16.1.1 Protocol and Protocol Amendments

The latest version of the study protocol all previous versions are provided on the following pages:

- V9.0 Final, 13 Jul 2018 (per Amendment 04)
- V8.0 Final, 19 Jan 2018 (per Amendment 03)
- V7.0 Final, 03 Dec 2017 (per Amendment 03)
- V6.0 Final, 19 Oct 2017 (per Amendment 02)
- V5.0 Final, 20 Apr 2017 (per Amendment 01)
- V4.0 Final, 02 Nov 2016 (per Administrative Change)
- V3.0 Final, 30 Aug 2016 (per Administrative Change)
- V2.0 Final, 17 May 2016 (per Administrative Change)
- V1.0 Final, 17 May 2016 (original protocol)

Revision History

Revisions to Version v8.0 **New version/date: Version 9.0/13 Jul 2018 (per Amendment 04, Version 9.0)**		
Change	**Rationale**	**Affected Protocol Section(s)**
Clarified, in the text, that the Pretreatment Phase consists of a Screening/Baseline period	Document quality	Synopsis (Section 2) – • Study Period and Phase of Development Section 7.2
Clarified, in the text, the approximate total study duration.	Document quality	Synopsis (Section 2) • Study Period and Phase of Development
Clarified, in the text, that subjects in Japan and and in countries where an extended access program (EAP) cannot be implemented can enroll in Extension B	To provide managed access of study drug to subjects until commercial availability of perampanel	Synopsis (Section 2) – • Study Period and Phase of Development • Study Design • Statistical Methods • Duration of Treatment Section 7.2 Figure 1 Section 9.1 Section 9.1.3 Section 9.1.3.2 Section 9.1.4.1 Section 9.4.1 Appendix 1 Appendix 2 Table 5 Table 6
Specified criteria for participation in Extension B for subjects in countries where an EAP cannot be implemented.	To provide managed access of study drug to subjects until commercial availability of perampanel	Synopsis (Section 2) – • Study Period and Phase of Development • Study Design • Duration of Treatment Section 9.1 Section 9.1.4.1 Appendix 2 Table 6
Clarified the CGI objective (CGIS is the baseline assessment and CGIC is the postbaseline assessment of the CGI)	Document quality	Synopsis (Section 2) – • Objectives • Assessments Section 8.2
Updated Medical Monitor information	Personnel change	Protocol Signature Page
Grammatical, typographical, and formatting changes were also made.	Document quality	Throughout the document

Revisions to Version v7.0 **New version/date: Version 8.0/19 Jan 2018 (per Amendment 03, Version 8.0)**		
Change	**Rationale**	**Affected Protocol Section(s)**
Clarified, in the text, that the Follow-up Visit would be conducted at 4 weeks ± 7 days after the last dose of study drug for all subjects, except for subjects entering into Extension A.	Document quality	Synopsis (Section 2) – • Study Design • Duration of Treatment Section 9.1.2 Section 9.1.2.2 Section 9.3.3
Clarified, in the text, that the follow-up period of Extension A was only for subjects not entering into Extension B and that Extension B will occur in Japan only.	Document quality	Synopsis (Section 2) – • Study Period and Phase of Development • Study Design • Duration of Treatment Section 7.2 Section 9.1 Section 9.1.3 Section 9.1.3.2 Appendix 1 Table 5
Clarified, in the text, that a follow-up period of Extension B, would include a Follow-up visit at 4 weeks ± 7 days after the Discontinuation Visit, and would occur for subjects who discontinue or who choose not to switch to the commercial product.	Document quality	Synopsis (Section 2) – • Study Period and Phase of Development • Study Design • Duration of Treatment Section 9.1 Appendix 2 Table 6
Clarified, in the text, that subjects in all countries can enroll in Extension A	Document quality	Section 9.1
Clarified that the study visit window during Extension B is ±6 days of the scheduled visit.	Document quality.	Table 6
Clarified that the initial assessment of Extension B was performed at the final visit of Extension A Maintenance period (ie, Visit 12)	Document quality	Table 6
Grammatical, typographical, and formatting changes were also made.	Document quality	Throughout the document

Revisions to Version v6.0 **New version/date: Version 7.0/03 Dec 2017 (per Amendment 03)**		
Change	**Rationale**	**Affected Protocol Section(s)**
Added an Additional Extension Phase (Extension B) for subjects in Japan only.	To provide managed access to perampanel for subjects in Japan.	Synopsis – Study Period and Phase of Development Synopsis – Study Design Synopsis – Duration of Treatment Synopsis – Statistical Methods Section 5.3 Section 7.2 Section 9.1 and Figure 1 Section 9.1.3 Section 9.1.3.2 Section 9.1.4 Section 9.4.1 Section 9.5.1.6 Section 9.5.2.1 Section 9.5.2.2 Appendix 1 Appendix 2
Updated references to the Extension Phase to Extension A.	Clarification to distinguish the original Extension Phase from the Additional Extension Phase in Japan.	Throughout the document
Clarified, in text, the study visit window during Extension A is ±6 days of the scheduled visit.	Document quality.	Synopsis – Study Design Section 9.1.3
Revised the Sponsor signature page.	To reflect updated team members.	PROTOCOL SIGNATURE PAGE
Grammatical, typographical, and formatting changes were also made.	Document quality.	Throughout the document

Revisions to Version v5.0 **New version/date: Version 6.0/19 Oct 2017 (per Amendment 02)**		
Change	**Rationale**	**Affected Protocol Section(s)**
Revised the Pretreatment Screening/Baseline Period (outside of Japan) to allow subjects to enrol sooner after a qualifying seizure, while maintaining the 4 weeks ±3 days required in Japan. Added that the study period durations were "up to" the specified nominal times.	To shorten the time to enroll (outside of Japan) and add flexibility to study period durations in line with visit windows.	Synopsis – Study Period and Phase of Development Synopsis – Pretreatment Phase Synopsis – Inclusion Criteria Synopsis – Duration of Treatment Section 7.2 Section 9.1 and Figure 1 Section 9.1.1 Section 9.1.2 Section 9.4.1 Section 9.5.2.1 (Table 4) Appendix 1
Revised inclusion #5, for subjects in Japan, such that the 4-week time-frame for partial-onset seizures (POS)/primary generalized tonic-clonic seizures (PGTC) seizure occurrence prior to Visit 2.	To assess efficacy only in the Japanese subjects, per agreement between the sponsor and The Pharmaceuticals and Medical Devices Agency (PMDA) in Japan.	Synopsis – Inclusion Criteria Section 9.3.1
Added that analyses for regional submissions may be performed during the course of the study.	To allow for regional data submission during the course of the study.	Synopsis – Interim Analyses Section 9.7.3 Appendix 1
Revised the sample size to state "at least" 160 subjects "(with up to 40 subjects with PGTC and the balance with POS)."	To allow flexibility in enrollment	Synopsis – Sample Size Rationale Section 9.7.2 Section 9.3
Added that each study visit is based on the actual prior visit (eg, Visit 3 is completed 2 weeks ±3 days of Visit 2, Visit 4 is completed 3 weeks ±3 days of Visit 3, etc).	Clarification.	Section 9.1.2.1 Section 9.1.2.2 Section 9.1.3 Section 9.5.2.1 (Table 4)
Revised study visit window during the Extension Phase back to ±6 days of the scheduled visit for Visits 10 through 12 (as per the original protocol).	The ±6 days window is necessary to ensure that investigational product (IP) is administered within the 90-day shelf life once opened.	Appendix 1 (Table 5)
Revised the Sponsor signature.	To reflect updated team members.	PROTOCOL SIGNATURE PAGE

Revisions to Version v5.0 **New version/date: Version 6.0/19 Oct 2017 (per Amendment 02)**		
Change	**Rationale**	**Affected Protocol Section(s)**
Grammatical, typographical, and formatting changes were also made.	Document quality	Throughout the document

Revisions toVersion v4.0 **New version/date: Version 5.0/20 Apr 2017 (per Amendment 01)**		
Change	**Rationale**	**Affected Protocol Section(s)**
Added that the Titration Period is a fixed duration of 11 weeks and subjects will remain on their optimum dose once it is achieved during this period.	For clarification	Synopsis – Study Design: Titration Period; Duration of Treatment Section 7.2 Section 9.1 Section 9.1.2.1 Section 9.4.1
Separated the Titration Period dosing schedule into separate presentations for Global sites and Japan sites.	For clarification	Synopsis – Study Design: Titration Period Section 9.4.1 (Table 4 and Table 5)
Increased the time prior to Visit 2 that subjects must meet the prior seizure criterion from 4 to 12 weeks.	To improve enrolment	Synopsis – Inclusion criteria Section 9.1.1 Section 9.3.1
Increased the number of approved antiepileptic drug (AEDs) subjects may currently be receiving from 2 to 3.	To improve enrolment	Synopsis – Inclusion criteria Section 9.1.1 Section 9.3.1
Expanded the exclusion criteria for renal impairment and defined moderate and severe renal impairment.	Regulatory request	Synopsis – Exclusion criteria Section 9.3.2
Removed exclusion of barbiturate use within 4 weeks before to Visit 1.	To improve enrolment	Synopsis – Exclusion criteria Section 9.3.2
Revised exclusion criteria for previous use of benzodiazepines for epilepsy (with exception for use as rescue medication for seizure control) or intermittent use for other indications.	For clarification	Synopsis – Exclusion criteria Section 9.3.2
Added exclusion criterion for cannabinoids.	For clarification	Synopsis – Exclusion criteria Section 9.3.2
Added exclusion of subjects with hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.	Regulatory request	Synopsis – Exclusion criteria Section 9.3.2

Revisions toVersion v4.0 **New version/date: Version 5.0/20 Apr 2017 (per Amendment 01)**		
Change	**Rationale**	**Affected Protocol Section(s)**
Added emphasis that efforts should be made to perform all clinical laboratory and screening tests on the scheduled day, or as close as possible to that day, within 4 week period prior Visit 2.	For clarification	Section 9.1
Added urine drug screen.	Assessment needed for exclusion criteria 18	Section 9.5.1.5.3 and Table 3
Added mandatory blood collection for pharmacokinetic (PK) assessment.	For clarification	Section 9.5.1.4.1
Removed “bands” from clinical hematology laboratory tests.	Correction	Section 9.5.1.5.3 (Table 3)
Revised text to stipulate that a serum pregnancy test is performed at screening and urine pregnancy tests are performed after screening, unless urine can not be obtained.	Correction	Section 9.5.1.5.7 Section 9.5.2.1 (Table 4)
Revised footnote “r” to indicate that blood for PK was collected for serious adverse events, rather than adverse events.	Correction	Section 9.5.2.1 (Table 4)
Added “Safety” to the section title.	For clarification	Section 9.7.3
Added additional information describing the Principal Investigator’s responsibility and use of data generated by the site or Principal Investigator regarding queries and future publications.	For clarification	Section 11.4 and Section 11.5
Revised study visit window to ±7 days of the scheduled visit.	For consistency with the Core study	Appendix 1 (Table 5)
Grammatical, typographical, and formatting changes were also made.	Document quality	Throughout

