

1. TITLE PAGE



Clinical Study Protocol

Study Protocol Number:	E2007-J081-240	
Study Protocol Title:	A multicenter, uncontrolled, open-label study to evaluate the safety and tolerability of intravenous perampanel as substitute for oral tablet in subjects with partial onset seizures (including secondarily generalized seizures) or primary generalized tonic-clonic seizures	
Sponsor:	Eisai Co., Ltd. 4-6-10 Koishikawa, Bunkyo-Ku, Tokyo 112-8088, Japan	
Investigational Product Name:	E2007/ Perampanel Hydrate (Japanese Accepted Names for Pharmaceuticals [JAN])	
Indication:	Partial-onset seizures with or without secondarily generalized seizures or primary generalized tonic-clonic seizures	
Phase:	2	
Approval Date:	V1.0	07 Sep 2018
	V2.0	09 Oct 2018
GCP Statement:	This study is to be performed in full compliance with all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by the regulatory authorities.	
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.	

2. CLINICAL PROTOCOL SYNOPSIS

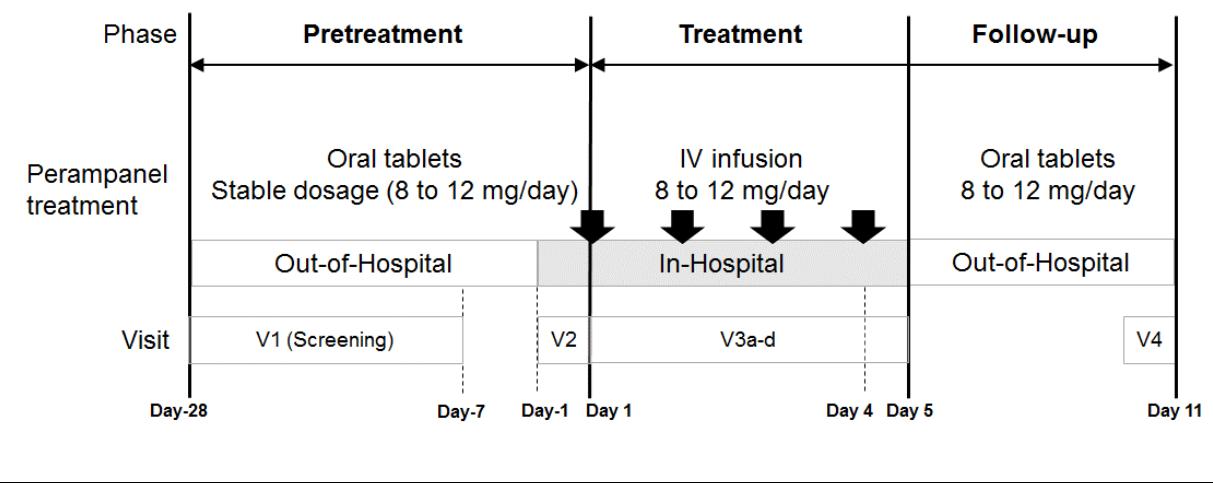
Compound No.
E2007
Name of Active Ingredient
perampanel
Study Protocol Title
A multicenter, uncontrolled, open-label study to evaluate the safety and tolerability of intravenous perampanel as substitute for oral tablet in subjects with partial onset seizures (including secondarily generalized seizures) or primary generalized tonic-clonic seizures
Sites
Japan, approximately 15 sites
Study Period and Phase of Development
Study Period: October 2018 to April 2020 (planned) Phase 2
Objectives
Primary Objective: To evaluate the safety and tolerability of 30-minute intravenous infusions of perampanel after switching from oral perampanel (8 to 12 mg/day) as an adjunctive therapy in subjects with partial-onset seizures (POS) with or without secondarily generalized seizures or primary generalized tonic-clonic (PGTC) seizures
Secondary Objectives:
<ul style="list-style-type: none"> • To evaluate the plasma concentration of perampanel before and after switching from oral perampanel to 30-minute intravenous infusions of perampanel • To evaluate the seizure frequency before and after switching from oral perampanel to 30-minute intravenous infusions of perampanel
Study Design
This is a multicenter, uncontrolled, open-label study in subjects with POS with or without secondarily generalized seizures or PGTC seizures. This study will consist of 3 phases: the Pretreatment Phase, Treatment Phase, and Follow-up Phase. During the Pretreatment Phase, subjects will be screened and assessed for eligibility to participate in the study. Subject informed consent/assent will be obtained before the screening, after which protocol eligibility will be established on any day from Day -28 to Day -7. Eligible subjects must be on a stable dosage (8 to 12 mg/day) of oral perampanel as an adjunctive therapy with 1 to a maximum of 3 marketed concomitant antiepileptic drugs (AEDs) for at least 28 days before the first dose of the study drug (ie, intravenous infusion of perampanel). Eligible subjects will return to and remain onsite (be "hospitalized") 1 day before switching from oral perampanel to intravenous infusion of perampanel (ie, on Day -1 [Visit 2]). During the Treatment Phase, hospitalized subjects will be switched from oral perampanel to intravenous infusion of perampanel at a dose equivalent to the oral perampanel dose. Subjects will receive 30-minute intravenous infusions of perampanel once a day for 4 days under inpatient conditions. Afterwards, the subject must be switched back to oral perampanel at the equivalent daily dose of the

intravenous infusion of perampanel.

If subjects cannot continue intravenous infusion of perampanel for any reason(s), they must discontinue the study.

Subjects will be discharged from the hospital the day after the last intravenous infusion of perampanel, and treatment must be switched back to their original dose of oral perampanel. The assessments at the Follow-up Visit will be conducted 7 days (allowance window: +7 days) after the last intravenous infusion of perampanel.

The study design is shown below.



Number of Subjects

20 subjects will be enrolled and treated.

Inclusion Criteria

- (1) Male or female aged 12 years or older at the time of informed consent/assent
- (2) Have a diagnosis of epilepsy with POS with or without secondarily generalized seizures or PGTC seizures according to the International League Against Epilepsy (ILAE) Classification of Epileptic Seizures (1981)
- (3) Have been receiving a stable dosage of oral perampanel (8 to 12 mg/day) for at least 28 days before Day 1 in the Treatment Phase
- (4) Have been receiving a concomitant stable dosage of 1 to a maximum of 3 marketed AED(s) (regarding phenobarbital used as an AED, phenytoin, and carbamazepine, only one is allowed) for at least 28 days before Day 1 in the Treatment Phase. No change of dosing regimen for concomitant AED(s) is planned during the Treatment and Follow-up Phases.
- (5) Are considered reliable and willing to be available for the study period by the investigator, and are able to record seizures and report adverse events (AEs) by themselves or have a caregiver who can record seizures and report AEs for them

Exclusion Criteria

- (1) Have a history of drug or alcohol dependency or abuse within the last 2 years before Visit 1
- (2) Have a history of status epilepticus within 6 months before Day 1 in the Treatment Phase
- (3) Are unsuitable for venipuncture and intravenous administration
- (4) Require medical intervention due to safety issues related to the concomitant administration of 1 to

3 AEDs

- (5)Have a history of suicidal ideation/attempt within 2 years before Day 1 in the Treatment Phase
- (6)Have clinically problematic psychological or neurological disorder(s)
- (7)Clinical symptoms or imaging suggest a progressive central nervous system (CNS) abnormality, disorder, or brain tumor
- (8)Current evidence of a clinically significant disease (eg, cardiac, respiratory, gastrointestinal, or renal disease) that in the opinion of the investigator(s) could affect the subject's safety, interfere with the study assessments, or require prohibited medications as specified in the study protocol
- (9)Clinically significant abnormal laboratory values
- (10)Concomitant use of the following drugs except for carbamazepine and phenytoin or foods known to induce CYP3A (not limited to these drugs or foods) within 14 days before Day 1 in the Treatment Phase:
enzalutamide, mitotane, phenobarbital (except for use as an AED), amobarbital, secobarbital, rifabutin, rifampicin, food containing St. John's Wort (*hypericum perforatum*), bosentan, efavirenz, etravirine, modafinil, aprepitant, echinacea, pioglitazone, vemurafenib, nevirapine, and glucocorticoid (except for topical use)
- (11)Hypersensitivity to the study drug or any of its excipients
- (12)A history of multiple drug allergies or a severe drug reaction to an AED(s), including dermatological (eg, Stevens-Johnson syndrome), hematological, or organ toxicity reactions
- (13)Females of childbearing potential who:
 - In the Pretreatment Phase, are breastfeeding or pregnant (as documented by a positive beta-human chorionic gonadotropin [β -hCG] test).
 - Within 28 days before Visit 1, did not use a highly effective method of contraception, which includes any of the following:
 - total abstinence (if it is their preferred and usual lifestyle)
 - an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
 - a contraceptive implant
 - an oral contraceptive (with additional barrier method)
(Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before Day 1 in the Treatment Phase and throughout the entire study period, and for 28 days after the last dose of the study drug)
 - have a vasectomized partner with confirmed azoospermia.
 - Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after the last dose of the study drug.

