maintenance Period, subjects whose dose has been reduced can have the dose increased again, as soon as the tolerability improves. Subjects who cannot tolerate 4 mg QD dose will be discontinued from the study. Adjustment of concomitant AED dose level during this period is not permitted.

9.1.4 Follow-up visit (Only withdrawn subject)

A Follow-up Visit will be applies to the subjects who are withdrawn from the study for any reason. There is the potential of increased seizure frequency in subjects with seizure disorders when antiepileptic drugs are withdrawn abruptly. Therefore, a gradual withdrawal, a taper, is provided after discontinuation, and it should be performed 4 weeks after the last dose of perampanel. But, prompt withdrawal can be considered when adverse drug reaction occurs.

The end of the study will be the date of the last study visit for the last subject. However, if there are AEs that be not resolved and present on the last visit scheduled, the subject(s) having the AE(s) should be monitored until resolution of AE(s) or deciding to stop the observation by the investigator(s).

9.2 Discussion of Study Design

9.2.1 Rationale for Efficacy Variables

According to 'Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders' of EMA, in add-on study, the primary endpoint should dichotomize the data into responders/non-responders, where responders are patients who obtained at least a certain pre-defined percentage reduction of seizure frequency.[41] The at least 50% reduction of seizure frequency is commonly used in the studies and these endpoints are used as primary or key secondary endpoint in previous global pivotal studies. Therefore, 50% responder rate in total seizures as the primary efficacy variable is adopted in this study for evaluating the efficacy in Korean subjects.

9.2.2 Rationale for Prohibited/Restricted Concomitant Drug/Therapy

During the study, the use of medications including AEDs and therapy that could affect the efficacy or safety of the study can be prohibited or restricted to minimize the confound factors.
However, for the evaluation of perampanel as first add on therapy, the use of only one concomitant AED is permitted, if it have be administrated at the stable dose for 8 weeks prior to the Visit 1 (Week 0) and will be provided at same dosage and by same route of administration during the study. The detailed prohibited/restricted concomitant drug or therapy is presented in the Section 9.4.7.

9.3 Selection of Study Population

Approximately 105 subjects will be enrolled at approximately 15 sites in Korea. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

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

1. Male or female and greater than or equal to 12 years of age
2. Have a diagnosis of epilepsy with partial onset seizures with or without secondarily generalized seizures according to the ILAE's Classification of Epileptic Seizures (1981)
3. Need an initial add-on therapy after failure to control seizures with the first or further monotherapy at the optimal dose and duration

4. Despite AED treatment within the last 8 weeks, subjects must have had ≥2 partial onset seizures and the interval between those seizures should be more than 24 hours prior to Visit 1 (Week 0).
5. Are currently being treated with stable doses of monotherapy for 8 weeks prior to Visit 1 (Week 0) [Standard AEDs]; Carbamazepine, phenytoin, zonisamide, phenobarbital, valproate, clobazam, clonazepam, primidone, gabapentin, topiramate, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, felbamate, vigabatrin
6. If antidepressants or antianxiety drugs are used, subjects on stable doses and administrations of antidepressants or antianxiety drugs for 8 weeks prior to Visit 1 (Week 0)

9.3.2 Exclusion Criteria

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

1. Females who are pregnant (positive β-hCG test) or breastfeeding
2. Presence of previous history of Lennox-Gastaut syndrome
3. Presence of nonmotor simple partial seizures only
4. Presence of primary generalized epilepsies or seizures such as absences and/or myoclonic epilepsies
5. A history of status epilepticus within 12 weeks before Visit 1 (Week 0)
6. 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 Visit 1 (Week 0)
7. Presence of a progressive CNS disease, including degenerative CNS diseases and progressive tumors
8. 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 1 (Week 0)
9. Use of intermittent rescue benzodiazepines (i.e., 1-2 doses over a 24-hr period considered one-time rescue) 2 or more times in 8 weeks period prior to Visit 1 (Week 0)
10. Moderate to severe kidney problems or patients who receive hemodialysis. (Amendment 01)
11. Severe liver problems. (Amendment 01)
12. Hypersensitivity to perampanel or any substances of this drug. (Amendment 01)
13. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption (Amendment 01)
14. Patient who is participating in other intervention clinical trial. (Amendment 01)
15. Patient who judged to be inadequate to participate in the study by investigator

9.3.3 Removal of Subjects from Therapy or Assessment

1) Scheduled Termination

Subjects will be considered to have completed the titration period after 12 weeks of titration treatment and completion of the Visit 3 (Week 12) visit procedures. Subjects who have completed the titration period will enter the maintenance period. The subject will be considered to have completed the maintenance period after 24 weeks of maintenance treatment and completion of the Visit 5 (Week 36) visit procedures. Upon completion of the titration period and the maintenance 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.