Previous Version (Revised protocol): v3.0
Current Version (Revised per administrative change): v4.0
Date of Revisions: 02 Nov 2016

Change	Rationale	Affected Protocol Section(s)
Change the sign of the prespecified threshold for median percent reduction in seizure frequency, from negative to positive.	To correct an error	Synopsis - Efficacy Analyses Synopsis - Sample Size Rationale Section 9.7.1.6 Section 9.7.2

Previous Version (Revised original): v2.0 **Current Version (Revised protocol): v3.0** **Date of Revisions: 30 Aug 2016**		
Change	**Rationale**	**Affected Protocol Section(s)**
Provide criteria for efficacy in Japanese subjects (ie, comparison of perampanel in the present study with placebo subjects in study E2007-J000-335).	Per request from PMDA	Synopsis - Objectives Section 8.2
Provide that subjects enrolled in Japan may not receive perampanel doses higher than 12 mg/day.	Per request from PMDA	Synopsis - Study Design Section 7.3 Figure 1 Section 9.1.2.1 Section 9.1.3.1 Section 9.4.1 Table 1
State threshold criterion for efficacy, for purposes of registration in Japan.	Per request from PMDA	Synopsis - Efficacy Analyses Section 9.7.1.6
Describe sample size for purposes of submission in Japan.	Per discussion with PMDA	Synopsis - Sample Size Rationale Section 9.7.2
Correct the window for Follow-up to 7 days.	For consistency and to correct an error	Section 9.1.3.2

Previous Version (Original): v1.0 **Current Version (Revised original): v2.0** **Date of Revisions: 17 May 2016**		
Change	**Rationale**	**Affected Protocol Section(s)**
Clarified Asia Pacific throughout	Clarification	Synopsis – Investigators Section 6 Section 9.3
Added a window of ±3 days to the Screening/Baseline Period.	The current version has screening period of 4 weeks. This windows will give operational/logistical flexibility.	Synopsis – Study Design Synopsis – Duration of Treatment Section 7.2 Section 9.1.1 Section 9.4.1
Revised cognitive testing from Vineland Adaptive Behavior Scale (VABS) to A-B neuropsychological assessment schedule (ABNAS).	The proposed A-B Neuropsychological Assessment Schedule (ABNAS), is simpler can be administered by any healthcare provider, caregiver. The logistics and burden of administering the scale is important consideration in this study population given the nature of the disease. We aim to achieve greater compliance and completeness of the data to compare at various time points during the study using the proposed scale. There is no negative impact or in any way to jeopardize the secondary endpoints proposed particularly cognitive assessments.	Synopsis – Safety Assessments Synopsis – Secondary Endpoints Synopsis – Safety Analyses Section 7.2 Section 9.5.1.5 Section 9.5.1.5.7 Table 4 Section 9.7.1.1.2 Section 9.7.1.8.6 Appendix 1
Removed requirement for placebo PK sample testing.	Not required as this is an open-label study	Section 9.5.1.4.1
Updated Statistician responsible for the study.	Change in Eisai personnel	Signature Page

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2007-G000-311
Study Protocol Title:	An Open-Label, Multicenter Study with an Extension Phase to Evaluate the Safety, Tolerability, and Exposure-Efficacy Relationship of Perampanel Oral Suspension when Administered as an Adjunctive Therapy in Pediatric Subjects (Age 4 to less than 12 years) with Inadequately Controlled Partial-Onset Seizures or Primary Generalized Tonic-Clonic Seizures
Sponsor:	Eisai Inc. 155 Tice Boulevard Woodcliff Lake, New Jersey 07677 USA Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 Japan
Investigational Product Name:	E2007/perampanel
Indication:	Partial-Onset Seizures or Primary Generalized Tonic-Clonic Seizures
Phase:	3
Approval Date:	V1.0 17 May 2016 (original protocol) V2.0 17 May 2016 (revised original protocol) V3.0 30 Aug 2016 (revised protocol) V4.0 02 Nov 2016 (revised per administrative change) V5.0 20 Apr 2017 (Amendment 01) V6.0 19 Oct 2017 (Amendment 02) V7.0 03 Dec 2017 (Amendment 03) V8.0 19 Jan 2018 (revised per administrative change) V9.0 13 Jul 2018 (Amendment 04)
IND Number:	112515
EudraCT Number:	2014-002167-16
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local GCP and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2007

Name of Active Ingredient: perampanel

Study Protocol Title

An Open-Label, Multicenter Study with an Extension Phase to Evaluate the Safety, Tolerability, and Exposure-Efficacy Relationship of Perampanel Oral Suspension when Administered as an Adjunctive Therapy in Pediatric Subjects (Age 4 to less than 12 years) with Inadequately Controlled Partial-Onset Seizures or Primary Generalized Tonic-Clonic Seizures

Investigators

Investigators in the US, EU, and Asia Pacific

Sites

Approximately 60 to 80 sites

Study Period and Phase of Development

The total study duration from 1st subject enrolled to last subject's last visit/last assessment will be approximately 112 weeks (52 weeks of recruitment, up to 4 weeks ±3 days of Screening/Baseline, up to 52 weeks of treatment [including up to an 11-week Titration Period, up to 12-week Maintenance Period, and up to 29-week Extension Phase (Extension A)], and up to 4 weeks of follow-up [only for those subjects not entering into Extension B]). (revised per Amendments 03 and 04) In Japan, 4 weeks ±3 days of baseline is required; however, subjects outside of Japan may begin treatment as soon as baseline procedures have been completed and documentation of eligibility has been established.

Extension Phase (Extension B) with open-label treatment will be available to subjects enrolled in Japan and in countries where an extended access program (EAP) cannot be implemented, after having completed Extension A. In Japan, participation in Extension B will continue as long as clinically appropriate according to the judgment of the investigator, until the subject reaches 12 years of age or perampanel is commercially available in Japan for treatment of partial-onset seizures (POS) in pediatric subjects (4 to less than 12 years of age). In countries where an EAP cannot be implemented, participation in Extension B will continue as long as clinically appropriate according to the judgment of the investigator, until the subject reaches 12 years of age or perampanel oral suspension is commercially available. (revised per Amendments 02, 03, and 04)

Phase 3

Objectives

Primary Objective

1. To evaluate the safety and tolerability of E2007/perampanel oral suspension when administered as an adjunctive therapy in children (ages 4 to <12 years) with inadequately controlled POS or primary generalized tonic-clonic seizures (PGTC)

Secondary Objectives

1. To characterize the pharmacokinetics (PK) of perampanel and the relationship between perampanel plasma concentrations, efficacy, and safety using population PK/pharmacodynamics (PD) modeling
2. To evaluate the effects of perampanel on cognition, behavior, visuomotor skills, and growth and

development in children during short-term (23 weeks) and long-term (up to 52 weeks) treatment

3. To evaluate the frequency of EEG abnormalities during awake and sleep state during 52 weeks of treatment
4. To evaluate suicidal ideation and suicidal behavior in children 6 years to less than 12 years as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS) during 52 weeks of treatment
5. To evaluate the efficacy of perampanel as measured by the median percent change per 28 days in seizure frequency, by the proportion of responders (≥25%, ≥50%, and ≥75%), and by the proportion of subjects who are seizure-free for POS, PGTC, and Generalized Tonic-Clonic (GTC) seizures
6. To evaluate, in Japanese subjects, the efficacy of perampanel on POS in the present study as compared with placebo in Study E2007-J000-335
7. To assess the effects of perampanel on the Clinical Global Impression (CGI), as measured by the CGI of Change (CGIC) (revised per Amendment 04)

Exploratory Objective

To assess the impact of perampanel on the health utility of children using the EuroQol 5 Dimensions-Youth (EQ-5D-Y) scale

Study Design

This is a multicenter, open-label single-arm study in children (ages 4 to less than 12 years) with inadequately controlled POS or PGTC. The study will consist of a Core Study, Extension Phase A, and Extension Phase B (for subjects in Japan and in countries where an EAP cannot be implemented, after having completed Extension A). (revised per Amendments 03 and 04)

Core Study

The Core Study will consist of the following 2 phases: Pretreatment and Treatment Phase.

Pretreatment Phase

The Pretreatment Phase will consist of a Screening/Baseline Period that lasts up to 4 weeks ±3 days. During this phase, subjects will be assessed for eligibility to participate in the study. Subjects in Japan are required to complete 4 full weeks ±3 days of the Screening/Baseline Period before they may enter the Treatment Phase (ie, Visit 2). However, subjects outside of Japan may begin treatment as soon as baseline procedures have been completed and documentation of eligibility (such as a documented seizure diary entry for a qualifying seizure during the preceding 12 weeks prior to Visit 2 or a qualifying seizure during the prospective Screening/Baseline Period) has been established. (revised per Amendment 02)

Treatment Phase

The Treatment Phase will consist of 3 periods: Titration (up to 11 weeks), Maintenance (up to 12 weeks), and Follow-up (up to 4 weeks; only for those subjects not rolling over into Extension A). (revised per Amendments 01, 02, and 03)

Titration Period

During the Titration Period, subjects will be stratified by the presence or absence of concomitant enzyme inducing antiepileptic drugs (EIAEDs) and will undergo dose titration using the dosing schedule below on the basis of individual clinical response and tolerability, but no more frequently

than at weekly intervals, up to 8 mg/day for subjects not receiving concomitant EIAEDs or 12 mg/day for subjects receiving EIAEDs. With the exception of subjects enrolled in Japan, subjects receiving concomitant EIAEDs may undergo dose titration beyond 12 mg/day and up to 16 mg/day if they tolerate 12 mg/day and are deemed likely to benefit from a higher dose. Subjects enrolled in Japan who are receiving concomitant EIAEDs will undergo a Japan-specific dosing schedule (see below). The dose of perampanel during this dose titration will not exceed 12 mg/day. Subjects not receiving EIAEDs may receive dose higher than 8 mg/day and up to 12 mg/day if they tolerate 8 mg/day and are deemed likely to benefit from a higher dose. Subjects will be flexibly dosed on the basis of individual tolerability. The Titration Period is a duration of up to 11 weeks, during which multiple dose adjustments are allowed in order to identify each subject's optimum dose. Each study visit is based on the actual prior visit (eg, Visit 3 is completed 2 weeks ±3 days of Visit 2, Visit 4 is completed 3 weeks ±3 days of Visit 3, Visit 5 is completed 3 weeks ±3 days of Visit 4. (revised per Amendment 02) Subjects will remain on their optimum dose once it is achieved during the Titration Period. (revised per Amendment 01)

Dosing Schedule (Global) (revised per Amendment 01)

Week	Subjects on Concomitant EIAEDs (mg/day)	Subjects not on Concomitant EIAEDs (mg/day)
0	4	2
1	6	4
2	8	6
3	10	6
4	10	8
5	12	8
6	12	10
7	14	10
8	14	12
9	16	12
10	16	—

Dosing Schedule (Japan Only) (revised per Amendment 01)

Week	Subjects on Concomitant EIAEDs (mg/day)	Subjects not on Concomitant EIAEDs (mg/day)
0	2	2
1	4	4
2	6	6
3	6	6
4	8	8
5	8	8
6	10	10
7	10	10
8	12	12
9	12	12
10	—	—

According to the investigator's clinical judgment, subjects experiencing intolerability at any dose may remain at the same dose or have their dose decreased 1 dose level down to the previously tolerated dose. If the subject continues to present significant intolerable adverse events (AEs) at the decreased dose and the investigator deems it is necessary, the dose can be decreased further to the next dose level down. Dose decreases can be done via telephone. Subjects whose dose has been decreased can have their dose increased again if tolerability improves; this can be done at the next clinic visit after the investigator has deemed it is appropriate in view of resolution of the AE(s). Multiple dose adjustments will be allowed during the Titration Period. Upon completion of the Titration Period, subjects will enter the Maintenance Period.