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

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

dosing).

- (14) Be considered inappropriate for evaluation in the investigator's judgment
- (15) Have participated in a study involving administration of an investigational drug or device within 28 days before Visit 1, or within approximately 5 half-lives of the previous investigational drug, whichever is longer
- (16) Have a prolonged QTcF interval (>450 ms) 2 or more times as demonstrated by a repeated electrocardiogram (ECG)
- (17) Have a vagal nerve stimulation (VNS) device implanted less than 5 months before Visit 1 or changes in stimulation parameters less than 28 days before Visit 1

Study Treatment

Test drug:

Perampanel will be administered as an intravenous infusion for 30 minutes once a day on Days 1 through 4 under inpatient conditions.

Comparator drug:

Not applicable

Duration

- Pretreatment Phase: Up to 29 days
- Treatment Phase: 4 days (the period beginning at the start of intravenous infusion of perampanel on Day 1 to immediately before the oral perampanel administration on Day 5)
- Follow-up Phase: Assessments at the Follow-up Visit will be conducted 7 days (allowance window: +7 days) after the last intravenous infusion of perampanel.

Concomitant Drug/Therapy

For at least 28 days before Day 1 in the Treatment Phase and throughout the study (or until the visit at the time of early discontinuation for discontinued subjects), subjects must be on a stable dosage of 1 to a maximum of 3 marketed concomitant AEDs.

Prohibited Concomitant Medications and Foods

For 14 days before Day 1 in the Treatment Phase and throughout the study (or until the visit at the time of early discontinuation for discontinued subjects), concomitant use of the following drugs and foods is prohibited.

- Other than carbamazepine and phenytoin, concomitant use of the following drugs or foods known to induce CYP3A (not limited to these):
enzalutamide, mitotane, phenobarbital (except for use as an AED), amobarbital, secobarbital, rifabutin, rifampicin, food containing St. John's Wort (*hypericum perforatum*), bosentan, efavirenz, etravirine, modafinil, aprepitant, echinacea, pioglitazone, vemurafenib, nevirapine, and glucocorticoids (except for topical use)

The use of the following drugs is prohibited within 28 days or approximately 5 half-lives of the previous investigational drug (whichever is longer) before Visit 1, as well as during the study (or until the visit at the time of early discontinuation for discontinued subjects).

- Other investigational drugs

The use of the following drug is prohibited during the Treatment Phase:

- Oral perampanel

Prohibited Concomitant Therapies

The following therapies must not be implemented during the study (or until the visit at the time of early discontinuation for discontinued subjects).

- Brain surgery
- Neuromodulation therapy except for VNS (transcranial magnetic stimulation, etc.)

The following therapies must not be implemented within 28 days before Visit 1, as well as throughout the study (or until the visit at the time of early discontinuation for discontinued subjects).

- Therapies with a medical device under clinical study

Restricted Concomitant Drugs

The dosing regimens of the following drugs must not be altered, newly introduced, or discontinued during the study (or until the visit at the time of early discontinuation for discontinued subjects).

- Antidepressants
- Antipsychotics
- Antianxiety drugs
- Benzodiazepine hypnotics

Restricted Concomitant Therapies

- A ketogenic diet must not be changed, initiated, or discontinued during the study (or until the visit at the time of early discontinuation for discontinued subjects).
- A VNS is allowed, however, stimulation parameters cannot be changed for 28 days before Visit 1 and throughout the study (or until the visit at the time of early discontinuation for discontinued subjects).

Assessments**Safety Assessments**

Safety assessments will consist of monitoring and recording all adverse events (AEs), clinical laboratory evaluations (biochemistry, hematology, urinalysis), vital signs, weight, 12-lead electrocardiogram (ECG), and physical examinations.

Efficacy Assessments

Seizure diaries will be used to collect all seizure counts and types.

Pharmacokinetic Assessments

The plasma concentration of perampanel will be determined.

Bioanalytical Method

The plasma concentration of perampanel will be measured by a validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) assay.

Statistical Methods**Study Endpoints**

The safety endpoints are AEs, clinical laboratory tests (biochemistry, hematology, and urinalysis), vital signs, weight, and 12-lead ECG.

The efficacy endpoint is the seizure frequency per day in each of the 3 phases (Pretreatment Phase, Treatment Phase, and Follow-up Phase). Seizure frequency per day will be derived from the information recorded in the subject diaries.

The pharmacokinetic endpoint is the plasma concentration of perampanel.

All observed data will be reported with no adjustments for missing data.

Analysis Sets

The Safety Analysis Set is the group of subjects who received at least 1 intravenous infusion of perampanel.

The Efficacy Analysis Set is the group of subjects who received at least 1 intravenous infusion of perampanel and had at least 1 postdose efficacy measurement.

The Pharmacokinetic Analysis Set is the group of subjects who received at least 1 intravenous infusion of perampanel and had at least 1 evaluable measurement of plasma perampanel concentration.

Efficacy Analyses

The efficacy analyses will be performed on the Efficacy Analysis Set. The seizure frequency per day for each of the 3 phases (Pretreatment Phase, Treatment Phase, and Follow-up Phase) will be summarized using descriptive statistics (eg, mean, SD, median, minimum, and maximum). The seizure frequency per day from the Pretreatment Phase to the Follow-up Phase for each subject will be displayed using a spaghetti-plot.

Pharmacokinetic Analyses

The PK analyses will be performed on the Pharmacokinetic Analysis Set using the plasma concentrations of perampanel. Summary statistics for the plasma concentrations will be obtained by sampling time point and dose. The plasma concentrations of perampanel before and after switching from oral tablet to intravenous infusion will be plotted. A similar analysis may be conducted using dose-normalized plasma concentration data.

Safety Analyses

The safety analyses will be performed on the Safety Analysis Set. Safety data will be summarized using descriptive statistics (eg, n, mean, SD, median, minimum, and maximum for continuous variables; n [%] for categorical variables). Safety variables include AEs, clinical laboratory parameters (biochemistry, hematology, and urinalysis), vital signs, weight, and 12-lead ECG results.

Interim Analysis

No interim analysis is planned for this study.

Sample Size Rationale

This is an uncontrolled, open-label study for the safety evaluation of intravenous infusion of perampanel and the sample size (20 subjects) is not based on statistical power considerations, but rather on feasibility. It is considered that a sufficient number of subjects will be obtained for the safety evaluation of intravenous infusion of perampanel if the sample size is 20.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
β -hCG	beta-human chorionic gonadotropin
BUN	blood urea nitrogen
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
GABA	gamma-aminobutyric acid
GGT	gamma-glutamyl transferase
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ILAE	International League Against Epilepsy
IUD	intrauterine device
IUPAC	International Union of Pure and Applied Chemistry
IUS	intrauterine hormone-releasing system
LDH	lactate dehydrogenase
LLN	lower limit of normal
LLT	lowest level term
LNH	low/normal/high
MedDRA	Medical Dictionary for Regulatory Activities
PT	preferred term
QTcF	QT interval corrected for heart rate using Fridericia's formula
SBECD	Sodium Sulphobutylether-beta-cyclodextrin
SI	Système International
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory value
ULN	upper limit of normal
VNS	vagal nerve stimulation
WHO DD	World Health Organization Drug Dictionary

5. ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) constituted and functioning in accordance with Japan's Good Clinical Practice (J-GCP). Any protocol amendment or revision to the ICF will be resubmitted to the IRB for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number). Documentation of IRB compliance with J-GCP regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB chairman must be sent to the head of the medical institution with a copy to the sponsor before study start and the release of any study drugs to the site by the sponsor or its designee. If the IRB decides to suspend or terminate the study, the head of the medical institution will immediately send a notice of study suspension or termination by the IRB to the sponsor.