2) Unscheduled Termination or Removal of Subjects from the Study

Subjects who had administered the study drug and could not participate the entire period of clinical trial are classified as 'withdrawals'. If the subject declines further participation or the investigator determines that a subject should be removed from the study, the subject can be withdrawn at any time.

Reasons for withdrawal are as the followings:

1) Withdrawal of informed consent
2) AE(s) requiring discontinuation of study therapy
3) Eligibility violation
4) Administration of prohibited medications
5) Lost to follow-up
6) Unable to continue the study in the investigator's judgment

The investigator will make every reasonable effort to keep each subject followed-up for any adverse events. He/she will use all possible ways to communicate (phone call, letters, and visit to home) with the subject. Reason for withdrawal should be documented on CRF. Final assessment to withdrawn subjects should be conducted and documented. Withdrawn subjects cannot re-participate to study.

The Sponsor can discontinue the entire study or study at a specific study site at any time with appropriate notification. The reasons for discontinuation of study can be as the followings:

1) The enrollment of stated objective number of subjects in all study sites or in a specific study site had failed
2) Emergence of any information regarding the efficacy or safety which could affect the continuation of the study

3) Any violation of GCP, study protocol or the contract by the study site or the investigator which could raise a problem to continue the study
4) Other administrative reason affecting the continuation of the study

9.4 Treatment

9.4.1 Treatment Administered

Perampanel will be administered to subjects in each period. Tablet(s) will be taken orally once daily before bedtime. The strength of one tablet is 2 mg and subjects can receive *N* x 2-mg tablet(s) of perampanel based on daily dose. At the beginning of the 12-week titration period, oral perampanel will start at a dose of 2 mg once daily. Then, doses of perampanel will be up-titrated in 2 mg/day increments no less than 2-week intervals to a maximum of 12 mg/day according to the investigator's judgment. Also, subjects who are taking concomitant AED known as CYP enzyme inducer (phenytoin, carbamazepine, oxcarbazepine, etc.) that shorten the half-life of perampanel can be up-titrated by 2 mg once daily no less than 1-week intervals.

The study drug will be dispensed to each subject or guardian/legally authorized representative at the Visit 1 (Week 0), Visit 2 (Week 6), Visit 3 (Week 12), Visit 4 (Week 24), Discontinuation Visit.
Tablet(s) cannot be split, broken or crushed prior to administration, and must be administrated whole with approximately 225 mL of water.

9.4.2 Identity of Investigational Product

Study drug, perampanel, will be supplied by the sponsor.

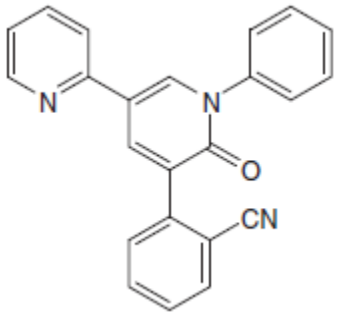
- Product name/ Manufacturer: Fycompa®/ Eisai Inc.
- Formulation/ Drug identification (appearance)/ Active ingredient and dosage/ Expiration date

Tablet strength	Tablet color/shape	Active ingredient and dosage	Expiration date
2 mg	Orange, round, biconvex, film-coated tablets	Perampanel 2.1 mg (2 mg as perampanel anhydrous)	60 months after manufacture

- Storage condition: at 1~30℃

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)
- Structural formula:



9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

The sponsor will provide study drug labeled with the followings;

1) Cautionary statement for “For clinical trial”
2) Product code or generic name of active ingredient
3) Lot number and expiration date
4) Storage condition
5) Name and address of the approved party for the clinical trial
6) Cautionary statement for "Investigational use only"
7) Statement for “Keep this product out of the reach of children” (Amendment 02)
8) Packing unit (Amendment 02)
9) Name, address, and contact number of the sponsor (Amendment 02)

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, 1°C to 30°C.

9.4.3 Method of Assigning Subjects to Treatment Group

This is an open-label, single-arm study. All subjects who provide signed informed consent to participate in this study and satisfy all eligibility requirements (see Section 9.3) will be assigned to receive perampanel for the titration period and maintenance period as initially added to monotherapy in patient with partial onset seizures. There is no randomization in this study.

9.4.4 Selection of Doses in the Study

Perampanel is approved from MFDS on May, 2015, as adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy 12 years of age and older. In label paper, initial dose of perampanel is 2 mg/day and can be escalated by increments of 2 mg/day no less than at 2-week intervals, up to 12 mg, a maximum dose, depending on the clinical response and tolerability in patient. Also, subjects who are taking concomitant AED known as CYP enzyme inducer (phenytoin, carbamazepine, oxcarbazepine, etc.) that shorten the half-life of perampanel can be up-titrated by 2 mg once daily no less than 1-week intervals.