Maintenance Period

During the Maintenance Period of the Core Study (up to 12-week), subjects will continue taking perampanel oral suspension once daily at the dose level they achieved at the end of the Titration Period. (revised per Amendment 02) Multiple dose adjustment is allowed if a subject is experiencing intolerable AE(s) or a higher dose is deemed to be beneficial. All visits are to be done within ±7 days of the schedule. Each study visit is based on the actual prior visit (eg, Visit 6 is completed 3 weeks ±7 days of Visit 5, Visit 7 is completed 4 weeks ±7 days of Visit 6, Visit 8 is completed 4 weeks ±7 days of Visit 7, Visit 9 is completed 4 weeks ±7 days of Visit 8. (revised per Amendment 02)

During the Titration and Maintenance Periods, all dose adjustments will be done via 1 dose level up or down. Those who cannot tolerate a minimum of 2 mg dose must discontinue from the study.

Follow-Up Period

Follow-up Visit should be conducted 4 weeks (±7 days) after the last dose of study drug for all subjects, except for subjects entering into Extension A. (revised per Amendments 03 and 04)

Extension A

Extension A will consist of a Maintenance Period (up to 29 weeks) and a Follow-up Period (up to 4 weeks; only for those subjects not entering into Extension B). Visit 10 is completed 5 weeks ±6 days of Visit 9. (revised per Amendments 02, 03, and 04)

All subjects who complete all scheduled visits up to and including Visit 9 in the Treatment Phase will be eligible to participate in Extension A of the study. (revised per Amendment 03)

Maintenance Period

During the Maintenance Period of the Extension A, all subjects will continue with their optimal perampanel dose (ie, that dose level that they completed on during the Core Study). Multiple dose adjustment is allowed if a subject is experiencing intolerable AE(s) or a higher dose is deemed to be beneficial. The maximum dose of perampanel is 12 mg/day for subjects who are not receiving EIAEDs. For subjects who are receiving EIAEDs, the maximum dose is 16 mg except that for subjects enrolled in Japan, the maximum dose is 12 mg/day.

Addition, deletion, and dose changes to the concomitant antiepileptic drugs (AEDs) are allowed during Extension Maintenance Period. Conversion to monotherapy on perampanel is also permitted at the discretion of the investigator, if it is considered appropriate to control the seizures.

Follow-Up Period

Subjects who do not continue in Extension A or B or those who prematurely discontinue from the study will enter a Follow-up Period (up to 4 weeks). (revised per Amendment 03)

Extension B

Subjects in Japan and in countries where an EAP cannot be implemented, and who complete Extension A, will be eligible to participate in Extension B.

Treatment Phase

Extension B will consist of a Treatment Phase which will continue as long as clinically appropriate according to the judgment of the investigator. In Japan, treatment of subjects in Extension B will be completed when the subject reaches 12 years of age or when perampanel is commercially available in Japan for treatment of POS in pediatric subjects (4 to less than 12 years of age). In countries where an EAP cannot be implemented, participation in Extension B will continue as long as clinically appropriate according to the judgment of the investigator, until the subject reaches 12 years of age or perampanel oral suspension is commercially available. (revised per Amendment 04)

Follow-Up Period

Subjects who discontinue or choose not to switch to the commercial product will require a Follow-up Visit which will be conducted 4 weeks (±7 days) after the Discontinuation Visit. (revised per Amendments 03 and 04)

Number of Subjects

At least 160 subjects will be enrolled and treated: at least 120 with POS and at least 40 with PGTC. A minimum of 30% of the subjects for each seizure type will be enrolled in the younger age group (4 to <7 years) (ie, at least 36 subjects with POS and at least 12 subjects with PGTC).

Inclusion Criteria (Core Study)

1. Have a diagnosis of epilepsy with POS with or without secondarily generalized seizures or PGTC according to the International League Against Epilepsy's (ILAE) Classification of Epileptic Seizures (1981). Diagnosis should have been established at least 6 months prior to Visit 1 by clinical history and an EEG that is consistent with the diagnosis; normal interictal EEGs will be allowed provided that the subject meets the other diagnosis criterion (ie, clinical history)
2. Male or female subject, from age 4 to less than 12 years at the time of informed consent/assent
3. Have a minimum weight of 16 kg (35 lb)
4. Have had a brain imaging (eg, magnetic resonance imaging [MRI] scan or computed tomography[CT]) before Visit 1 that ruled out a progressive cause of epilepsy
5. During the 12 weeks ±3 days (4 weeks ±3 days in Japan only) before Visit 2, subjects must have had equal or greater than 1 POS or 1 PGTC seizure. (revised per Amendments 01 and 02) Only simple POS with motor signs, complex POS, and complex POS with secondary generalization are counted toward this inclusion for POS.
6. Are currently being treated with stable doses of 1 to a maximum of 3 approved AEDs. (revised per Amendment 01) Doses must be stable for at least 4 weeks before to Visit 1; in the case where a new AED regimen has been initiated for a subject, the dose must be stable for at least 8 weeks prior to Visit 1. Only 1 EIAED (defined as carbamazepine, phenytoin, oxcarbazepine, or eslicarbazepine) out of the maximum of 3 AEDs is allowed (A vagal nerve stimulator [VNS] will be counted as one of the 3 allowed AEDs). (revised per Amendment 01)

Exclusion Criteria (Core Study)

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG [or hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the 1st dose of study drug.
2. Females of childbearing potential who:
   - Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period or for 28 days after study drug discontinuation. If a highly effective method is not appropriate or acceptable for the subject, then the subject may use a medically effective method (eg, a double barrier method such as condom plus diaphragm with spermicide).
   - Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexually active during the study period or for 28 days after study drug discontinuation.

- Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study or for 28 days after study drug discontinuation.

3. Current or history of pseudo-seizures (psychogenic nonepileptic seizures) within approximately 5 years before Visit 1.
4. Have a history of status epilepticus that required hospitalization during the 6 months before to Visit 1.
5. Have an unstable psychiatric diagnosis that may confound subjects' ability to participate the study or that may prevent completion of the protocol specified tests (eg, significant suicide risk, including suicidal behavior and ideation within 6 months before Visit 1, current psychotic disorder, acute mania).
6. Any suicidal ideation with intent with or without a plan within 6 months before Visit 2 (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the C-SSRS) in subjects aged 6 and above.
7. Are scheduled and/or confirmed to have epilepsy surgery within 6 months after Visit 1; however, those who have previously documented "failed" epilepsy surgery will be allowed.
8. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments.
9. Evidence of moderate or severe renal insufficiency as defined by estimated glomerular filtration rates (eGFRs) of 31 to <60 mL/min and <30 mL/min, respectively. (revised per Amendment 01)
10. Evidence of significant active hepatic disease. Stable elevation of liver enzymes, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) due to concomitant medication(s), will be allowed if they are less than 3 times the upper limit of normal (ULN).
11. Evidence of significant active hematological disease; white blood cell (WBC) count equal or less than 2500/μL (2.50 1E+09/L) or an absolute neutrophil count equal or less than 1000/μL (1.00 1E+09/L).
12. Clinically significant ECG abnormality, including prolonged corrected QT interval (QTc) defined as greater than 450 msec.
13. Have a progressive central nervous system (CNS) disease, including degenerative CNS diseases and progressive tumors.
14. Multiple drug allergies or a severe drug reaction to an AED(s), including dermatological (eg, Stevens-Johnson syndrome), hematological, or organ toxicity reactions.
15. Concomitant use of felbamate as an AED for less than 2 years or where the dose has not been stable for at least 8 weeks before Visit 1. They must not have a history of WBC count below equal or less than 2500/μL (2.50 1E+09/L), platelets below 100,000, liver function tests (LFTs) above 3 times the ULN, or other indication of hepatic or bone marrow dysfunction while receiving felbamate. If subjects received felbamate in the past, it must have been discontinued 8 weeks before Visit 1 to be eligible for study participation.
16. Concomitant use of vigabatrin: Subjects who took vigabatrin in the past must be off vigabatrin for at least 5 months before Visit 1 and with documentation showing no evidence of a vigabatrin associated clinically significant abnormality in a visual perimetry test.
17. Concomitant use of cannabinoids. (revised per Amendment 01)
18. Used benzodiazepines for epilepsy during which the dose has not been stable for greater than 4 weeks prior to Visit 1. Benzodiazepines use as rescue medication for seizure control is allowed; however, intermittent use of benzodiazepines for any other indications (eg, anxiety/sleep

disorders) is prohibited. (revised per Amendment 01)

19. A VNS implanted less than 5 months before Visit 1 or changes in parameter less than 4 weeks before Visit 1 (or thereafter during the study)
20. On a ketogenic diet for which the diet is not stable regimen for at least 4 weeks before to Visit 1.
21. History of or a concomitant medical condition that in the opinion of the investigator(s) would preclude the subject's participation in a clinical study or compromise the subject's ability to safely complete the study.
22. Have previously been exposed to perampanel in a clinical trial or by prescription for more than 2 months or discontinued for AEs.
23. Have participated in a study involving administration of an investigational drug or device within 4 weeks before Visit 1, or within approximately 5 half-lives of the previous investigational compound, whichever is longer.
24. Subjects with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. (revised per Amendment 01)

Study Treatment

Test drug:

Perampanel will be provided as 0.5 mg/mL oral suspension stock. Perampanel will be administered orally and daily. Dosing should occur at bedtime.