Study progress is to be reported to the IRB annually (or as required) by the investigator via the head of the medical institution, depending on J-GCP. The sponsor will submit, depending on the regulations, periodic reports and inform the investigator, the head of the medical institution, and the relevant IRB (directly or via the head of the medical institution) of any reportable adverse events (AEs) per J-GCP guidelines and local IRB standards of practice. Upon completion of the study, the investigator will provide the sponsor and the relevant IRB via the head of the medical institution with a brief report of the outcome of the study, if required.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with the 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
- J-GCP guidelines
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

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

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable representative should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to the 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 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 before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

If an underage subject is able to understand participation in the study, the investigator should explain the nature of the study and other information to the subject with the ICF or an informed-assent document prepared separately from the ICF, and should obtain the written informed consent/assent. In such cases, the written informed consent for the subject's participation in the study must be obtained from the subject's legally acceptable representative (ie, an individual who exercises parental rights over the subject).

If a subject is unable to give a written informed consent/assent, the investigator should confirm that the subject has orally consented to the subject's participation in the study, and must obtain the written informed consent from the subject's legally acceptable representative, and record it in the ICF.

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

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

6. INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai Co., Ltd. (the sponsor) at investigational sites in Japan (See Attachment 2).

The name, and telephone and fax numbers of the sponsor are listed in Attachment 1.

7. INTRODUCTION

7.1 Indication

Epilepsy is a common serious neurological disorder with an overall prevalence of 0.5% to 1%. Epilepsy is characterized by the spontaneous recurrence of seizures and requires long term, often life-long pharmacological management. There are 3 major types of clinical seizures: generalized, partial (focal), and unclassified seizures. The most frequent type is partial-onset seizures (POS).

Patients suffering from POS often have poor seizure control. Uncontrolled seizures lead to a wide variety of medical consequences (eg, severe trauma due to seizures, sudden death, depression, or intermittent psychotic disorders). In addition, uncontrolled seizures lead to significant lifestyle limitations and social handicaps (eg, loss of driving privileges, difficulties getting and maintaining a job).

Like other types of seizures, primary generalized tonic-clonic (PGTC) seizures are caused by a paroxysmal, uncontrolled discharge of cerebral cortical neurons, leading to neurologic dysfunction. Unlike most other types of seizures, however, this cerebral hyperactivity is not confined to a localized area, but extends to the entire brain. The onset of PGTC seizures is age-related and typically starts in older children, adolescents, and young adults. PGTC seizures are associated with an increased risk of injury and death. Therefore, effective control of PGTC seizures is necessary to reduce epilepsy-related morbidity and mortality.

7.1.1 Current Drug Treatment

In the guidelines for the drug treatment of adult patients with epilepsy by the Japan Epilepsy Society, carbamazepine and valproic acid are recommended as the first-line drugs for POS and generalized seizures, respectively.

Intravenous formulations of levetiracetam and fosphenytoin sodium hydrate are the only marketed drugs which have an indication for short-term replacement therapy when oral administration is temporarily infeasible (eg, in cases of patients undergoing surgical procedures, experiencing difficulty swallowing, suffering from consciousness disturbance, or acute gastrointestinal disorders).

7.1.2 E2007

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

Perampanel was approved for marketing as an adjunctive therapy for the treatment of POS with or without secondarily generalized seizures in patients aged 12 years and older in Europe and the United States in 2012, and in subsequently more than 59 countries. Perampanel was also approved for marketing as an adjunctive therapy for the treatment of PGTC seizures in patients

with epilepsy aged 12 years and older in Europe and the United States in 2015. In Japan, the above 2 indications were approved in March 2016. Furthermore, perampanel was approved for marketing as a monotherapy for the treatment of POS with or without secondarily generalized seizures in patients aged 12 years and older in the United States in 2017. In addition, Eisai applied for approval in the United States to expand the indications of adjunctive therapy for the treatment of POS with or without secondarily generalized seizures and PGTC seizures in patients aged 2 years and older in 2018.

Depending on the mechanism of action, existing antiepileptic drugs (AEDs) are divided into 2 groups, the first of which decrease neuronal excitation, and the second of which enhance inhibition. Major target sites for AEDs are blockage of voltage-operated sodium channels or calcium channels, regulation of neuronal transmitter release, inhibition of glutamatergic neural transmission, and facilitation of gamma-aminobutyric acid (GABA)-ergic neurotransmission. Current major AEDs are speculated to have a selective or mixed action on these targets. Perampanel is the only available drug showing noncompetitive and selective antagonism to AMPA receptors.

Further detailed information on perampanel including the data of the nonclinical and clinical studies that have been completed so far are provided in the Investigator's Brochure.

7.2 Study Rationale

In advance of this study, Eisai conducted a survey that aimed to investigate the needs of antiepileptic-injection use among epileptologists, and the results suggested that a need for antiepileptic-injection use exists for patients for whom it is temporarily not feasible to receive oral AEDs due to undergoing surgical procedures or other reasons.

Perampanel is the only available noncompetitive and selective AMPA receptor antagonist. For that reason, when patients cannot temporarily receive a safe and effective dose of oral perampanel, and are forced to switch to another oral AED, risks such as poor tolerability and seizure control are likely to result for the patients. Therefore, the development of a perampanel intravenous formulation to be used as an alternative to the oral formulation is significant.

Thus, conducting this study, which aims to evaluate the safety and tolerability, as well as the pharmacokinetics and efficacy of intravenous infusion of perampanel as a substitute for oral perampanel, is considered appropriate.

8. STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of 30-minute intravenous infusions of perampanel after switching from oral perampanel (8 to 12 mg/day) as an adjunctive therapy in subjects with POS with or without secondarily generalized seizures or PGTC seizures.

8.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the plasma concentration of perampanel before and after switching from oral perampanel to 30-minute intravenous infusions of perampanel
- To evaluate the seizure frequency before and after switching from oral perampanel to 30-minute intravenous infusions of perampanel

9. INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, uncontrolled, open-label study in subjects with POS with or without secondarily generalized seizures or PGTC seizures. This study will consist of 3 phases: the Pretreatment Phase, Treatment Phase, and Follow-up Phase.

During the Pretreatment Phase, 8 to 12 mg/day of oral perampanel will be administered. During the Treatment Phase, eligible subjects will be switched from oral perampanel on Day 1 to intravenous infusion of perampanel at a dose equivalent to the oral perampanel dose. Subjects will receive 30-minute intravenous infusions of perampanel once a day for 4 days under inpatient conditions. Afterwards, the subject must be switched back to oral perampanel at the equivalent daily dose of the intravenous infusion of perampanel. In addition, subjects must receive a stable dosage of 1 to a maximum of 3 marketed AED(s) throughout the study.

An overview of the study design is presented in Figure 1.

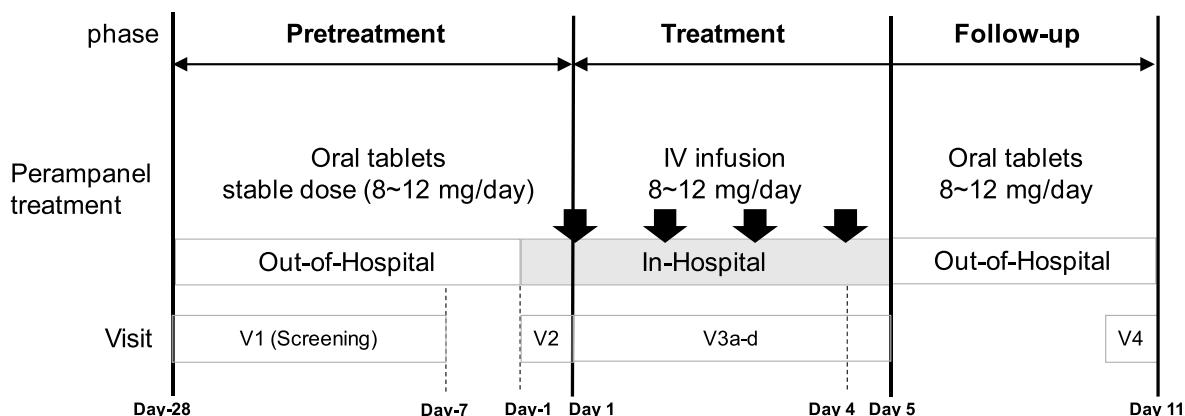


Figure 1 Study Design

9.1.1 Pretreatment Phase

The Pretreatment Phase is defined as the period from Day -28 to immediately before intravenous infusion of perampanel on Day 1. On any day from Day -28 to Day -7, informed consent/assent will be obtained from the subjects, and the subjects will be screened.