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 up to 12 mg depending on the clinical response and tolerability in each subject. Subjects will start taking study drug in the bedtime at Visit 1 (Week 0). Study drugs will be taken orally once daily in the bedtime throughout the study.

9.4.6 Blinding

The study will not be blinded.

9.4.7 Prior and Concomitant Drug/Therapy

1) Concomitant antiepilepsy drug
   a: Only one AED can be used
   A concomitant AED must be used at the stable dose and administration between 8 weeks prior to Visit 1 (Week 0) and the end of follow-up examination.
2) Concomitant medication
   a: Prohibited concomitant drug
   The following concomitant drugs are prohibited throughout the study period (up to early discontinuation visit).

- The CYP3A4-inducing drugs and food below. If having been treated at enrollment, washout of these drugs is to start at the enrollment.
  [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*)]
- Antipsychotics
- Other trial drugs

b: Restricted concomitant drug
The dosing regimen of the following drugs must not be altered, newly introduced, or discontinued throughout the study (up to early discontinuation visit).
[Antidepressants and antianxiety drugs]

3) Concomitant therapy
a: Prohibited concomitant therapy
The following therapies must not concurrently implemented during the study.

- Brain surgery
- Medical device under clinical trial

b: Restricted concomitant therapy
A VNS is allowed, but stimulator parameters cannot be changed for 8 weeks prior to Visit 1 (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 1 (Week 0). Additionally, a ketogenic diet cannot be newly added or discontinued during the study.

9.4.8 Treatment Compliance

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

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 drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, 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, MFDS). 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 the Visit 1 (Week 0). Demography information includes date of birth (or age), sex.

9.5.1.1.2 DIAGNOSIS

Subject must be/have diagnosed with epilepsy with partial onset seizures with or without secondarily generalized seizures according to the ILAE's Classification of Epileptic Seizures (1981). In addition, Subject should need the first add-on therapy after failure to control seizure with the first or further monotherapy at the optimal dose and duration.

9.5.1.1.3 SEIZURE TYPE AND FREQUENCY

Seizure type and frequency/interval within 8 weeks prior to the Visit 1 (Week 0) will be collected, retrospectively.

9.5.1.1.4 MEDICAL HISTORY

Medical and surgical history and current medical conditions will be recorded at the Visit 1 (Week 0). All pertinent medical and surgical history within 5 years prior to the Visit 1 (Week 0) must be noted on the appropriate CRF.
Vital signs including blood pressure, body temperature, respiratory rate and pulse rate will be performed as designated in the Schedule of Procedures/Assessments (Table 2). Documentation of vital signs will be included in the source documentation at the site. Significant findings at the Visit 1 (Week 0) will be recorded on the Medical History and Current Medical Conditions CRF.

9.5.1.1.5 PRIOR AND CONCOMITANT MEDICATIONS

The medications including drug name, dosage, administration route, within 24 weeks prior to the Visit 1 (Week 0) will be obtained.

9.5.1.1.6 CONCOMITANT AED

AED treatment including drug name, dosage, administration route, within 8 weeks prior to the Visit 1 (Week 0) will be obtained.

9.5.1.2 Efficacy Assessments

Primary efficacy variable and secondary efficacy variables are based on seizure counts (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 during 8 weeks prior to the Visit 1 (Week 0) is collected by subjects or guardian/legally authorized representative, retrospectively. The investigators or designees will be given standardized training on seizure identification to ensure that subjects will be educated in the same standardized fashion at each visit. Seizure frequency data in subject diaries will be reviewed with the investigator(s) at Visit 2, 3, 4 and 5.

50% Responder rate
The 50% responder rate is defined the proportion of subjects achieving at least 50% reduction in seizure frequency during the Maintenance Period relative to the Baseline.

75% Responder rate
The 75% responder rate is defined the proportion of subjects achieving at least 75% reduction in seizure frequency during the Maintenance Period relative to the Baseline.

100% Responder rate (seizure free rate)
The 100% responder rate, seizure free rate, is defined the proportion of subjects achieving 100% reduction in seizure frequency during the Maintenance Period relative to the Baseline.

The percent change in total seizure frequency in the Titration and Maintenance Period relative to the Baseline
The Percentage change is defined the reduction rate in seizure frequency during the Titration Period and the Maintenance Period relative to the Baseline.

50% responder rate in secondarily generalized tonic clonic seizures
The 50% responder rate in secondarily generalized tonic clonic seizures is defined the proportion of subjects with secondarily generalized tonic clonic seizures achieving at least 50% reduction in seizure frequency during the Maintenance Period relative to the Baseline.

75% responder rate in secondarily generalized tonic clonic seizures

The 75% responder rate in secondarily generalized tonic clonic seizures is defined the proportion of subjects with secondarily generalized tonic clonic seizures achieving at least 75% reduction in seizure frequency during the Maintenance Period relative to the Baseline.