Comparator Drug (if applicable): Not applicable

Duration of Treatment

Core Study:

- Pretreatment Phase: (Screening/Baseline): up to 4 weeks ±3 days. Subjects in Japan are required to complete 4 full weeks ±3 days of the Screening/Baseline Period before they may enter the Treatment Phase (ie, Visit 2). However, subjects outside of Japan may begin treatment as soon as baseline procedures have been completed and documentation of eligibility (such as a documented seizure diary entry for a qualifying seizure during the preceding 12 weeks prior to Visit 2 or a qualifying seizure during the prospective Screening/Baseline Period) has been established. (revised per Amendment 02)
- Treatment Phase: Titration (up to 11 weeks), Maintenance (up to 12 weeks), Follow-up (up to 4 weeks; only for those subjects not entering into Extension A): 27 weeks total (23 weeks for subjects continuing into Extension A). (revised per Amendments 01, 02, and 03)

Extension A:

- Maintenance (up to 29 weeks) and Follow-up (up to 4 weeks; only for those subjects not entering into Extension B): up to 33 weeks total (revised per Amendments 02, 03, and 04)

Extension B:

- Treatment Phase: In Japan, treatment will continue as long as clinically appropriate according to the judgment of the investigator. However, treatment of subjects in Extension B will end when the subject reaches 12 years of age or when perampanel is commercially available in Japan for treatment of POS in pediatric subjects (4 to less than 12 years of age). In countries where an EAP cannot be implemented, participation in Extension B will continue as long as clinically appropriate according to the judgment of the investigator, until the subject reaches 12 years of age or perampanel oral suspension is commercially available. (revised per Amendment 04)
- Follow-up (for subjects who discontinue or choose not to switch to the commercial product):

4 weeks ±7 days after the Discontinuation Visit. (revised per Amendment 03)
Concomitant Drug/Therapy Other than carbamazepine, oxcarbazepine, phenytoin, and eslicarbazepine, concomitant use of medications known to be inducers of cytochrome (CYP) 3A including, but not limited to: rifampin, troglitazone, St John's Wort, efavirenz, nevirapine, glucocorticoids (other than topical usage), modafinil, pioglitazone, and rifabutin will not be permitted and are to be discontinued within 28 days before Visit 1. VNS implanted less than 5 months before Visit 1 or changes in parameter less than 4 weeks before Visit 1 (or thereafter during the study) will be prohibited.
Assessments **Efficacy Assessments** Seizure diaries will be used to collect seizure counts. All seizure types will be counted. **Pharmacokinetic Assessments** Plasma concentrations of perampanel will be determined via collection of blood samples during the Maintenance Phase using a sparse sampling technique at specified visits for subsequent population PK analysis. **Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments** Not applicable. **Safety Assessments** Safety will be assessed by monitoring and recording all AEs and serious adverse events (SAEs). Additional assessments will include regular monitoring of hematology, blood chemistry, and urine values, regular measurement of vital signs, ECGs, physical, and neurological examinations. Growth and development will be assessed by weight, height, thyroid, and insulin-like growth factor-1 (IGF-1). Cognitive testing A-B neuropsychological assessment schedule (ABNAS), behavioral questionnaires Child Behavior Checklist (CBCL), and visuomotor skills testing using the Lafayette Grooved Pegboard Test (LGPT) will be administered. An assessment of suicidal ideation and behavior using the C-SSRS will be performed throughout the study for subjects aged 6 years and older at the time of consent/assent. Suicidal ideation and behavior will be monitored in subjects less than 6 years at the time of consent/assent based upon clinical impression. An EEG will be performed over a minimum of 1-hour up to a 2-hour period in an awake and sleep state at specified visits. **Other Assessments** A health related quality of life questionnaire (EQ-5D-Y) will be administered. For patients with mental disabilities and patients ages 4 to 7, caregivers or parents will complete the proxy EQ-5D-Y. For ages 8 to 11 with no mental disabilities, patients will self-complete the EQ-5D-Y. Patients ages 8 to 11 with physical disabilities but no mental disabilities may have the EQ-5D-Y read to them and their responses recorded by a caregiver, parent, or study coordinator. The CGI (Clinical Global Impression of Severity [CGIS], and CGIC) will be administered. (revised per Amendment 04)
Bioanalytical Methods Plasma concentrations of perampanel will be analyzed using validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) methodology.

Statistical Methods

Study Endpoints

Primary Endpoint

1. Safety and tolerability, which include incidence of treatment-emergent adverse events (TEAEs) and SAEs, laboratory parameters, vital signs, and ECG parameters, of perampanel oral suspension in children (ages 4 to <7 years and ≥7 years to <12 years) with POS or PGTC.

Secondary Endpoints

1. The relationship between plasma levels of perampanel and efficacy endpoints (ie, change in average seizure frequency over 28 days, responder probability, and the proportion of subjects who are seizure-free in the Maintenance Period of the Core Study) separately for each seizure type.
2. The relationship between plasma levels of perampanel and cognition endpoints including change from baseline in ABNAS, CBCL, and LGPT. In addition, depending on the AE data, the relationship between plasma levels of perampanel and select AEs will be assessed.
3. Change from baseline at Week 23 and Week 52 in ABNAS, CBCL, and LGPT.
4. Changes from baseline at Week 23 and Week 52 in growth and development parameters (height, weight, thyroid, and IGF-1).
5. Change from baseline in EEG and the frequency of EEG abnormalities during awake and sleep state.
6. Proportion of subjects (aged 6 or older at time of consent/assent) with any treatment-emergent reports of suicidal ideation and behavior on the C-SSRS and intensity of these behaviors assessed using C-SSRS scores.
7. The median percent change in seizure frequency per 28 days during Treatment Phase (Titration Period and Maintenance Period) of the Core Study, and during the long-term treatment (up to 52 weeks) relative to the Pretreatment Phase. Seizure frequency will be based on the number of seizures per 28 days, calculated as the number of seizures over the entire time interval divided by the number of days in the interval and multiplied by 28.
8. Proportion of responders (25% responders defined as a decrease in 28-day seizure frequency of equal or greater than 25% compared to baseline seizure frequency; 50% responders defined as a decrease in 28-day seizure frequency of equal or greater than 50% compared to baseline seizure frequency; 75% responders defined as a decrease in 28-day seizure frequency of equal or greater than 75% compared to baseline seizure frequency) during Maintenance Period of Core Study, and during the long term treatment (up to 52 weeks).
9. Proportion of subjects who are seizure-free during Maintenance Period of Core Study, and during the long term treatment (up to 52 weeks).
10. CGI of Change.

Exploratory Endpoint

1. Change from baseline at Week 23 and Week 52 in EQ-5D-Y.

Analysis Sets

Core Study

Safety Analysis Set: The group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment in the Core Study.

Full Analysis Set: The group of subjects who received at least 1 dose of study drug and had at least 1 postdose seizure measurement in the Core Study.

Pharmacokinetic Analysis Set: The group of subjects receiving perampanel and with at least

1 quantifiable perampanel concentration at one of the visits during the Maintenance Period of the Core Study and with adequately documented dosing history.

Pharmacokinetic/Pharmacodynamic Analysis Set: The group of subjects receiving perampanel who have seizure frequency, cognition, or AE data with documented dosing history. Subjects receiving perampanel should have at least 1 quantifiable perampanel concentration at one of the visits during the Maintenance Period of the Core Study as per the PK Analysis Set.

Extension A

Safety Analysis Set: The group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment in the Extension A. (revised per Amendment 03)

Full Analysis Set: The group of subjects who received at least 1 dose of study drug and had at least 1 postdose seizure measurement in the Extension A. (revised per Amendment 03)

Extension B

Safety Analysis Set: The group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment in Extension B. (revised per Amendments 03 and 04)

Efficacy Analyses

Core Study

The percent change in seizure frequency per 28 days will be summarized using descriptive statistics (n, mean, median, minimum and maximum) by age cohorts (4 to <7 years, ≥7 to <12 years), by disease cohorts (POS, PGTC, and GTC), and by the presence or absence of concomitant EIAED in the Full Analysis Set (FAS).

The proportion of responders and the proportion of subjects who are seizure-free will be summarized using frequency count (number and percentage) by age cohorts (4 to <7 years, ≥7 to <12 years), by disease cohorts (POS, PGTC, and GTC), and by the presence or absence of concomitant EIAED in the FAS.

The CGIC will be summarized using frequency count (number and percentage) by age cohorts (4 to <7 years, ≥7 to <12 years), by disease cohorts (POS, PGTC, and GTC), and by the presence or absence of concomitant EIAED in the FAS.

For purposes of registration in Japan, perampanel will be determined to be efficacious if, in subjects enrolled in Japan, the upper limit of the 95% CI for the median percent change in POS frequency per 28 days is below the pre-specified threshold. This pre-specified threshold consists of the median percent reduction in seizure frequency (ie, 10.5%) in subjects who received placebo during the Randomization Phase of Study E2007-J000-335.

Extension A

The efficacy endpoints will be summarized using descriptive statistics or frequency by age cohorts (4 to <7 years, ≥7 to <12 years), by disease cohorts (POS, PGTC, and GTC), and by the presence or absence of concomitant EIAED in the FAS. (revised per Amendment 03)

Pharmacokinetic Analyses

Determination of PK will be performed on the PK Analysis Set. Perampanel plasma concentrations will be listed.

Population PK analysis will be performed to characterize the PK of perampanel by pooling the concentration data with other studies, including 19 Phase 1 studies, 2 Phase 2 studies (232 and 235), and 5 Phase 3 studies (304, 305, 306, 332, and 335). A 2-compartment PK model will be fit to the data and the effect of intrinsic and extrinsic factors, including body weight and age, on the PK of perampanel will be evaluated. The post-hoc estimates of both maximum observed concentration (C_{max}) and area under the curve (AUC) from the final PK model will be derived for all subjects. In

addition, average steady-state drug concentration (Css,av) will be calculated. Subsequently, the dose-normalized derived exposure parameters will be summarized descriptively by age group (≤4 years, >4 to ≤8 years, >8 to <12 years, ≥12 to <18 years, and ≥18 years) for subjects with and without inducing AEDs, and also presented in box-plots.

Pharmacodynamic Analyses

PD endpoints to be evaluated as part of PK/PD analyses include endpoints for efficacy, cognition, and selected safety parameters.

Pharmacokinetic/Pharmacodynamic Analyses

Population PK/PD analysis will be conducted for the relationship between model-predicted average exposure to perampanel at steady-state (Css,av) vs responder rate and percent reduction in seizure frequency during the Maintenance Phase. In addition, the relationship between Css,av and the cognition endpoints and most frequent AEs will be explored graphically. Any emergent relationship will be subjected to population PK/PD modeling. The effect of intrinsic and extrinsic factors (ie, most common concomitant AEDs, demographics) on the PK/PD relationship will be evaluated. Two separate analyses will be performed, one for POS, where data from subjects with POS from Study 311 will be pooled with data from POS subjects from Studies 304, 305, 306, and 335, and another for PGTC, where data from subjects with PGTC from Study 311 will be pooled with data from PGTC subjects from Study 332.

Safety Analyses

Core Study

Safety analyses will be conducted on the Safety Analysis Set. The data will be summarized by age cohorts (4 to <7 years, ≥7 to <12 years), by disease cohorts (POS, PGTC, and GTC), and by the presence or absence of concomitant EIAEDs.