Subject informed consent/assent will be obtained before the screening, and protocol eligibility will subsequently be established. Eligible subjects must be on a stable dosage (8 to 12 mg/day) of oral perampanel as an adjunctive therapy with 1 to a maximum of 3 marketed concomitant AEDs for at least 28 days before the first dose of the study drug (ie, intravenous infusion of perampanel).

Eligible subjects will return to and remain onsite (be “hospitalized”) 1 day before switching

from oral perampanel to intravenous infusion of perampanel (ie, on Day –1 [Visit 2]).

9.1.2 Treatment Phase

The Treatment Phase is defined as the period beginning at the start of intravenous infusion of perampanel on Day 1 to immediately before the oral perampanel administration on Day 5.

Hospitalized subjects will be switched from oral perampanel on Day 1 to intravenous infusion of perampanel at a dose equivalent to the oral perampanel dose. Subjects will receive 30-minute intravenous infusions of perampanel once a day for 4 days under inpatient conditions (Days 1 through 4).

Subjects will be discharged from the hospital the day after the last intravenous infusion of perampanel (ie, Day 5), and treatment must be switched back to their original dose of oral perampanel.

If subjects cannot continue intravenous infusion of perampanel for any reason(s), they must discontinue the study.

9.1.3 Follow-up Phase

The Follow-up Phase is defined as the period after switching back to oral perampanel administration.

The assessments at the Follow-up Visit will be conducted 7 days (allowance window: +7 days) after the last intravenous infusion of perampanel.

9.2 Discussion of Study Design, Including Choice of Control Groups

Study Design

This study was designed to be conducted as an open-label, uncontrolled study, as with the Japanese study of levetiracetam injection (Inoue Y, et al., 2014), for which the indication as a substitute for oral formulation has been approved, in patients with epilepsy taking perampanel oral formulation as an adjunctive therapy with other AED(s) to evaluate the safety, tolerability, pharmacokinetics, and efficacy when perampanel oral formulation is temporarily replaced with perampanel injection.

Doses of the Study Drug

Perampanel oral formulation has been approved for the indication as an adjunctive therapy with other AED(s) for POS with or without secondarily generalized seizures and PGTC seizures, in patients with epilepsy aged 12 years or older, and is used at maintenance doses of 8 to 12 mg/day.

In this study, with a view to obtain approval for the indication as a substitute for perampanel oral formulation, the doses of the study drug (perampanel injection) are set to the same levels (8 to 12 mg/day) as the maintenance doses of perampanel oral formulation taken for at least 28

days before starting administration of the study drug.

Duration of Study Drug Administration

The duration of study drug administration is set at 4 days.

A review of the data on the prescription of levetiracetam intravenous infusion formulation, approved as a substitute for oral formulation (Medical Data Vision Co., Ltd.; Review period: November 2016 to October 2017), demonstrated that the mean duration of administration was 4.8 days, and the percentage of patients with an administration duration of 4 days or shorter was 73.1% (7688/10510 patients).

In consideration of feasibility, this study will be conducted not only in inpatients, but also in patients who will be able to be admitted to the hospital to participate in the study. Because an unnecessarily prolonged hospital stay may lead to a disadvantage for these patients, the duration of study drug administration is set at 4 days, as a duration of administration for which the safety of the study drug can be evaluated appropriately, with reference to the duration of administration of the Japanese study of other antiepileptic injections (Inoue Y, et al., 2014).

Time of Study Drug Administration

In the United States, a clinical pharmacology study (E2007-A001-050 study, hereinafter the “Study 050”) was conducted in Japanese and non-Japanese healthy subjects to evaluate bioavailability of a single 12 mg dose of perampanel for 3 intravenous infusion durations (for 30 minutes [n=20], 60 minutes [n=20], and 90 minutes [n=8]) relative to a single 12 mg perampanel oral tablet. As a result, it was demonstrated that the AUC after intravenous administration for 30 minutes and 60 minutes was within the range of the criteria for bioequivalence (two-sided 90% confidence interval of 0.8 to 1.25 for the ratio of the means after intravenous administration/oral administration) to the AUC after oral administration. On the other hand, the C_{max} did not satisfy the bioequivalence criteria for the ratio of the means after intravenous administration for 30, 60, and 90 minutes versus oral administration. Therefore, we developed a population pharmacokinetic model using the plasma concentration data in the Study 050, in order to simulate and estimate changes in the plasma concentration after switching to intravenous administration under steady-state conditions after multiple oral administration. As a result, it was estimated that, under steady-state conditions, the C_{max} after intravenous administration for 30 minutes and 60 minutes fell within the range of the criteria for bioequivalence to the C_{max} after oral administration.

In addition, based on a hearing from specialists in epilepsy regarding the time of administration of antiepileptic injection as an alternative therapy, it was suggested that an injection should be administered for no longer than 30 minutes in actual clinical settings.

Based on the above findings, the time of study drug administration is set at 30 minutes.

9.3 Selection of Study Population

Twenty subjects will be randomized and treated in this study. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive

the 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 aged 12 years or older at the time of informed consent/assent
2. Have a diagnosis of epilepsy with POS with or without secondarily generalized seizures or PGTC seizures according to the International League Against Epilepsy (ILAE) Classification of Epileptic Seizures (1981)
3. Have been receiving a stable dosage of oral perampanel (8 to 12 mg/day) for at least 28 days before Day 1 in the Treatment Phase
4. Have been receiving a concomitant stable dosage of 1 to a maximum of 3 marketed AED(s) (regarding phenobarbital used as an AED, phenytoin, and carbamazepine, only one is allowed) for at least 28 days before Day 1 in the Treatment Phase. No change of dosing regimen for concomitant AED(s) is planned during the Treatment and Follow-up Phases.
5. Are considered reliable and willing to be available for the study period by the investigator, and are able to record seizures and report adverse events (AEs) by themselves or have a caregiver who can record seizures and report AEs for them

9.3.2 Exclusion Criteria

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

1. Have a history of drug or alcohol dependency or abuse within the last 2 years before Visit 1
2. Have a history of status epilepticus within 6 months before Day 1 in the Treatment Phase
3. Are unsuitable for venipuncture and intravenous administration
4. Require medical intervention due to safety issues related to the concomitant administration of 1 to 3 AEDs
5. Have a history of suicidal ideation/attempt within 2 years before Day 1 in the Treatment Phase
6. Have clinically problematic psychological or neurological disorder(s)
7. Clinical symptoms or imaging suggest a progressive central nervous system (CNS) abnormality, disorder, or brain tumor
8. Current evidence of a clinically significant disease (eg, cardiac, respiratory, gastrointestinal, or renal disease) that in the opinion of the investigator(s) could affect the subject's safety, interfere with the study assessments, or require prohibited medications as specified in the study protocol
9. Clinically significant abnormal laboratory values
10. Concomitant use of the following drugs except for carbamazepine and phenytoin or foods known to induce CYP3A (not limited to these drugs or foods) within 14 days before Day 1 in the Treatment Phase:

enzalutamide, mitotane, phenobarbital (except for use as an AED), amobarbital, secobarbital, rifabutin, rifampicin, food containing St. John's Wort (*hypericum perforatum*), bosentan, efavirenz, etravirine, modafinil, aprepitant, echinacea, pioglitazone, vemurafenib, nevirapine, and glucocorticoid (except for topical use)

11. Hypersensitivity to the study drug or any of its excipients
12. A history of multiple drug allergies or a severe drug reaction to an AED(s), including dermatological (eg, Stevens-Johnson syndrome), hematological, or organ toxicity reactions
13. Females of childbearing potential who:
 - In the Pretreatment Phase, are breastfeeding or pregnant (as documented by a positive beta-human chorionic gonadotropin [β -hCG] test).
 - Within 28 days before Visit 1, did not use a highly effective method of contraception, which includes any of the following:
 - total abstinence (if it is their preferred and usual lifestyle)
 - an intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
 - a contraceptive implant
 - an oral contraceptive (with additional barrier method)
(Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before Day 1 in the Treatment Phase and throughout the entire study period, and for 28 days after the last dose of the study drug)
 - have a vasectomized partner with confirmed azoospermia.
 - Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after the last dose of the study drug.