100% responder rate (seizure free rate) in secondarily generalized tonic clonic seizures
The 100% responder rate, seizure free rate, in secondarily generalized tonic clonic seizures is defined the proportion of subjects with secondarily generalized tonic clonic seizures achieving 100% reduction in seizure frequency during the Maintenance Period relative to the Baseline.

The percent change in secondarily generalized tonic clonic seizure frequency in the Titration and Maintenance Period relative to the Baseline
The Percentage change in secondarily generalized tonic clonic seizures is defined the reduction rate in seizure frequency in subjects with secondarily generalized tonic clonic seizures during the Titration Period and the Maintenance Period relative to the Baseline.

9.5.1.3 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Not applicable.

9.5.1.4 Safety Assessments

9.5.1.4.1 Adverse Events and Events Associated with Special Situations

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug 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: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, electrocardiography (ECG) or X-ray) that results in symptoms, a change in treatment, or discontinuation of study drug

- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs observed during the study will be reported on the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected 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 CRF. SAEs will be collected for 28 days after the last dose.
Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.
Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

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

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

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.4.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

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

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments

- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

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

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

(Amendment 01)

1) Probable/Likely

2) Possible

3) None

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

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

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 one of

the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.
All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.
The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

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

9.5.1.4.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 1. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 2) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected.

Table 1 Clinical Laboratory Tests

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

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

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.4.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.5.1.4.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic blood pressure (BP) [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 2) by a validated method. Blood pressure and pulse will be measured after the subject has been sitting for at least 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

9.5.1.4.5 PREGNANCY TEST

A urine or serum-hCG pregnancy test will be performed for premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months during the Screening Period and/or at the Visit 1 (Week 0), Visit 5 (Week 36) and Follow-up Visit.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 2 Schedule of Procedures/Assessments in Study E2007-M065-412

Period	Screening Period	Titration[a]			Maintenance[b]		Discontinuation	Follow-up[b,c]	Unscheduled[i]
Study Week(s)	Week -8~0	Week 0	Week 6	Week 12	Week 24	Week 36			
Study Day(s)	Day -56~0	Day 0	Day 42	Day 84	Day 168	Day 252			
Visit Number	(Retrospectively)	1	2	3	4	5			
Procedure/Assessment									
Informed consent/assent[d]		X							
Inclusion/exclusion criteria		X							
Demographic data		X							
Seizure type and frequency		X							
Medical history[e]		X							
Concomitant medications		X[f]	X	X	X	X	X	X	X
Concomitant AED		X[g]	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X
Clinical laboratory evaluations		X				X	X	X	
Pregnancy test		X				X	X	X	
Adverse events[h]			X	X	X	X	X	X	X

Table 2 Schedule of Procedures/Assessments in Study E2007-M065-412

Period	Screening Period	Titration[a]			Maintenance[b]		Discontinuation	Follow-up[b,c]	Unscheduled[i]
Study Week(s)	**Week -8~0**	**Week 0**	**Week 6**	**Week 12**	**Week 24**	**Week 36**			
Study Day(s)	**Day -56~0**	**Day 0**	**Day 42**	**Day 84**	**Day 168**	**Day 252**			
Visit Number	**(Retrospectively)**	**1**	**2**	**3**	**4**	**5**			
Procedure/Assessment									
Dispense the study drug		X	X	X	X		X		
Return the study drug			X	X	X	X	X	X	
Study drug compliance			X	X	X	X	X	X	
Dispense subject diary		X	X	X	X		X		
Return and review subject diary			X	X	X	X	X	X	

a: All visits to be done within ±5 days of the schedule.
b: Visit to be done within ±7 days of the schedule.
c: To be completed by subjects who are withdrawn from the study for any reason after Visit 1 (Week 0) and before Visit 5 (Week 36). When a taper is provided after discontinuation, it should be performed 4 weeks after the last dose.
d: Informed consent/assent may be obtained prior to study start; it must be obtained prior to any study related procedures.
e: All pertinent medical and surgical history within 5 years before Visit 1 (Week 0).
f: Prior and concomitant medication(s) within 24 weeks before Visit 1 (Week 0).
g: Prior and concomitant AED.
h: Adverse events will be collected from the time subject starts to receive the study drug form through the last visit. Serious adverse events will be collected for 28 days after the subject's last dose or last visit, whichever is longer.
i: At the unscheduled visit, only the assessments that the investigator(s) judged the necessity based on the subject's condition will be performed.

9.5.2.2 Description of Procedures/Assessments Schedule

9.5.2.2.1 DEMOGRAPHIC/BASELINE ASSESSMENTS

Visit 1 (Week 0, Day 0)
Written informed consent is obtained from the subjects and/or legal guardian prior to study start. Once informed consent has been obtained, the following procedures and evaluations will be performed.