The incidence of TEAEs, SAEs, AEs associated with fatal outcomes or leading to discontinuations, and AEs leading to dose adjustment will be summarized. The incidence of TEAEs will be summarized by severity (mild, moderate, or severe), as well as by relationship to treatment (related or not related). The incidence of TEAEs of special interest defined by standardized Medical Dictionary for Regulatory Activities (MedDRA) query will also be summarized.

Changes from baseline in laboratory values will be summarized for continuous variables. Laboratory shift tables showing incidence of new or worsening clinically significant findings from baseline to the postbaseline visits will be displayed. Shift from baseline to the highest postbaseline laboratory value and from baseline to the lowest postbaseline laboratory value will also be displayed.

Incidence of treatment-emergent markedly abnormal laboratory values (TEMAV) in laboratory safety test variables will be tabulated. TEMAVs will be obtained from the modified National Cancer Institute (NCI) criteria.

For ALT and AST analysis, the number of subjects with greater than 3 times, but less than 5 times the ULN and the number of subjects with greater than 5 times the ULN will be summarized. For bilirubin, a summary of the number of subjects with serum concentrations greater than 2 times the ULN will be created.

The change from baseline in vital signs and ECG parameters will be summarized.

The duration of treatment, (Titration Period and Maintenance Period of the Core Study) will be calculated as the number of days between the date the subject receives their 1st treatment dose and the date the subject receives the last dose of treatment. These values will be used to summarize the extent of exposure to study medication.

The change from baseline in ABNAS, CBCL, and LGPT will be summarized.

The change from baseline in growth (height, weight, thyroid, and IGF-1) will be summarized.

The change from baseline in EEG parameters and the frequency of EEG abnormalities will be summarized.

Proportion of subjects with any treatment-emergent report of suicidal ideation and behavior and intensity of these behaviors will be summarized.

Extension A

Safety analyses will be performed similarly to the Core Study analyses and all analyses will be on the perampanel treatment duration (Core Study and Extension A). (revised per Amendment 03) The incidence of TEAEs, SAEs, AEs associated with fatal outcomes or leading to discontinuations, and AEs leading to dose adjustment will be summarized. Laboratory parameters, vital signs, and ECG parameters will be summarized. Change from baseline in CBCL, ABNAS, and LGPT, change from baseline in growth parameters, change from baseline in EEG parameters, the frequency of EEG abnormalities, and the proportion of subjects with any treatment-emergent report of suicidal ideation and behavior and intensity of these behaviors, will also be summarized descriptively. Baseline for these parameters is the last non-missing value before the 1st perampanel dose.

Extension B

Safety analyses for Extension B are described in Appendix 2. (revised per Amendments 03 and 04)

Exploratory Analyses

The change from baseline in EQ-5D-Y at Week 23 and Week 52 will be summarized.

Interim Analyses

An independent data monitoring committee (DMC) will be constructed to monitor the safety data. The responsibilities, membership, and purpose of the DMC, the timing of the meeting(s), and an outline of the plan for review of the safety data will be documented in the DMC Charter.

Analyses for regional submissions may be performed during the course of the study. (revised per Amendment 02)

Sample Size Rationale

A sample size of at least 160 subjects (with up to 40 subjects with PGTC and the balance with POS), is deemed sufficient for safety evaluation in this age group (age 4 to <12 years). (revised per Amendment 02) This sample size matches the total number of adolescents who were enrolled in the 4 global Phase 3 efficacy and safety studies that support the POS and PGTC indications.

For purposes of registration in Japan, it has been determined that a sample size of 65 subjects enrolled in Japan will provide 80% power to exclude the possibility that there would be a reduction smaller than that observed in the placebo arm of Study E2007-J000-335 (ie, 10.5%).

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ABNAS	A-B neuropsychological assessment schedule
AE(s)	adverse event(s)
AED	antiepileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BP	blood pressure
CBCL	Child Behavior Checklist
CGI	Clinical Global Impression
CGIC	Clinical Global Impression of Change
CGIS	Clinical Global Impression of Severity
CNS	central nervous system
CRAs	Clinical research associates
CRF	case report form
CRO(s)	contract research organization (s)
Css,av	average steady-state drug concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
CL/F	Clearance
DEA	Drug Enforcement Administration
DMC	Data Monitoring Committee
EAP	extended access program
eGFR	estimated glomerular filtration rate
EIAED	enzyme inducing antiepileptic drug
EMA	European Medicines Agency
EQ-5D-Y	EuroQol 5 Dimensions-Youth
FAS	Full Analysis Set
GTC	Generalized Tonic-Clonic
hCG	human chorionic gonadotropin
HRQL	health-related quality of life
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee

Abbreviation	Term
IGF-1	insulin-like growth factor-1
IP	investigational product
IRB	Institutional Review Board
IxRS	interactive and response system
LGPT	Lafayette Grooved Pegboard Test
LNH	low/normal/high
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamics
PGTC	primary generalized tonic-clonic seizures
PI	principal investigator
PK	Pharmacokinetics
POS	partial-onset seizures
PT	preferred term
QTc	corrected QT interval (time from the beginning of the QRS complex to the end of the T wave, corrected for heart rate)
SAE	serious adverse event
SAP	statistical analysis plan
SMQ	standardized MedDRA queries
SOC	system organ class
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
ULN	upper limit of normal
VNS	vagal nerve stimulator
WBC	white blood cell

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

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

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

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

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. The sponsor should also provide the IRB/IEC with a summary of the study's outcome.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and Competent Authority within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures (SOP) 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 (2013).

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

- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312.

- European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the Competent Authorities of all involved EU member states.

- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP.

5.3 Subject Information and Informed Consent

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

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

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

informed consent will be obtained before entering the Extension Phase(s). (revised per Amendment 03)

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

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 60 to 80 investigational sites in the US, EU, and Asia Pacific.

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

7 INTRODUCTION

7.1 Planned Indication

Perampanel is approved in the US and EU and other countries as an adjunctive treatment of partial-onset seizures (POS) with or without secondarily generalized seizures and primary generalized tonic-clonic seizures (PGTC) in patients with epilepsy aged 12 years and older. Eisai is seeking to expand both the POS indication and the PGTC indication to pediatric patients aged 4 years to less than 12 years.

7.2 Study Rationale

In the EU, Study E2007-G000-311 is part of the approved Pediatric Investigation Plan (PIP) to which Eisai is committed to perform. In the US, Post Marketing Requirement (PMR) studies were issued by the FDA as deferred Pediatric Research Equity Act (PREA) requirements to evaluate perampanel in subjects less than 12 years of age for patients with epilepsy with both POS and PGTC.

An alternative regulatory pathway is being pursued by Eisai to attain the POS and PGTC indications in children ages 4 to equal or less than 12 years via extrapolation of adult and adolescent adjunctive therapy efficacy to this age group, in lieu of conducting pivotal efficacy studies.

This approach is based on the results of discussions amongst global epileptologist key opinion leaders as part of the Pediatric Epilepsy Academic Consortium on Extrapolation (PEACE) concerning whether efficacy and safety data established in adults for adjunctive POS can be extrapolated to establish efficacy and safety in children as young as 4 years of age. This extrapolation approach is also consistent with criteria outlined in the draft European Medicines Agency (EMA) Concept paper on extrapolation of efficacy and safety in medicine development (EMA/129698/2012, June 2012).

The Dec 2014 FDA Draft Guidance algorithm, outlined in the EMA Concept paper, provides an assumptions-based framework to evaluate if the extrapolation of efficacy from adults to the pediatric population is supported by available data. Based on this algorithm, the pediatric study decision tree allows extrapolation if there is sufficient similarity of both disease progression and response to intervention between source and target population. If the exposure-response relationship of the medicinal product is assumed to be similar, only pharmacokinetics (PK) studies for dose determination and safety studies are required. Similar principles are discussed in the EMA guidelines 'ICH E11 Clinical Investigation of medicinal products in the pediatric population (CPMP/ICH/2711/99)' and 'Role of Pharmacokinetics in the development of medicinal products in the Pediatric Population (CHMP/EWP/147013/2004).'

Due to the challenges inherent in performing clinical trials in children, a systematic review of published clinical trials was performed to determine whether the efficacy of antiepileptic drugs (AEDs) in adults can be used to predict the efficacy of AEDs in the pediatric population. This systematic review supports the extrapolation and efficacy results in adults to predict a similar adjunctive treatment response in 2 to 18 year old pediatric patients with POS (Pellock, et al., 2012). Therefore, AEDs that are shown to be effective in adults with partial seizures also can be expected to be effective in children 4 years and older.

There is a growing body of data indicating that AEDs used in pediatric populations have similar exposure-response profiles to those used in adults. The FDA Algorithm of the Dec 2014 guidance offers the structure to assess when extrapolation is appropriate. As part of the PEACE initiative and supported by the FDA Critical Path Project, FDA has been analyzing exposure-response similarity between adults and pediatric patients using the data of those marketed AEDs. In November 2015, FDA communicated with Eisai as a sponsor of several approved AEDs that they have determined it is acceptable to extrapolate to pediatric patients 4 years of age and older the effectiveness of drugs approved for the treatment of POS in adults.

Existing data on the efficacy and safety of perampanel as treatment of POS and PGTC in adults and adolescents support exposure-response similarity in adolescents and adults. These data include characterization of the PK data of perampanel in treatment of pediatric epilepsy patients from Study 232 (ages ≥2 to <12), as well as a consistent pattern of data demonstrating exposure-response similarity between adults and pediatrics among AEDs as a class.

Eisai considers that placebo-controlled efficacy and safety studies of perampanel in POS and PGTC therapy in children equal or greater than 4 to less than 12 years old may pose difficulties with regard to placebo use and recruitment challenges and proposed that the registration of perampanel for pediatric use be replaced with study designs consistent with the data extrapolation model.

The study will also address the potential concerns that a new AED could induce an aggravation of the clinical picture and/or have a negative impact on neuropsychological functioning, and growth and development. One-hour (minimum) to 2-hour continuous EEG

recording at baseline and during treatment will be collected and all types of seizures that subjects experience prior and during the study will be recorded in patient seizure diary. Neuropsychological functioning and growth and development assessments will be included.