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

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

14. Be considered inappropriate for evaluation in the investigator's judgment
15. Have participated in a study involving administration of an investigational drug or device within 28 days before Visit 1, or within approximately 5 half-lives of the previous investigational drug, whichever is longer
16. Have a prolonged QTcF interval (>450 ms) 2 or more times as demonstrated by a repeated electrocardiogram (ECG)

17. Have a vagal nerve stimulation (VNS) device implanted less than 5 months before Visit 1 or changes in stimulation parameters less than 28 days before Visit 1

9.3.3 Removal of Subjects From Therapy or Assessment

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

Further details are provided in Section 9.5.5 .

9.4 Treatment

9.4.1 Treatment Administered

The study drug, perampanel intravenous formulation, is a lyophilized powder for injection containing 8 mg of perampanel (anhydride) in a vial.

Subjects will be switched from oral perampanel (8 to 12 mg/day; stable-dosage treatment during the Pretreatment Phase) on Day 1 to intravenous infusion of perampanel at a dose equivalent to the oral perampanel dose. Subjects will receive 30-minute intravenous infusions of perampanel once a day in a supine position for 4 days under inpatient conditions (Days 1 through 4).

The start time of intravenous infusions of perampanel from Day 1 to Day 4 will be designated as the same time as the administration time of oral perampanel on Day –1 (allowance window: ± 1 hour).

As for the procedure for preparation of the intravenous infusion of perampanel, refer to the Instructions for Handling of Investigational Products provided by the sponsor.

Recording of Information Regarding the Study Treatment (Perampanel Intravenous Infusion)

The following information will be recorded in the CRF: Dose of perampanel; timing of dose (before/after a meal); planned intravenous-perampanel-infusion dose (mg); planned intravenous-perampanel-infusion volume (mL); actual intravenous-perampanel-infusion volume (mL); start date and time of infusion; end date and time of infusion; as well as date and time of both stopping infusion and resuming infusion, if applicable. In addition, if the intravenous-perampanel infusion is not performed as planned, the reason(s) will also be recorded on the CRF.

Recording of Information Regarding Oral Perampanel

Information regarding the oral perampanel will be obtained for the CRF. In addition, as for the administration time of the oral perampanel on Day –1, the day and time of the dose, as well as the timing of the dose (before/after a meal), will be recorded on the CRF.

9.4.2 Identity of Investigational Product

The study drug will be supplied by the sponsor in labeled containers.

9.4.2.1 Chemical Name of E2007

- Test drug code: E2007
- Generic name: Perampanel Hydrate
- Chemical name: 2-(2-Oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl) benzonitrile hydrate (4:3)
- Molecular formula: C₂₃H₁₅N₃O·3/4H₂O
- Molecular weight: 362.90 (3/4 hydrate); 349.38 (anhydrous)

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

The following information has to be provided:

- For clinical study use only
- Name and address of the sponsor
- Study drug code
- Drug identifier
- Lot number
- Storage conditions

9.4.2.4 Storage Conditions

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

9.4.3 Method of Assigning Subjects to Treatment Groups

There is no randomization in this study.

9.4.4 Selection of Doses in the Study

See Section 9.2 .

9.4.5 Selection and Timing of Dose for Each Subject

See Section 9.4.1 .

9.4.6 Blinding

The study will not be blinded.

9.4.7 Prior and Concomitant Therapy

All medications (including over-the-counter medications) and non-pharmacological procedures administered to the subject during the study (or until the visit at the time of early discontinuation for discontinued subjects) will be recorded on the CRF.

9.4.7.1 Antiepileptic Drugs Other Than Perampanel

For at least 28 days before Day 1 in the Treatment Phase and throughout the study (or until the visit at the time of early discontinuation for discontinued subjects), subjects must be on a stable dosage of 1 to a maximum of 3 marketed concomitant AEDs.

9.4.7.2 Prohibitions and Restrictions During Study Period

9.4.7.2.1 PROHIBITED CONCOMITANT MEDICATIONS AND FOODS

For 14 days before Day 1 in the Treatment Phase and throughout the study (or until the visit at the time of early discontinuation for discontinued subjects), concomitant use of the following drugs and foods is prohibited.

- Other than carbamazepine and phenytoin, concomitant use of the following drugs or foods known to induce CYP3A (not limited to these):
enzalutamide, mitotane, phenobarbital (except for use as an AED), amobarbital, secobarbital, rifabutin, rifampicin, food containing St. John's Wort (*hypericum perforatum*), bosentan, efavirenz, etravirine, modafinil, aprepitant, echinacea, pioglitazone, vemurafenib, nevirapine, and glucocorticoids (except for topical use)

The use of the following drugs is prohibited within 28 days or approximately 5 half-lives of the previous investigational drug (whichever is longer) before Visit 1, as well as during the study (or until the visit at the time of early discontinuation for discontinued subjects).

- Other investigational drugs

The use of the following drug is prohibited during the Treatment Phase:

- Oral perampanel

9.4.7.2.2 PROHIBITED CONCOMITANT THERAPIES

The following therapies must not be implemented during the study (or until the visit at the time of early discontinuation for discontinued subjects).

- Brain surgery
- Neuromodulation therapy except for VNS (transcranial magnetic stimulation, etc.)

The following therapies must not be implemented within 28 days before Visit 1, as well as throughout the study (or until the visit at the time of early discontinuation for discontinued subjects).

- Therapies with a medical device under clinical study

9.4.7.2.3 RESTRICTED CONCOMITANT DRUGS

The dosing regimens of the following drugs must not be altered, newly introduced, or discontinued during the study (or until the visit at the time of early discontinuation for discontinued subjects).

- Antidepressants
- Antipsychotics
- Antianxiety drugs
- Benzodiazepine hypnotics

9.4.7.2.4 RESTRICTED CONCOMITANT THERAPIES

- A ketogenic diet must not be changed, initiated, or discontinued during the study (or until the visit at the time of early discontinuation for discontinued subjects).
- A VNS is allowed, however, stimulation parameters cannot be changed for 28 days before Visit 1 and throughout the study (or until the visit at the time of early discontinuation for discontinued subjects).

9.4.8 Treatment Compliance

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

9.4.9 Drug Supplies and Accountability

The designated pharmacist (or designee) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions (Instructions for Handling of Investigational Products) and adherence to J-GCP guidelines as well as other 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 designated pharmacist (or designee) must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, unused study drugs that are returned by the subjects (unused study drug-1), unused study drugs that are

shipped to the site but not dispensed to subjects (unused study drug-2), and return of reconciled study drugs to the sponsor (sum of unused study drugs 1 and 2), or destruction of reconciled study drugs at the site (if applicable). This includes, but may not be limited to: (a) documentation of the receipt of study drugs, (b) a study drug dispensing/return reconciliation log, (c) a study drug accountability log, and (d) documentation of returns to 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. Upon completion of unused drug accountability and reconciliation procedures by the designated pharmacist (or designee) and documentation procedures by the designated pharmacist (or designee) and the sponsor's personnel, unused study drugs must be returned to the sponsor by the designated pharmacist (or designee). Unused study drugs will be removed from the site and hand-delivered to the sponsor's designated depot by sponsor representatives (ie, CRA).

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

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be recorded in the CRF at Visit 1. Demography information includes date of birth, age, sex, race, and ethnicity.

9.5.1.2 Pretreatment Assessments

9.5.1.2.1 EPILEPSY HISTORY

Epilepsy history (date of diagnosis, etiology, epileptic syndrome, suspected localization of the epileptogenic region, and seizure types) will be recorded in the CRF at Visit 1.

9.5.1.2.2 MEDICAL HISTORY OTHER THAN EPILEPSY

Medical history (other than epilepsy) within 1 year before Visit 1, and current medical conditions will be noted in the CRF at Visit 1.

9.5.1.2.3 HEIGHT MEASUREMENT

Height at Visit 1 will be recorded in the CRF.

9.5.1.2.4 URINE DRUG SCREEN

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

9.5.1.3 Efficacy Assessments

Efficacy will be assessed by seizure counts and types as recorded in the diary. Diaries will be dispensed to all subjects and returned from all subjects at the visits designated in the Schedule of Procedures/Assessments (Table 2).