- Review of inclusion/exclusion criteria for subject.
- Diagnosis: epilepsy with partial onset seizures with or without secondarily generalized seizures according to ILAE's Classification of Epileptic Seizures (1981)
- Subject medical history: subject demographic information
- Record prior and concomitant medication use over the past 24-week.
- Record prior and concomitant AED use over the past 8-week.

Only subjects who continue to meet all of the inclusion and none of the exclusion criteria are eligible to continue in the study and perform the following procedures and evaluations.

- Vital signs (systolic and diastolic BP in sitting position, pulse), body temperature, , weight and height
- Blood and urine samples for clinical laboratory evaluations and pregnancy testing (serum or urine, only females of childbearing potential)
- Dispense study drug.
- Dispense subject diary.
- Schedule Visit 2.

9.5.2.2.2 TREATMENT PERIOD ASSESSMENTS

TITRATION PERIOD ASSESSMENTS
Visit 2 (Week 6, Day 42±5)
The following procedures and evaluations will be performed:

- Vital signs (systolic and diastolic BP in sitting position, pulse), body temperature
- Record all concomitant medication use.
- Record concomitant AED use.
- Record any AEs.
- Collect unused study drug and record compliance.
- Return and review subject diary.

- Dispense study drug.
- Dispense subject diary.
- Schedule Visit 3.

Visit 3 (Week 12, Day 84±5)
The following procedures and evaluations will be performed:

- Vital signs (systolic and diastolic BP in sitting position, pulse), body temperature
- Record all concomitant medication use.
- Record concomitant AED use.
- Record any AEs.
- Collect unused study drug and record compliance.
- Return and review subject diary.
- Dispense study drug.
- Dispense subject diary.
- Schedule Visit 4.

MAINTENANCE PERIOD ASSESSMENTS
Visit 4 (Week 24, Day 168±7)
The following procedures and evaluations will be performed:

- Vital signs (systolic and diastolic BP in sitting position, pulse), body temperature
- Record all concomitant medication use.
- Record concomitant AED use.
- Record any AEs.
- Collect unused study drug and record compliance.
- Return and review subject diary.
- Dispense study drug.
- Dispense subject diary.
- Schedule Visit 5.

Visit 5 (Week 36, Day 252±7) or Discontinuation
The following procedures and evaluations will be performed:

- Vital signs (systolic and diastolic BP in sitting position, pulse), body temperature, weight.
- Blood and urine samples for clinical laboratory evaluations and pregnancy testing (serum, only females of childbearing potential)
- Record all concomitant medication use.
- Record concomitant AED use.

- Record any AEs.
- Collect unused study drug and record compliance.
- Return and review subject diary.
- Dispense study drug. (Discontinuation Only) (Amendment 02)
- Dispense subject diary. (Discontinuation Only) (Amendment 02)

9.5.2.2.3 FOLLOW-UP ASSESSMENTS (ONLY WITHDRAWN SUBJECT)

Follow-up Visit (4 weeks after the last dose±7)
The following procedures and evaluations will be performed:

- Vital signs (systolic and diastolic BP in sitting position, pulse), body temperature, weight.
- Blood and urine samples for clinical laboratory evaluations and pregnancy testing (serum, only females of childbearing potential)
- Record all concomitant medication use.
- Record concomitant AED use.
- Record any AEs.
- Collect unused study drug and record compliance. (Amendment 02)
- Return and review subject diary. (Amendment 02)

9.5.2.2.4 UNSCHEDULED ASSESSMENTS

Unscheduled Visit
The following procedures and evaluations will be performed:

- Vital signs (systolic and diastolic BP in sitting position, pulse), body temperature
- Record all concomitant medication use.
- Record concomitant AED use.
- Record any AEs.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of initial add-on treatment for partial onset seizures with or without secondary generalized seizure.
The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, and assessment of AEs, are standard evaluations to ensure subject safety.

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

9.5.4.1 Reporting of Serious Adverse Events

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

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.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy 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

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

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

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.4 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

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.
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 (SUSARs) 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 2).
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 CRF.
A subject removed from the study for any reason may not be replaced.

9.5.6 Abuse or Diversion of Study Drug

Not applicable.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. 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 CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.
Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee must sign the completed CRF to attest to its accuracy, authenticity, and completeness.
Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

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

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released. Statistical analyses will be performed using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

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

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

50% responder rate in total seizures: 50% responders are defined as subjects who have at least 50% reduction in total seizure frequency during the Maintenance Period relative to the Baseline.

9.7.1.1.2 SECONDARY ENDPOINTS

- 75% responder rate in total seizures
- 100% responder rate (seizure free rate) in total seizures
- The percent change in total seizure frequency in the Titration and Maintenance Period relative to the Baseline
- 50% responder rate in secondarily generalized tonic clonic seizures
- 75% responder rate in secondarily generalized tonic clonic seizures
- 100% responder rate (seizure free rate) in secondarily generalized tonic clonic seizures
- The percent change in secondarily generalized tonic clonic seizure frequency in the Titration and Maintenance Period relative to the Baseline

9.7.1.1.3 EXPLORATORY ENDPOINT

Not applicable.