Study E2007-G000-311 is a multi-center, open-label study followed by an Extension Phase (Extension A) designed to evaluate the safety, tolerability, PK, and PK/pharmacodynamics (PD) of perampanel as an adjunctive therapy for POS or PGTC or both. The Core Study consists of a Pretreatment and Treatment Phase. The Pretreatment Phase will consist of a Screening/Baseline Period, which may last for up to 4 weeks ±3 days outside of Japan. Subjects in Japan are required to complete 4 full weeks ±3 days of the Screening/Baseline Period. However, subjects outside of Japan may begin treatment as soon as baseline procedures have been completed and documentation of eligibility (such as a documented seizure diary entry for a qualifying seizure during the preceding 12 weeks prior to Visit 2 or a qualifying seizure during the prospective Screening/Baseline Period) has been established. (revised per Amendment 02) During this phase, subjects will be assessed for eligibility to participate in the study. The Treatment Phase will consist of 3 periods: Titration (up to 11 weeks), Maintenance (up to 12 weeks), and Follow-up (up to 4 weeks; only for those subjects not rolling over into Extension A). Extension A will consist of a Maintenance Period (up to 29 weeks) and a Follow-up Period (up to 4 weeks; only for those subjects not entering into Extension B [Japan and countries where an extended access program (EAP) cannot be implemented]). (revised per Amendments 01, 02, 03, and 04) Subjects in Japan and in countries where an EAP cannot be implemented, after having completed Extension A, will be eligible to participate in an Extension B. (revised per Amendments 03 and 04) Subjects will be stratified by age groups (≥4 to <7 years, ≥7 to <12 years) with at least 30% of the subjects enrolled in the equal or greater than 4 to less than 7 years age group.

The primary objective of this study is to determine the safety and tolerability of perampanel oral suspension when administered as an adjunctive therapy in children equal or greater than 4 to less than 12 years old with POS or PGTC. Plasma PK sampling will be optimized to confirm that the PK profile in children is characterized. Clinical efficacy data will be collected to confirm the PK/PD relationship for both POS and PGTC.

Since many other seizure types may coexist in children presenting with PGTC, seizure diaries will collect all types of seizures to evaluate whether perampanel contributes to the deterioration of other seizure types.

In addition to other safety parameters, EEGs will be recorded at awake and sleep states to evaluate whether perampanel could induce an aggravation of the clinical picture, which was incorporated per recommendation by the Committee for Medicinal Products for Human Use (CHMP) Scientific Advice.

The effect of perampanel on neuropsychological parameters, including cognition, behavior, visuomotor skills, and growth and development will also be evaluated per recommendation by the CHMP Scientific Advice. The A-B neuropsychological assessment schedule (ABNAS), a measure of patient-perceived cognitive effects of AEDs. The Child Behavior Checklist (CBCL) obtains reports from the parent/caregiver regarding the subject's

competencies and behavioral/emotional problems. Visuomotor skills will be assessed using the Lafayette Grooved Pegboard Test (LGPT), which is a manipulative dexterity test.

The EuroQol 5 Dimensions-Youth (EQ-5D-Y) questionnaire will be administered to assess how perampanel impacts patients' health-related quality of life (HRQL). HRQL assessment is a requirement for reimbursement submissions both as a qualitative assessment of the net impact of a drug's clinical benefit and AE profile on patients as well as to quantitatively adjust incremental life-year estimates in economic models by the quality of those life-years gained. The EQ-5D is a well-accepted instrument for assessing HRQL for these purposes. The EQ-5D-Y been developed by EuroQol to assess HRQL in children ages 15 and younger. The same five concepts of mobility, self-care, ability to participate in usual activities, pain, and anxiety/depression are assessed; only the language utilized to elicit this information has been modified to be child-appropriate (eg, simpler vocabulary and child-appropriate examples of usual activities). A proxy version of the EQ-5D-Y is available for children aged 4 to 7 so that caregivers may complete the questionnaire for children whose literacy level may be insufficient.

During the Core Study, no change of concomitant AEDs is allowed. However, during the Extension Maintenance Period, addition, deletion, and dose changes to the concomitant AEDs are allowed. Conversion to monotherapy on perampanel is also permitted at the discretion of the investigator, if it is considered appropriate to control the seizures.

7.3 Dosing Rationale

Support for the dosing regimen was based on the population PK analysis of the pooled data including the data from the clinical study in subjects 2 to 12 years of age with epilepsy (E2007-G000-232). A PK analysis of data from Study 232 comparing dose-normalized perampanel concentrations in 42 pediatric epilepsy subjects (aged ≥2 to <12 years) with dose-normalized perampanel concentrations from adolescent subjects (aged ≥12 to <18 years) in Studies 304, 305, and 306 was conducted. Of the 42 subjects with wide range of body weights (ie, 12.2 to 90.9 kg) analyzed to date, 20 were aged equal or greater than 2 to less than 7 years and 22 were aged equal or greater than 7 to less than 12 years. A total of 28 subjects were without any concomitant enzyme inducing co-medications (carbamazepine, phenytoin, and oxcarbazepine) and 14 subjects were receiving one of these inducers. Subjects in Study 232 were administered perampanel suspension (0.5 mg/mL) according to a weight-based regimen compared to tablets in Studies 304, 305, and 306.

The results of the analysis demonstrated that perampanel PK was linear as there was no dose or time-dependency to oral clearance (CL/F). The CL/F was not significantly affected by age, body weight, gender, race, hepatic function markers (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]), renal function marker (creatinine CL/F) or the use of the oral suspension formulation in this population. The predicted perampanel average steady state plasma concentration dose normalized to 0.12 mg/kg in pediatrics (intended to correspond to 8 mg/70 kg in adults/adolescents) for Study 232 were lower than that at 8 mg dose in adolescents from previous Phase 2 and 3 studies. Since predicted CL/F was comparable among the 3 categorical groups (age ≥2 to <7, ≥7 to <12, and ≥12 to <18 years)

independent of weight, the lower steady state concentration was deemed to be due to the lower total dose (mg/person) administered in pediatric subjects. The results of the analysis suggested that a flat dosing approach will be more appropriate in patients within the age range of 2 to less than 12 years.

In Study 311, subjects will be stratified by concomitant use of enzyme inducing antiepileptic drugs (EIAED) and will be titrated as per a dosing schedule (Section 9.4) based on individual clinical response and tolerability no more frequently than at weekly intervals to up to 8 mg/day for non-EIAED subjects or 12 mg/day for EIAED subjects. With the exception of subjects enrolled in Japan, EIAED subjects may go beyond 12 mg/day and up to 16 mg/day if they tolerate 12 mg/day and are deemed likely to benefit from a higher dose. Non-EIAED subjects may go beyond 8 mg/day and up to 12 mg/day if they tolerate 8 mg/day and are deemed likely to benefit from a higher dose. Regardless of EIAED status, subjects enrolled in Japan may not receive doses higher than 12 mg/day.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of perampanel oral suspension when administered as an adjunctive therapy in children (ages 4 to <12 years) with inadequately controlled POS or PGTC.

8.2 Secondary Objective(s)

The secondary objectives of the study are:

1. To characterize the PK of perampanel and the relationship between perampanel plasma concentrations, efficacy, and safety using population PK/PD modeling.

2. To evaluate the effects of perampanel on cognition, behavior, visuomotor skills, and growth and development in children during short-term (23 weeks) and long-term (up to 52 weeks) treatment.

3. To evaluate the frequency of EEG abnormalities during awake and sleep state during 52 weeks of treatment.

4. To evaluate suicidal ideation and suicidal behavior in children 6 years to less than 12 years as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS) during 52 weeks of treatment.

5. To evaluate the efficacy of perampanel as measured by the median percent change per 28 days in seizure frequency, by the proportion of responders (≥25%, ≥50%, and ≥75%), and by the proportion of subjects who are seizure-free for POS, PGTC, and Generalized Tonic-Clonic (GTC) seizures.

6. To evaluate, in Japanese subjects, the efficacy of perampanel on POS in the present study as compared with placebo in Study E2007-J000-335.

7. To assess the effects of perampanel on the Clinical Global Impression (CGI), as measured by CGI of Change (CGIC). (revised per Amendment 04)

8.3 Exploratory Objective

To assess the impact of perampanel on the health utility of children using the EuroQol 5 Dimensions-Youth (EQ-5D-Y) scale.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, open-label single-arm study in children (ages 4 to <12 years) with inadequately controlled POS or PGTC. The study will consist of a Core Study and Extension Phase (Extension A, for all countries in the study) with Extension Phase (Extension B) available for subjects enrolled in Japan and in countries where an EAP cannot be implemented, after having completed Extension A. (revised per Amendments 03 and 04) Subjects will be stratified by age (≥4 to <7 years, 7 to <12 years) with at least 30% of subjects enrolled in the equal or greater than 4 to less than 7 year age group for each seizure type (ie, at least 36 with POS and at least 12 with PGTC).

Core Study

The Core Study will consist of the following 2 phases: Pretreatment and Treatment Phase.

The Pretreatment Phase will consist of a Screening/Baseline Period that lasts up to 4 weeks ±3 days outside of Japan. Subjects in Japan are required to complete 4 full weeks ±3 days of the Screening/Baseline Period. However, subjects outside of Japan may begin treatment as soon as baseline procedures have been completed and documentation of eligibility (such as a documented seizure diary entry for a qualifying seizure during the preceding 12 weeks prior to Visit 2 or a qualifying seizure during the prospective Screening/Baseline Period) has been established. (revised per Amendment 02) During this phase, subjects will be assessed for eligibility to participate in the study. Efforts should be made to perform all clinical laboratory and screening tests on the scheduled day of Visit 1, or as close as possible to that day, within the 4 week period prior to Visit 2. (revised per Amendment 01)

The Treatment Phase will consist of 3 periods: Titration (up to 11 weeks), Maintenance (up to 12 weeks), and Follow-up (up to 4 weeks; only for those subjects not rolling over into Extension A). (revised per Amendments 01, 02, and 03)

Extension A

Extension A will consist of a Maintenance Period (up to 29 weeks) and a Follow-up Period (up to 4 weeks; only for those subjects not entering into Extension B). (revised per Amendments 02, 03, and 04)

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

Extension B

Extension B will be available to subjects enrolled in Japan and in countries where an EAP cannot be implemented. Extension B will consist of an open-label Treatment Phase. In Japan, treatment will continue as long as clinically appropriate according to the judgment of the investigator. However, treatment of subjects in Extension B will be completed when the subject reaches 12 years of age or when perampanel is commercially available in Japan for

treatment of POS in pediatric subjects (4 to less than 12 years of age). In countries where an EAP cannot be implemented, participation in Extension B will continue as long as clinically appropriate according to the judgment of the investigator, until the subject reaches 12 years of age or perampanel oral suspension is commercially available. Subjects who discontinue or choose not to switch to the commercial product will require a Follow-up Visit which will be conducted 4 weeks (±7 days) after the Discontinuation Visit. (revised per Amendments 03 and 04)