The diary is to be completed by the subject, the designated subject's caregiver, clinical nurses, or other site staff. In the diary, all seizure counts and types will be recorded. At each visit, the subject or the caregiver will be instructed by the investigator or the designated investigator's staff as to how to complete the diary and reminded that they must bring the diary to their next scheduled visits including the Early Discontinuation Visit and the Follow-up Visit. Based on the diary, seizure counts and types will be recorded on the CRF.

The investigator should review the diary for each subject at the visits designated in the Schedule of Procedures/Assessments (Table 2). Subjects or caregivers must be counseled if diary compliance is not satisfactory.

The retrieved diaries for each subject will be maintained appropriately at each investigational site throughout the required retention period (See Section 11.6).

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected as specified in Table 2. For procedures to collect, handle, and ship samples, see the separately specified written procedure. The sampling date and time will be recorded in the CRF.

Plasma concentration of perampanel will be measured by a validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) assay.

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ASSESSMENTS

Not applicable.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; laboratory evaluations for biochemistry, hematology, and urine values; periodic measurements of vital signs, weight, and 12-lead ECG; and the performance of physical examinations as detailed in Table 2.

9.5.1.5.1 ADVERSE EVENTS

An AE is any untoward medical occurrence in a 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 intravenous formulation.

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 use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of the study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of the study drug, or withholding of the study drug, whether prescribed in the protocol or not.

All AEs, regardless of relationship to the study drug or procedure, should be recorded in the CRF beginning from the time the subject signs the study ICF through the last visit and for 21 days after the subject's last dose of the study drug. Serious AEs will be collected for 28 days after the last dose of the study drug. In addition, the start date and time of an adverse event, and the end date and time of the adverse event will be recorded in the CRF.

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 CRF.

All events associated with suicidal ideation/attempt, regardless of severity, must be recorded as an AE in the CRF.

All AEs must be followed for 28 days after the subject's last dose of the study drug, or until resolution, whichever comes first. All SAEs and AEs of special interest (see Section 9.5.1.5.3) must be followed to resolution or, if resolution is unlikely, to stabilization.

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

Assessing Severity of Adverse Events

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

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

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

Assessing Relationship to Study Treatment

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

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of the 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 that are known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

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

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

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

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

9.5.1.5.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

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

- Results in death
- Is life-threatening (ie, the subject was at an 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, other events associated with special situations include: pregnancy or exposure to the study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, and medication errors (See Sections 9.5.4.2 and 9.5.4.3). 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 post study drug administration)
- Hospitalization for administration of the study drug or insertion of access for administration of the study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

9.5.1.5.3 STUDY-SPECIFIC ADVERSE EVENTS

In a non-clinical toxicity study of sodium sulphobutylether-beta-cyclodextrin (hereinafter “SBECD”), which is one of the additives in this study drug, vacuolation was observed in tubular epithelial cells, suggesting that patients with impaired renal function have a risk of SBECD accumulation (Luke, et al., 2010). In addition, there have been reports of anaphylaxis, possibly due to SBECD, with other formulations containing SBECD.

In this study, based on the above findings, adverse events associated with renal dysfunction, and adverse events associated with anaphylaxis will be handled as “adverse events of special interest (AESIs)” and recorded in the CRF.

For the procedures for reporting adverse events of special interest, see Section 9.5.4.3.2

1. Adverse Events Associated With Renal Dysfunction

If an adverse event associated with renal dysfunction occurs, and does not resolve at the time point when the Follow-up Phase is completed, the investigator will monitor the subject for 14 days from the follow-up visit, regardless of severity, and will continue following up the subject as needed until resolution of the event or, if resolution is unlikely, until stabilization of the symptom or sign. During this period, the subject will be followed up continuously by renal function monitoring at unscheduled visits (eg, once weekly, or at a frequency deemed necessary by the investigator).

2. Adverse Events Associated With Anaphylaxis

In the event of an adverse event associated with anaphylaxis, the investigator will take the following responsive actions:

- Take the first response, for example, by immediately referring the subject to an appropriate clinical department;
- Make a decision regarding whether or not to continue administration of the study drug to the subject, based on advice from the physician in the above-mentioned department;
- In the event of an adverse event associated with anaphylaxis while continuing intravenous administration of the study drug, discontinue the administration. In the event of any symptom or sign that is suspected of anaphylaxis while continuing intravenous administration of the study drug, careful judgment will be exercised in determining whether or not to continue the administration.

The follow-up of anaphylaxis will be continued until resolution of the event or, if resolution is unlikely, until stabilization of the symptom or sign.

9.5.1.5.4 LABORATORY MEASUREMENTS

The clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 1. 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 in the study. The sampling date will be recorded in the CRF.

Table 1 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	Sodium, potassium, chloride, calcium
Liver function tests	Alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transpeptidase, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, cholesterol, glucose, lactate dehydrogenase, phosphorus, total protein, triglycerides, uric acid
Urinalysis	glucose, ketones, occult blood, pH, protein, specific gravity

RBC = red blood cell, WBC = white blood cell

The clinical laboratory tests indicated above will be performed by the central laboratory.

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

9.5.1.5.5 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], pulse [beats per minute], respiratory rate [per minute], and body temperature [in centigrade]), and weight (kg) will be recorded on the CRF 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 resting for 5 minutes. All BP measurements should be performed on the same arm, and preferably by the same person.

9.5.1.5.6 PHYSICAL EXAMINATIONS

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 2). Documentation of the physical examination will be included in the source documentation at the site. Only changes from the screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

9.5.1.5.7 ELECTROCARDIOGRAMS

Twelve-lead electrocardiograms will be obtained as designated in the Schedule of Procedures/Assessments (Table 2) after the subject has been resting for 5 minutes. The

investigator will record the presence or absence of any ECG abnormalities (Normal/Abnormal, Not Clinically Significant/Abnormal Clinically Significant) based on the relevant ECG findings in the CRF.

In the Pretreatment Phase, only if the QTcF interval is more than 450 ms, an additional 2 consecutive ECGs separated by 5 or more minutes will be recorded.

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

9.5.1.5.8 OTHER SAFETY ASSESSMENTS

Not applicable.

9.5.1.6 Other Assessments

9.5.1.6.1 PREGNANCY TEST

At Visit 1, all females of childbearing potential will undergo the serum β -hCG pregnancy test (the measurements will be performed by the central laboratory). At Visit 2 and thereafter, all females of childbearing potential will undergo the urine β -hCG pregnancy test (the measurements will be performed by each investigational site).

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 2 presents the schedule of procedures/assessments.

Table 2 Schedule of Procedures / Assessments in Study E2007-J081-240

Phase	Pretreatment Phase		Treatment Phase ^a				Follow-up Phase ^{b, c}	Unscheduled Visit ^k	Early Discontinuation Visit
	Day -28 to -7 (Screening)	Day -1	Day 1	Day 2	Day 3	Day 4			
Study Day(s) (from Day 1 of Treatment Phase)							7 days after the last intravenous infusion		
Visit	1	2	3a	3b	3c	3d		4	
Procedure/Assessment									
Informed consent/assent ^d	X								
Inclusion/exclusion criteria	X	X	X						
Physical examinations	X	X	X ^m	X ^m	X ^m	X ^m	X	X	X
Medical history	X								
Concomitant medications/therapies	X ^e	X ^e	X ^e	X	X	X	X	X	X
Hospitalization		X	X	X	X	X ^l			
Intravenous administration of the study drug (intravenous infusion of perampanel)			X	X ⁿ	X ⁿ	X ⁿ			
Oral perampanel administration at the hospital		X ⁿ							
Adverse events ^f	X	X	X	X	X	X	X	X	X
Oral perampanel/study drug compliance	X	X	X	X	X	X	X		X
Dispense subject diary	X		X			X			X
Return and review subject diary			X			X	X ^o		X
Discontinuation/continuation judgment ^g		X	X	X	X	X			
Vital signs and weight/height ^h	X	X	X ^m	X ^m	X ^m	X ^m	X	X	X
Clinical laboratory evaluations	X	X				X ^m	X	X	X
PK blood sampling for perampanel ⁱ		X	X	X	X	X			
Urine drug screen	X								
Urine pregnancy test ^j		X					X	X	X
Serum pregnancy test ^j	X							X	
12-lead ECG	X	X				X ^m	X	X	X