9.7.1.2 Definitions of Analysis Sets

The Safety Analysis Set 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 is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose primary efficacy measurement.

The Per Protocol Analysis Set is the group of subjects who sufficiently complied with the protocol. Details of the evaluability criteria will be determined before database lock and will be specified in the SAP.

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 populations;

- discontinued from the study early, summarized by reason for discontinuation.
  The number of subjects 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, etc.) for Full Analysis Set will be summarized using descriptive statistics. Continuous variables will be summarized in mean, SD, median, minimum, maximum and categorical variables will be summarized in number and percentages of subjects.
The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Full Analysis Set, Anatomical Therapeutic Chemical (ATC) class. Prior medication is defined as any medication that stopped before the first dose of study drug. Concomitant medication is defined as any medication that (1) started before the first dose of study drug and was continuing at the time of the first dose of study drug, or (2) started on or after the date of the study drug until the last dose of study drug.

9.7.1.5 Efficacy Analyses

The efficacy analysis will be performed on the Full Analysis Set. The analysis performed on Per Protocol Analysis Set will be supportive. This is a single-arm study having no reference arm. Therefore, formal hypothetical inferences are not necessary and only descriptive statistics will be given. Continuous variables will be summarized with mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized by number and percentages of subjects. Seizure frequency will be based on number of seizures per 28 days, calculated as the number of seizures over the entire time interval divided by the number of days in the interval and multiplied by 28. (Amendment 02)

9.7.1.5.1 PRIMARY EFFICACY ANALYSIS

For 50% Responder rate in total seizures, the following will be provided:
- Number of 50% responders
- 50% responder rate and its 95% confidence interval (CI)

9.7.1.5.2 SECONDARY EFFICACY ANALYSES

For 75% Responder rate in total seizures, the following will be provided:
- Number of 75% responders
- 75% responder rate and its 95% CI

For 100% Responder rate (seizure free) in total seizures, the following will be provided:
- Number of 100% responders
- 100% responder rate and its 95% CI

For total seizure frequency and the percent change in total seizure frequency in the Titration and the Maintenance Period relative to the Baseline, the following will be provided:
- Mean, standard deviation, median, minimum, maximum and 95% CI

For 50% Responder rate in secondarily generalized tonic clonic seizures, the following will be provided:
- Number of 50% responders
- 50% responder rate and its 95% CI

For 75% Responder rate in secondarily generalized tonic clonic seizures, the following will be provided:
- Number of 75% responders
- 75% responder rate and its 95% CI

For 100% Responder rate (seizure free) in secondarily generalized tonic clonic seizures, the following will be provided:
- Number of 100% responders
- 100% responder rate and its 95% CI

The percent change in secondarily generalized tonic clonic seizure frequency in the Titration and Maintenance Period relative to the Baseline:
- Mean, standard deviation, median, minimum, maximum and 95% CI

9.7.1.5.3 EXPLORATORY EFFICACY ANALYSES

Not applicable.

9.7.1.6 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable.

9.7.1.6.1 PHARMACOKINETIC ANALYSES

Not applicable.

9.7.1.6.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Not applicable.

9.7.1.7 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set.
Safety variables include TEAEs, clinical laboratory parameters, vital signs results.

9.7.1.7.1 EXTENT OF EXPOSURE

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

9.7.1.7.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (most recent version) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.
A TEAE is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

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

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.
The 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]).

9.7.1.7.3 LABORATORY VALUES

For all quantitative parameters listed in Section 9.5.1.4.3 Laboratory Measurements, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit using descriptive statistics. Qualitative parameters listed in Section 9.5.1.4.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

9.7.1.7.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

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

9.7.2 Determination of Sample Size

This study will be evaluated for the efficacy of adjunctive perampanel for partial-onset seizures. Primary endpoint is 50% responder rate in total seizures.

There is no statistical hypothesis to be tested in this study and 105 subjects is set to keep 94 subjects for the primary analysis with approximately 10% drop-out rate from the view point of feasibility.

When 94 subjects for the primary analysis is kept and 50% responder rates can be assumed as 35.3% in test group and 19.3% as reference value according to Bernhard J. Steinhoff *et al.*[1], lower limit of 95% confidence interval of 50% responder rate will be more than 19.3% with more than 90% power.

$$n = \frac{\left(Z_{\alpha/2} + Z_{\beta}\right)^2 \left[p_T(1 - p_T)\right]}{(p_T - p_R)^2}$$
$$= \frac{(1.96 + 1.282)^2 \left[0.353(1 - 0.353)\right]}{(0.353 - 0.193)^2}$$

$$= 93.78 \approx 94$$

$Z_{\alpha/2}$: Type I error (0.05/2)
Z_{β} : Type II error (0.1)
p_T : 50% responder rate in test group
p_R : reference value

Considering a drop-out rate of 10%, total sample size require 105.