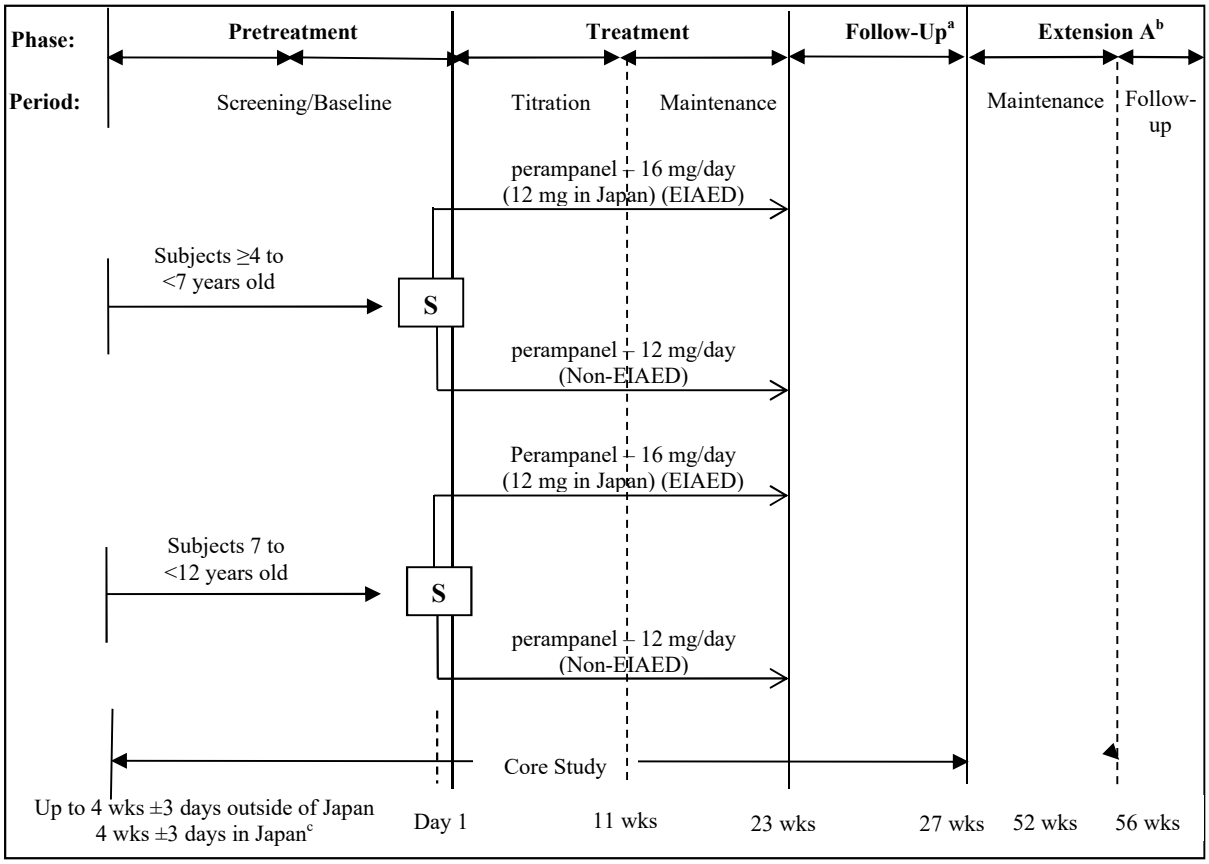


Figure 1 Study Design for Study E2007-G000-311

Note: (revised per Amendments 02 and 03)
Follow-up can occur during the Core Study (if the subject discontinued during the Core Study), or during Extension A or Extension B, after the termination of study treatment.
EIAED = enzyme inducing antiepileptic drug, S = stratified, wks = weeks.

a: Subjects will have a Follow-up Visit 4 weeks (±7 days) after the end of the treatment and a final assessment completed if they are not rolling over into Extension A.

b: Subjects who are enrolled in Japan and in countries where an EAP cannot be implemented, and have completed the Extension A, will be eligible to enroll in Extension B, as detailed in Appendix 2. (revised per Amendments 03 and 04) Subjects in Japan are required to complete 4 full weeks ±3 days of the Screening/Baseline Period. (revised per Amendment 02)

9.1.1 Pretreatment Phase

The Pretreatment Phase will consist of a Screening/Baseline Period that last up to 4 weeks ±3 days outside of Japan. Subjects in Japan are required to complete 4 full weeks ±3 days of the Screening/Baseline Period. However, subjects outside of Japan may begin treatment as soon as baseline procedures have been completed and documentation of eligibility (such as a documented seizure diary entry for a qualifying seizure during the preceding 12 weeks prior to Visit 2 or a qualifying seizure during the prospective Screening/Baseline Period) has been established. (revised per Amendment 02) During this phase, subjects will be assessed for eligibility to participate in the study. Subjects will be stratified by age (≥4 to <7 years, 7 to <12 years) with at least 30% of subjects enrolled in the equal or greater than 4 to less than 7 year age group for each seizure type (ie, at least 36 with POS and at least 12 with PGTC).

The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3.

Subjects must have a diagnosis of epilepsy with partial seizures, with or without secondary generalized seizures, or PGTC, according to International League Against Epilepsy's (ILAE) Classification of Epileptic seizures and confirmed by EEG and clinical history.

The Screening Disposition case report form (CRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

During the 12-week period preceding Visit 2 (up to 8 weeks prior to Visit 1 and up to 4 weeks prior to Visit 2, inclusive), subjects must have had 1 or more POS or PGTC. (revised per Amendments 01 and 02) The POS should include simple partial seizures with motor signs, complex POS, and complex POS with secondary generalization. Subjects must be on stable doses of 1 to a maximum of 3 approved AEDs. Only 1 EIAED out of the maximum of 3 AEDs is allowed. (revised per Amendment 01)

Subjects who complete the Screening/Baseline Period and meet the criteria for inclusion/exclusion (Sections 9.3.1 and 6) will begin the Treatment Phase.

9.1.2 Treatment Phase

The duration of the Treatment Phase will be up to 27 weeks and will include 3 periods: Titration, Maintenance, and Follow-up (only for those subjects not entering into Extension A). (revised per Amendments 02 and 03) Subjects whose screening assessments and evaluations are completed and reviewed by the PI and who continue to meet all of the inclusion/exclusion criteria will enter the Treatment Phase.

9.1.2.1 Titration Period

During the Titration Period, subjects will be stratified by the presence or absence of concomitant EIAEDs and will be titrated using the dosing schedule based on individual clinical response and tolerability no more frequently than at weekly intervals, up to 8 mg/day for non-EIAED subjects or 12 mg/day for EIAED subjects. With the exception of subjects enrolled in Japan, EIAED subjects may titrate beyond 12 mg/day and up to 16 mg/day if they tolerate 12 mg/day and are deemed likely to benefit from a higher dose. Non-EIAED subjects may go beyond 8 mg/day and up to 12 mg/day if they tolerate 8 mg/day and are deemed likely to benefit from a higher dose. Subjects will be flexibly dosed based on individual tolerability. Regardless of EIAED status, subjects enrolled in Japan may not received doses higher than 12 mg/day. The Titration Period is a duration of up to 11 weeks, during which multiple dose adjustments are allowed in order to identify each subject's optimum dose. All visits are to be done within ±3 days of the schedule. Each study visit is based on the actual prior visit (eg, Visit 3 is completed 2 weeks ±3 days of Visit 2, Visit 4 is completed 3 weeks ±3 days of Visit 3, Visit 5 is completed 3 weeks ±3 days of Visit 4). (revised per Amendment 02) Subjects will remain on their optimum dose once it is achieved during the Titration Period. (revised per Amendment 01) The dosing schedule is illustrated in Table 1.

According to the investigator's clinical judgment, subjects experiencing intolerability at any dose may remain at the same dose or have their dose decreased 1 dose level down to the previously tolerated dose. If the subject continues to present significant intolerable AEs at the decreased dose and the investigator deems it is necessary, the dose can be decreased further to the next dose level down. Dose decreases can be done via telephone. Subjects whose dose has been decreased can have their dose increased again if tolerability improves; this can be done at the next clinic visit after the investigator has deemed it is appropriate in view of resolution of the AE(s). Multiple dose adjustments will be allowed during the Titration Period. Only upon completion of the 11 weeks Titration Period, subjects will enter the Maintenance Period. (revised per Amendment 01)

9.1.2.2 Maintenance Period

During the Maintenance Period of the Core Study (up to 12-week), subjects will continue taking perampanel oral suspension once daily at the dose level they achieved at the end of the Titration Period. (revised per Amendment 02) Multiple dose adjustment is allowed if a subject is experiencing intolerable AE(s) or a higher dose is deemed to be beneficial. All visits are to be done within ±7 days of the schedule. Each study visit is based on the actual prior visit (eg, Visit 6 is completed 3 weeks ±7 days of Visit 5, Visit 7 is completed 4 weeks ±7 days of Visit 6, Visit 8 is completed 4 weeks ±7 days of Visit 7, Visit 9 is completed 4 weeks ±7 days of Visit 8). (revised per Amendment 02)

During the Titration and Maintenance Periods, all dose adjustments will be done via 1 dose level up or down. Those who cannot tolerate a minimum of 2 mg dose must discontinue from the study.

9.1.2.3 Follow-Up Period

Follow-up Visit should be conducted 4 weeks (±7 days) after the last dose of study drug for all subjects, except for subjects entering into Extension A. (revised per Amendment 03)

9.1.3 Extension Phase (Extension A)

Extension A will consist of a Maintenance Period (up to 29 weeks) and a Follow-up Period (up to 4 weeks; only for those subjects not entering into Extension B). Visit 10 is completed 5 weeks ±6 days of Visit 9. (revised per Amendments 02, 03, and 04)

All subjects who complete all scheduled visits up to and including Visit 9 in the Treatment Phase will be eligible to participate in Extension A of the study. (revised per Amendment 03)

See Appendix 1 for a full description of the Extension A. (revised per Amendment 03)

9.1.3.1 Maintenance Period

During the Maintenance Period of Extension A, all subjects will continue with their optimal perampanel dose (ie, that dose level that they completed on during the Core Study). (revised per Amendment 03) Multiple dose adjustment is allowed if a subject is experiencing intolerable AE(s) or a higher dose is deemed to be beneficial. The maximum dose is up to 12 mg/day for non-EIAED subjects or up to 16 mg/day for EIAED subjects, except that subjects enrolled in Japan may not receive doses higher than 12 mg/day regardless of EIAED status. Addition, deletion, and dose changes to the concomitant AEDs are allowed during Extension Maintenance Period. Conversion to monotherapy on perampanel is also permitted at the discretion of the investigator, if it is considered appropriate to control the seizures.