- a: The date of each visit to be specified based on the date of Visit 3a. The Treatment Phase is defined as the period beginning at the start of the study treatment (intravenous infusion of perampanel) on Day 1 to immediately before the oral perampanel administration on Day 5.
- b: Visit to be performed within +7 days of the schedule. The visit is to be specified based on the date of the last intravenous infusion of perampanel.
- c: To be completed by subjects who received at least 1 intravenous infusion of perampanel, in principle.
- d: Informed consent must be obtained before any study-related procedure.
- e: Prior and concomitant medication(s)/therapies(s).
- f: Adverse events will be collected from the time the subject signs the informed consent form through the 21 days after the subject's last intravenous infusion of perampanel. Serious adverse events will be collected for 28 days after the subject's last intravenous infusion of perampanel.
- g: During the period from Visit 3a to Visit 3d, if a subject experiences seizures or has safety issue, the investigator will make as judgment regarding study continuation/discontinuation based on the subject's tolerability and efficacy.
- h: Height is to be measured only at Visit 1.
- i: Blood samples for the plasma perampanel concentration will be collected at predose and at 0.5, 1, and 1.5 hours after the oral administration of perampanel on Visit 2 (Day -1), predose and at 0.5 hours after the start of intravenous infusions of perampanel on Visits 3a, 3b, 3c, and 3d (Days 1, 2, 3, and 4). In addition, for the blood samplings at 0.5 hours after the start of intravenous infusions of perampanel on Days 1 through 4, they should be performed immediately after completion of the intravenous perampanel infusions (ie, within 5 minutes after completion).
- j: All females of childbearing potential will undergo the serum β -hCG pregnancy test at Visit 1. At Visit 2 and thereafter, all females of childbearing potential will undergo the urine β -hCG pregnancy test.
- k: At an Unscheduled Visit, only the procedures/assessments that the investigator has judged as necessary according to the subject's condition will be performed.
- l: Subjects will be discharged from the hospital the next day following Day 4 (ie, on Day 5).
- m: The examinations will be conducted predose.
- n: The start time of intravenous infusions of perampanel from Day 1 to Day 4 will be designated as the same time as the administration time of oral perampanel on Day -1 (allowance window: ± 1 hour).
- o: As for subjects who have been withdrawn from the study, recording in the diary after discontinuation will continue as far as possible. Further, the investigator or the designated investigator's staff should record seizure counts and types on the CRF for up to 14 days after the subject's last intravenous infusion of perampanel.

9.5.3 Appropriateness of Measurements

The safety assessments in this study are standard evaluations to ensure subject safety.

The efficacy assessment (ie, seizure counts and types) comprises standard measurements commonly used in studies evaluating the effect of AEDs.

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 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 and for 28 days after the subject's last dose of study drug. 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 Attachment 1.

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

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

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

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in a female subject in which the estimated date of conception is either before the last visit or within 28 days of the last study treatment or any exposure to the study drug through breastfeeding during study treatment or within 28 days of the 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 the perinatal period, an induced abortion, or a spontaneous abortion is considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Section 9.5.4.1).

Pregnancies or exposure to the 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 the study drug through breastfeeding is provided in Attachment 1. The Pregnancy Report Form (Attachment 4) must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported using the Pregnancy Outcome Report Form (Attachment 5) 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 errors refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication errors 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 the study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of the 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

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

9.5.4.3.2 REPORTING OF STUDY-SPECIFIC EVENTS

In this study, adverse events associated with renal dysfunction and adverse events associated with anaphylaxis will be handled as “adverse events of special interest (AESIs)”

(see Section 9.5.1.5.3).

If an adverse event of special interest associated with renal dysfunction, with an elevated creatinine level $>3\times$ the upper limit of normal (ULN), or an adverse event associated with anaphylaxis (regardless of severity) is observed, it will be reported according to the procedures specified in “Reporting of Serious Adverse Events” (Section 9.5.4.1) even if the AEs do not meet serious criteria. If the event does not meet the definition of a SAE, 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 the investigator, the head of the medical institution, and regulatory authorities of reportable events, in compliance with applicable regulatory requirements. For this reason, it is imperative that the investigator provides complete SAE information in the manner described in Section 9.5.4.1 .

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 to the regulatory authorities in compliance with regulatory requirements and established guidance. The format of these reports will be dictated by the regulatory requirements.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason. 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.

All subjects who discontinue the study between the start of the first study treatment (Day 1) and Day 4 are to complete the procedures/assessments at the Early Discontinuation Visit indicated in the Schedule of Procedures/Assessments (Table 2). In addition, when the discontinuation has occurred before the start of the study treatment on Day 2, Day 3, or Day 4, the procedures/assessments that had been performed on that day of discontinuation can be deemed to be those at the Early Discontinuation Visit.

Even if the procedures/assessments at the Early Discontinuation Visit have been conducted, the procedures/assessments at the Follow-up Visit designated in the Schedule of Procedures/Assessments (Table 2) will be performed 7 days (allowance window: +7 days) after the last dose of study drug, as far as possible. In addition, between the Early Discontinuation Visit and the Follow-up Visit, the study treatment will be switched back to the original dose of oral perampanel used in the Pretreatment Phase, and a stable dosage of another AED(s) as an adjunctive therapy as well as recording of seizures (recording by

the subjects' caregiver is also acceptable) will be continued, as far as possible. The results of these procedures/assessments and the relevant drug information regarding oral perampanel and the other AED(s) will be recorded in the CRF.

If by any chance the procedures/assessments at the Early Discontinuation Visit cannot be conducted before the Follow-up Visit which is to occur 7 days (allowance window: +7 days) after the last dose of study drug, the procedures/assessments at the Follow-up Visit can be omitted.

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 primary reason. 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.

If subjects cannot continue the study drug for any reason(s), they must discontinue the study. In addition, a subject who becomes pregnant must be withdrawn from the study.

9.5.6 Abuse or Diversion of Study Drug

Not applicable.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator or the designated investigator's staff will instruct the subjects and the subjects' legally acceptable representatives (if applicable) to inform site personnel when the subjects are planning to receive medical care from another physician. At each visit, the investigator or the designated investigator's staff will ask the subject and the subject's legally acceptable representative (if applicable) whether the subject has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent(s) of the subject and the subject's legally acceptable representative (if applicable), will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

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

9.6.1 Data Collection

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

subject.

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

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

9.6.2 Clinical Data Management

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

9.7 Statistical Methods

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

9.7.1 Statistical and Analytical Plans

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

9.7.1.1 Study Endpoints

The safety endpoints are AEs, clinical laboratory tests (biochemistry, hematology, and urinalysis), vital signs, weight, and 12-lead ECG.

The efficacy endpoint is the seizure frequency per day in each of the 3 phases (Pretreatment Phase, Treatment Phase, and Follow-up Phase). Seizure frequency per day will be derived from the information recorded in the subject diaries.

The pharmacokinetic endpoint is the plasma concentration of perampanel.

All observed data will be reported with no adjustments for missing data.

9.7.1.2 Definitions of Analysis Sets

The Safety Analysis Set is the group of subjects who received at least 1 intravenous infusion of perampanel.

The Efficacy Analysis Set is the group of subjects who received at least 1 intravenous

infusion of perampanel and had at least 1 postdose efficacy measurement.

The Pharmacokinetic Analysis Set is the group of subjects who received at least 1 intravenous infusion of perampanel and had at least 1 evaluable measurement of plasma perampanel concentration.

9.7.1.3 Subject Disposition

The number (percentage) of subjects who discontinued the Pretreatment Phase will be summarized for those who gave informed consent.

The number (percentage) of subjects who completed and discontinued the study will be summarized for those who received study drug.

In addition, the number of subjects who discontinued the study will be described according to the reason(s) for discontinuation.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set will be summarized using descriptive statistics. Continuous demographic and baseline variables include age, height, weight, and others (if necessary); categorical variables include sex, age group, and others (if necessary).

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD). The number (percentage) of subjects who took prior and concomitant medications will be summarized in the Safety Analysis Set by Anatomical Therapeutic Chemical (ATC) class (ie, anatomical class, therapeutic class, pharmacologic class, and chemical class) and WHO DD preferred term.

Prior medications/non-pharmacological procedures will be defined as medications/non-pharmacological procedures that stopped before the start of doses of the study drug. Concomitant medications/non-pharmacological procedures will be defined as medications/non-pharmacological procedures that were used on or after the start of doses of the study drug. All medications/non-pharmacological procedures will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

The efficacy analyses will be performed on the Efficacy Analysis Set.