[Reference]

Bernhard J. Steinhoff*et al*., Efficacy and safety of adjunctive perampanel for the treatmentof refractory partial seizures: A pooled analysisof three phase III studies, Epilepsia, 54(8):1481–1489, 2013doi: 10.1111/epi.12212

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Not applicable

10 REFERENCE LIST

1. French JA, Krauss GL, Biton V, Squillacote D, Yang H, *et al*. Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. Neurology. 2012;79(6):589-96.
2. Zhang X, Cui SS, Wallace AE, Hannesson DK, Schmued LC, *et al*. Relations between brain pathology and temporal lobe epilepsy. J Neurosci. 2002;22(14):6052-61.
3. Reynolds EH. Jackson, Todd, and the concept of "discharge" in epilepsy. Epilepsia. 2007;48(11):2016-22.
4. World Health Organization. Epilepsy. Fact Sheet No 999. May 2015. Available from: http://www.who.int/mediacentre/factsheets/fs999/en/index.html. [Assessed 09Nov 2015]
5. Shorvon SD. The etiologic classification of epilepsy. Epilepsia. 2011;52(6):1052-7.
6. Engel J Jr; International League Against Epilepsy (ILAE). A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. Epilepsia. 2001;42(6):796-803.
7. Engel J Jr. ILAE classification of epilepsy syndromes. Epilepsy Res. 2006;70 Suppl

1:S5-10.
8. The epilepsies. The diagnosis and management of the epilepsies in adults and children in primary and secondary care. Pharmacological update of clinical guideline 20. NICE Clinical Guidelines, No. 137. National Clinical Guideline Centre. London: Royal College of Physicians (UK). Jan 2012.
9. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, *et al*. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia. 2010;51(4):676-85.
10. Berg AT, Cross JH. Towards a modern classification of the epilepsies? Lancet Neurol. 2010;9(5):459-61.
11. Blume WT, Lüders HO, Mizrahi E, Tassinari C, van Emde Boas W, *et al*. Glossary of descriptive terminology for ictal semiology: report of the ILAE task force on classification and terminology. Epilepsia. 2001;42(9):1212-8.
12. Semah F, Picot MC, Adam C, Broglin D, Arzimanoglou A, *et al*. Is the underlying cause of epilepsy a major prognostic factor for recurrence? Neurology. 1998;51(5):1256-62.
13. Epidemiological study of seizure and epilepsy using nationwide database for corean epilepsy patients (ESSENCE). Korean epilepsy society. Jun 2012.
14. Harris LW, Sharp T, Gartlon J, Jones DN, Harrison PJ. Long-term behavioural, molecular and morphological effects of neonatal NMDA receptor antagonism. Eur J Neurosci. 2003;18(6):1706-10.
15. Meldrum BS, Rogawski MA. Molecular targets for antiepileptic drug development. Neurotherapeutics. 2007;4(1):18-61.
16. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000;342(5):314-9.
17. Beghi E, Messina P, Pupillo E, Crichiutti G, Baglietto MG, *et al*. Satisfaction with antiepileptic drugs in children and adolescents with newly diagnosed and chronic epilepsy. Epilepsy Res. 2012;100(1-2):142-51.
18. Patsalos PN. Antiepileptic drug interactions. A clinical guide. Second edition. Springer. 2013.
19. Patsalos PN. Drug interactions with the newer antiepileptic drugs (AEDs)-part 1: pharmacokinetic and pharmacodynamic interactions between AEDs. Clin Pharmacokinet. 2013;52(11):927-66.
20. Rektor I. Perampanel, a novel, non-competitive, selective AMPA receptor antagonist as adjunctive therapy for treatment-resistant partial-onset seizures. Expert Opin Pharmacother. 2013;14(2):225-35.
21. Hanada T, Hashizume Y, Tokuhara N, Takenaka O, Kohmura N, *et al*. Perampanel: a novel, orally active, noncompetitive AMPA-receptor antagonist that reduces seizure activity in rodent models of epilepsy. Epilepsia. 2011;52(7):1331-40.
22. Rogawski MA. Astrocytes get in the act in epilepsy. Nat Med. 2005;11(9):919-20.
23. McKenna MC. The glutamate-glutamine cycle is not stoichiometric: fates of glutamate