The seizure frequency per day for each of the 3 phases (Pretreatment Phase, Treatment Phase, and Follow-up Phase) will be summarized using descriptive statistics (eg, mean, SD, median, minimum, and maximum). The seizure frequency per day from the Pretreatment Phase to the Follow-up Phase for each subject will be displayed using a

spaghetti-plot.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

The PK analyses will be performed on the Pharmacokinetic Analysis Set using the plasma concentrations of perampanel. Summary statistics for the plasma concentrations will be obtained by sampling time point and dose. The plasma concentrations of perampanel before and after switching from oral tablet to intravenous infusion will be plotted. A similar analysis may be conducted using dose-normalized plasma concentration data.

9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Not applicable.

9.7.1.8 Safety Analyses

The safety analyses will be performed on the Safety Analysis Set.

Safety data will be summarized using descriptive statistics (eg, n, mean, SD, median, minimum, and maximum for continuous variables; n [%] for categorical variables). Safety variables include AEs, clinical laboratory parameters (biochemistry, hematology, and urinalysis), vital signs, weight, and 12-lead ECG results.

9.7.1.8.1 EXTENT OF EXPOSURE

The extent of exposure to the study drug will be summarized using descriptive statistics.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 21.0 or higher) lowest level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges on or after the start of the study treatment, having been absent at pretreatment or

- Reemerges on or after the start of the study treatment, having been present at pretreatment but stopped before the start of the study treatment, or
- Worsens in severity on or after the start of the study treatment relative to the pretreatment state, when the AE is continuous.

All AEs, treatment-emergent or otherwise, will be presented in the subject data listings.

The incidences of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT,

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

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

The number (percentage) of subjects with AEs by SOC and PT will be summarized by Phase (Pretreatment Phase, Treatment Phase, and Follow-up Phase) of onset.

Subject data listings of all AEs leading to death, all SAEs, and all AEs leading to discontinuation from the study will be provided.

9.7.1.8.3 LABORATORY VALUES

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

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

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

9.7.1.8.4 VITAL SIGNS AND WEIGHT

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

9.7.1.8.5 ELECTROCARDIOGRAMS

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

9.7.1.8.6 OTHER SAFETY ANALYSES

Not applicable.

9.7.2 Determination of Sample Size

This is an uncontrolled, open-label study for the safety evaluation of intravenous infusion of perampanel and the sample size (20 subjects) is not based on statistical power considerations, but rather on feasibility. It is considered that a sufficient number of subjects will be obtained for the safety evaluation of intravenous infusion of perampanel if the sample size is 20.

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

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

10. REFERENCE LIST

Inoue Y, Suzuki A, Yoshida K, Yamamoto K. An open-label, multicenter study to evaluate the safety of adjunctive treatment with intravenous infusion of levetiracetam in adult epilepsy patients with partial seizures. *Jpn J Clin Psychopharmacol.* 2014; 17 (3): 413-22.

Luke DR, Tomaszewski K, Damle B, Schlamm HT. Review of the basic and clinical pharmacology of sulfobutylether-beta-cyclodextrin (SBECD). *J Pharm Sci.* 2010; 99 (8): 3291-301.

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 the subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRBs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor and the IRB for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to the IRB. In these cases, the sponsor may be required to send a letter to the head of the medical institution detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol.

11.3 Monitoring Procedures

The sponsor's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to the site will be conducted by the assigned CRA as described in the monitoring plan. The head of the medical institution will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with J-GCP and other 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 the study protocol and data accuracy in accordance with J-GCP. All records at the site are subject to inspection by the auditing agency and to IRB review.

In accordance with J-GCP, source documents include, but are not limited to the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes which have been certified for accuracy after production
- Recorded data from automated instruments
- 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
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRB

11.4 Recording of Data

A CRF is required and must be completed for each subject who has consented/assented to participate in the study by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF is itself 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 copies of the CRFs.

11.5 Identification of Source Data

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

The data collected directly on the CRF are considered source data. For instance, the following data recorded directly on the CRF are to be considered source data:

- Status of the study treatment (eg, reasons for discontinuation of the study treatment)
- Indication for prior or concomitant therapy
- Information on withdrawal from the study, for example, in the case of being lost to follow-up
- Sampling date and time for drug concentrations and clinical laboratory tests
- Information on AEs (eg, severity, relationship to the study drug, and outcome)

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the head of the medical institution (or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of the CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, ICFs, and IRB correspondence). The site should retain study documents until the approval date of a marketing application, at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product, at least 3 years have elapsed since receipt of a notice that the registration application should not include the results of the study, or at least 3 years have elapsed since the formal discontinuation or termination of the study, whichever comes last.

It is requested that at the completion of the required retention period, the site contact the

sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to the 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 J-GCP and other applicable regulations. In addition, there is the possibility that a government regulatory authority will conduct an inspection.

11.8 Handling of Study Drug

All study drug will be supplied to the designated pharmacist or the designee 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 designated pharmacist or the designee must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger. 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 the 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 designated pharmacist or the designee 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 designated pharmacist or the designee will return all unused study drug to the sponsor.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the head of the medical institution and the sponsor. 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 Clinical Trial Agreement executed between the head of the medical institution and the sponsor, 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 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 the Clinical Trial Agreement executed between the head of the medical institution and the sponsor.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in the Clinical Trial Agreement executed between the head of the medical institution and the sponsor.

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/head of the medical institution and the regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/head of the medical 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 the prior agreement of the sponsor, the investigator should inform the head of the medical institution where applicable, and the investigator/head of the medical institution should promptly inform the sponsor and the IRB and provide the sponsor and the IRB with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

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

12. APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values

Sponsor's Grading for Laboratory Values				
	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10 ⁹ /L <LLN – 3000/mm ³	<3.0 – 2.0×10 ⁹ /L <3000 – 2000/mm ³	<2.0 – 1.0×10 ⁹ /L <2000 – 1000/mm ³	<1.0×10 ⁹ /L <1000/mm ³
Lymphocytes	<LLN – 800/mm ³ <LLN – 0.8×10 ⁹ /L	<800 – 500/mm ³ <0.8 – 0.5×10 ⁹ /L	<500 – 200/mm ³ <0.5 – 0.2×10 ⁹ /L	<200/mm ³ <0.2×10 ⁹ /L
Neutrophils	<LLN – 1.5×10 ⁹ /L <LLN – 1500/mm ³	<1.5 – 1.0×10 ⁹ /L <1500 – 1000/mm ³	<1.0 – 0.5×10 ⁹ /L <1000 – 500/mm ³	<0.5×10 ⁹ /L <500/mm ³
Platelets	<LLN – 75.0×10 ⁹ /L <LLN – 75,000/mm ³	<75.0 – 50.0×10 ⁹ /L <75,000 – 50,000/mm ³	<50.0 – 25.0×10 ⁹ /L <50,000 – 25,000/mm ³	<25.0×10 ⁹ /L <25,000/mm ³
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low (hypophosphatemia, a low concentration of phosphates in the blood)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L life-threatening consequences

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

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ -glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

List of Changes of Protocol (from Version 1 to Version 2)

Title: A multicenter, uncontrolled, open-label study to evaluate the safety and tolerability of intravenous perampanel as substitute for oral tablet in subjects with partial onset seizures (including secondarily generalized seizures) or primary generalized tonic-clonic seizures

Protocol Sections	Before (Version 1 dated 07 Sep 2018)	After (Version 2 dated 09 Oct 2018)	Rationale
9.5.1.5.1 ADVERSE EVENTS	<p>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 CRF.</p> <p>All AEs must be followed for 28 days after the subject's last dose of the study drug, or until resolution, whichever comes first. All SAEs and AEs of special interest (see Section 9.5.1.5.3) must be followed to resolution or, if resolution is unlikely, to stabilization.</p>	<p>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 CRF.</p> <p><u>All events associated with suicidal ideation/attempt, regardless of severity, must be recorded as an AE in the CRF.</u></p> <p>All AEs must be followed for 28 days after the subject's last dose of the study drug, or until resolution, whichever comes first. All SAEs and AEs of special interest (see Section 9.5.1.5.3) must be followed to resolution or, if resolution is unlikely, to stabilization.</p>	Added the handling of events associated with suicidal ideation/attempt based on the sponsor's response to PMDA's inquiry issued after the first Clinical Trial Notification (CTN) for perampanel intravenous formulation.