in brain. J Neurosci Res. 2007;85(15):3347-58.
24. Coulter DA, Eid T. Astrocytic regulation of glutamate homeostasis in epilepsy. Glia. 2012;60(8):1215-26.
25. Rogawski MA, Hanada T. Preclinical pharmacology of perampanel, a selective non-competitive AMPA receptor antagonist. Acta Neurol Scand Suppl. 2013;(197):19-24.
26. Ceolin L, Bortolotto ZA, Bannister N, Collingridge GL, Lodge D, *et al*. A novel anti-epileptic agent, perampanel, selectively inhibits AMPA receptor-mediated synaptic transmission in the hippocampus. Neurochem Int. 2012;61(4):517-22.
27. Balannik V, Menniti FS, Paternain AV, Lerma J, Stern-Bach Y. Molecular mechanism of AMPA receptor noncompetitive antagonism. Neuron. 2005;48(2):279-88.
28. Sobolevsky AI, Rosconi MP, Gouaux E. X-ray structure, symmetry and mechanism of an AMPA-subtype glutamate receptor. Nature. 2009;462(7274):745-56.
29. Abstracts from the 2009 Annual Meeting of the American Epilepsy Society. December 4-8, 2009. Boston, Massachusetts, USA. Epilepsia. 2009;50 Suppl 11:1-502.
30. FDA Approved labeling text. Prescribing information: Fycompa® (perampanel) tablets, for oral use, CIII. NDA 202834/S-005. Jun 2015.
31. Krauss GL, Bar M, Biton V, Klapper JA, Rektor I, *et al*. Tolerability and safety of perampanel: two randomized dose-escalation studies. Acta Neurol Scand. 2012;125(1):8-15.
32. French JA, Krauss GL, Steinhoff BJ, Squillacote D, Yang H, *et al*. Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global phase III study 305. Epilepsia. 2013;54(1):117-25.
33. Krauss GL, Serratosa JM, Villanueva V, Endziniene M, Hong Z, *et al*. Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. Neurology. 2012;78(18):1408-15. [Abstract]
34. Steinhoff BJ, Ben-Menachem E, Ryvlin P, Shorvon S, Kramer L, *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.
35. Rektor I, Krauss GL, Bar M, Biton V, Klapper JA, *et al*. Perampanel Study 207: long-term open-label evaluation in patients with epilepsy. Acta Neurol Scand. 2012;126(4):263-9.
36. Krauss GL, Perucca E, Ben-Menachem E, Kwan P, Shih JJ, *et al*. Long-term safety of perampanel and seizure outcomes in refractory partial-onset seizures and secondarily generalized seizures: results from phase III extension study 307. Epilepsia. 2014;55(7):1058-68.
37. Kennedy GM, Lhatoo SD. CNS adverse events associated with antiepileptic drugs. CNS Drugs. 2008;22(9):739-60.
38. Rugg-Gunn F. Adverse effects and safety profile of perampanel: a review of pooled data. Epilepsia. 2014;55 Suppl 1:13-5.
39. Krauss GL, Perucca E, Ben-Menachem E, Kwan P, Shih JJ, *et al*. Perampanel, a

selective, noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist, as adjunctive therapy for refractory partial-onset seizures: interim results from phase III, extension study 307. Epilepsia. 2013;54(1):126-34.
40. Zadeh WW, Escartin A, Byrnes W, Tennigkeit F, Borghs S, *et al*. Efficacy and safety of lacosamide as first add-on or later adjunctive treatment for uncontrolled partial-onset seizures: A multicentre open-label trial. Seizure. 2015;31:72-9.
41. Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders. European medicines Agency. CHMP/EWP/566/98 Rev.2/Corr. London. Jul 2010.

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 CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

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

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

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the

original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.
The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

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

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 CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.
It is requested that at the completion of the required retention period, 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. (Amendment 01)

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor’s Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor’s SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. 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 principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. 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

Appendix 1 Expected Adverse Events and Precautions

The up-to-date label of Fycompa® (Perampanel) in Korea is included in this section.

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E2007-M065-412

Study Protocol Title: Multicenter, open-label trial, evaluating the efficacy and safety of perampanel added to monotherapy in patients with partial onset seizures with or without secondary generalized seizures

Investigational Product Name: E2007/Fycompa® (Perampanel)

SIGNATURES

Authors:

Study Director (always include) <Name, degree(s)> <function> <title, department> <legal name of sponsoring company>	Date
Designated Medical Monitor (include only if the Study Director is not medically qualified) <Name, degree(s)> <function> <title, department> <legal name of sponsoring company>	Date
Clinical pharmacologist (include only if PK samples are analyzed) <Name, degree(s)> <function> <title, department> <legal name of sponsoring company>	Date
Primary statistician (always include) <Name, degree(s)> <function> <title, department> <legal name of sponsoring company>	Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number: E2007-M065-412

Study Protocol Title: Multicenter, open-label trial, evaluating the efficacy and safety of perampanel added to monotherapy in patients with partial onset seizures with or without secondary generalized seizures

Investigational Product Name: E2007/Fycompa® (Perampanel)

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

Medical Institution

Investigator	Signature	Date