9.1.3.2 Follow-Up Period

Follow-up Visit should be conducted 4 weeks (±7 days) after the last dose of study drug for all subjects, except for subjects in Japan or in countries where an EAP cannot be implemented, who are entering into Extension B. (revised per Amendments 03 and 04)

9.1.4 Extension Phase B

9.1.4.1 Treatment Phase

Subjects in Japan and in countries where an EAP cannot be implemented, after having completed Extension A, will be eligible to participate in Extension B. Extension B will consist of a Treatment Phase which will continue as long as clinically appropriate according to the judgment of the investigator. In Japan, treatment of subjects in Extension B will be completed when the subject reaches 12 years of age or when perampanel is commercially available in Japan for treatment of POS in pediatric subjects (4 to less than 12 years of age). In countries where an EAP cannot be implemented, participation in Extension B will continue as long as clinically appropriate according to the judgment of the investigator, until

the subject reaches 12 years of age or perampanel oral suspension is commercially available. (revised per Amendment 04)

Subjects will enter Extension B with their optimal perampanel dose (ie, the same dose of perampanel that they were maintained on at the end of Extension A). During the course of the Extension B, doses of perampanel and concomitant AEDs can be adjusted (concomitant AEDs can be used in accordance with the approved dosage and indication) based on clinical judgment. In Japan, the maximum dose of perampanel is 12 mg/day. (revised per Amendment 04)

In countries where an EAP cannot be implemented, the maximum dose of perampanel is 12 mg/day in subjects not taking any concomitant EIAEDs, or 16 mg/day in subjects taking a concomitant EIAED. (revised per Amendment 04)

Tolerability at a minimum perampanel dose of 2 mg/day is required to continue in the program. Subjects who do not tolerate the minimum perampanel dose of 2 mg/day during the study will be discontinued from the study. (revised per Amendment 04)

Conversion to monotherapy on perampanel is also permitted at the discretion of the investigator, if it is considered appropriate to control the seizures.

See Appendix 2 for a full description of Extension B. (revised per Amendment 03)

9.1.4.2 Follow-up Period

Subjects who discontinue or choose not to switch to the commercial product will require a Follow-up Visit which will be conducted 4 weeks (±7 days) after the Discontinuation Visit. (revised per Amendment 04)

9.2 Discussion of Study Design, Including Choice of Control Groups

Study E2007-G000-311 is a multi-center, open-label study followed by an Extension Phase designed to evaluate the safety, tolerability, PK, and PK/PD of perampanel as an adjunctive therapy for POS and PGTC.

To maintain seizure control in subjects with POS or PGTC during studies of investigational AEDs, the investigational AEDs are administered as adjunctive treatment while maintaining the subject's existing AED regimen.

9.3 Selection of Study Population

At least 160 subjects at approximately 60 to 80 sites in the US, EU, and Asia Pacific will be enrolled. (revised per Amendment 02) Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

The study population of at least 160 subjects who will be enrolled and treated will include up to 40 subjects with PGTC and the balance with POS. (revised per Amendment 02) A

minimum of 30% of the subjects for each seizure type will be enrolled in the younger age group (4 to <7 years) (ie, at least 36 with POS and at least 12 with PGTC)

9.3.1 Inclusion Criteria

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

1. Have a diagnosis of epilepsy with POS with or without secondarily generalized seizures or PGTC according to the ILAE Classification of Epileptic Seizures (1981). Diagnosis should have been established at least 6 months prior to Visit 1 by clinical history and an EEG that is consistent with the diagnosis; normal interictal EEGs will be allowed provided that the subject meets the other diagnosis criterion (ie, clinical history).
2. Male or female subject, from age 4 to less than 12 years at the time of informed consent/assent.
3. Have a minimum weight of 16 kg (35 lb).
4. Have had a brain imaging (eg, magnetic resonance imaging [MRI] scan or computed tomography [CT]) before Visit 1 that ruled out a progressive cause of epilepsy.
5. During the 12 weeks ±3 days (4 weeks ±3 days in Japan only) prior to Visit 2, subjects must have had equal or greater than 1 POS or 1 PGTC seizure. (revised per Amendments 01 and 02) Only simple POS with motor signs, complex POS, and complex POS with secondary generalization are counted toward this inclusion for POS.
6. Are currently being treated with stable doses of 1 to a maximum of 3 approved AEDs. (revised per Amendment 01) Doses must be stable for at least 4 weeks before to Visit 1; in the case where a new AED regimen has been initiated for a subject, the dose must be stable for at least 8 weeks prior to Visit 1. Only 1 EIAED (defined as carbamazepine, phenytoin, oxcarbazepine, or eslicarbazepine) out of the maximum of 3 AEDs is allowed (A vagal nerve stimulator [VNS] will be counted as one of the 3 allowed AEDs). (revised per Amendment 01)

9.3.2 Exclusion Criteria

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

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG [or hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the 1st dose of study drug.
2. Females of childbearing potential who:
   - Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period or for 28 days after study drug discontinuation. If a highly effective method is not appropriate or acceptable for the subject, then the subject may use a medically

effective method (eg, a double barrier method such as condom plus diaphragm with spermicide).

- Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexually active during the study period or for 28 days after study drug discontinuation.
- Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study or for 28 days after study drug discontinuation.

3. Current or history of pseudo-seizures (psychogenic nonepileptic seizures) within approximately 5 years before Visit 1.
4. Have a history of status epilepticus that required hospitalization during the 6 months before to Visit 1.
5. Have an unstable psychiatric diagnosis that may confound subjects' ability to participate the study or that may prevent completion of the protocol specified tests (eg, significant suicide risk, including suicidal behavior and ideation within 6 months before Visit 1, current psychotic disorder, acute mania).
6. Any suicidal ideation with intent with or without a plan within 6 months before Visit 2 (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the C-SSRS) in subjects aged 6 and above.
7. Are scheduled or confirmed or both to have epilepsy surgery within 6 months after Visit 1; however, those who have previously documented "failed" epilepsy surgery will be allowed.
8. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments.
9. Evidence of moderate or severe renal insufficiency as defined by estimated glomerular filtration rates (eGFRs) of 31 to <60 mL/min and <30 mL/min, respectively. (revised per Amendment 01)
10. Evidence of significant active hepatic disease. Stable elevation of liver enzymes, ALT and AST due to concomitant medication(s), will be allowed if they are less than 3 times the upper limit of normal (ULN).
11. Evidence of significant active hematological disease; white blood cell (WBC) count equal or less than 2500/μL (2.50 1E+09/L), or an absolute neutrophil count equal or less than 1000/μL (1.00 1E+09/L).
12. Clinically significant ECG abnormality, including prolonged corrected QT interval (QTc) defined as greater than 450 msec.
13. Have a progressive central nervous system (CNS) disease, including degenerative CNS diseases and progressive tumors.
14. Multiple drug allergies or a severe drug reaction to an AED(s), including dermatological (eg, Stevens-Johnson syndrome), hematological, or organ toxicity reactions.

15. Concomitant use of felbamate as an AED for less than 2 years or where the dose has not been stable for at least 8 weeks before Visit 1. They must not have a history of WBC count below equal or less than 2500/μL (2.50 1E+09/L), platelets below 100,000, liver function tests (LFTs) above 3 times the ULN, or other indication of hepatic or bone marrow dysfunction while receiving felbamate. If subjects received felbamate in the past, it must have been discontinued 8 weeks before Visit 1 to be eligible for study participation.
16. Concomitant use of vigabatrin: Subjects who took vigabatrin in the past must be off vigabatrin for at least 5 months before Visit 1 and with documentation showing no evidence of a vigabatrin associated clinically significant abnormality in a visual perimetry test.
17. Concomitant use of cannabinoids. (revised per Amendment 01)
18. Used benzodiazepines for epilepsy during which the dose has not been stable for greater than 4 weeks prior to Visit 1. Benzodiazepines use as rescue medication for seizure control is allowed; however, intermittent use of benzodiazepines for any other indication (eg, anxiety/sleep disorders) is prohibited. (revised per Amendment 01)
19. A VNS implanted less than 5 months before Visit 1 or changes in parameter less than 4 weeks before Visit 1 (or thereafter during the study).
20. On a ketogenic diet for which the diet is not stable regimen for at least 4 weeks before to Visit 1.
21. History of or a concomitant medical condition that in the opinion of the investigator(s) would preclude the subject's participation in a clinical study or compromise the subject's ability to safely complete the study.
22. Have previously exposed to perampanel in a clinical trial or by prescription for more than 2 months or discontinued for AEs.
23. Have participated in a study involving administration of an investigational drug or device within 4 weeks before Visit 1, or within approximately 5 half-lives of the previous investigational compound, whichever is longer.
24. Subjects with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. (revised per Amendment 01)

9.3.3 Removal of Subjects From Therapy or Assessment

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

In the event a subject discontinues the study early for any reason after Visit 2 in Core Study, an Early Discontinuation Visit will be performed. The subject should also return 4 weeks (±7 days) after Visit 9 or the last dose of study drug to complete the Follow-up Visit procedures. In the event a subject discontinues the study early for any reason before Visit 12 in Extension A, an Early Discontinuation Visit and a Follow-up visit 4 weeks (±7 days) after the last dose of study drug will be performed. (revised per Amendment 03) The Subject Disposition CRF will be completed indicating the primary reason for discontinuation and all

other reasons contributing to the subject's discontinuation from treatment. In addition, the date of last dose of study drug will be recorded on the Study Drug Dosing CRF.

9.4 Treatment

Test drug for this study will be perampanel, oral solution, 0.5 mg/mL. Dosing will be administered orally and daily. Dosing will occur at bedtime.

9.4.1 Treatment(s) Administered

Core Study

Pretreatment Phase:

The Pretreatment Phase will consist of a Screening/Baseline Period that lasts up to 4 weeks ±3 days outside of Japan. Subjects in Japan are required to complete 4 full weeks ±3 days of the Screening/Baseline Period before they may enter the Treatment Phase (ie, Visit 2). However, subjects outside of Japan may begin treatment as soon as baseline procedures have been completed and documentation of eligibility (such as a documented seizure diary entry for a qualifying seizure during the preceding 12 weeks prior to Visit 2 or a qualifying seizure during the prospective Screening/Baseline Period) has been established. (revised per Amendment 02) During this phase, subjects will continue to take their baseline AEDs regimen as allowed per inclusion/exclusion criteria. No study drug will be administered to subjects during this phase.

Treatment Phase:

The treatment phase will consist of 3 periods: Titration (up to 11 weeks), Maintenance (up to 12 weeks), and Follow-up (up to 4 weeks; only for those subjects not rolling over into Extension A). (revised per Amendments 01, 02, and 03)

- ***Titration Period***

During the Titration Period, subjects will be stratified by the presence or absence of concomitant EIAEDs and will be titrated using the dosing schedule presented in Table 1 (Global) and Table 2 (Japan only) based on individual clinical response and tolerability no more frequently than at weekly intervals, up to 8 mg/day of perampanel for non-EIAED subjects or 12 mg/day for EIAED subjects. (revised per Amendment 01) EIAED subjects who are not enrolled in Japan may titrate beyond 12 mg/day and up to 16 mg/day if they tolerate 12 mg/day and are deemed likely to benefit from a higher dose. Subjects enrolled in Japan and receiving EIAEDs may not receive doses higher than 12 mg/day. Non-EIAED subjects may go beyond 8 mg/day and up to 12 mg/day if they tolerate 8 mg/day and are deemed likely to benefit from a higher dose. Subjects will be flexibly dosed based on individual tolerability. The Titration Period is a duration of up to 11 weeks during which multiple dose adjustments are allowed in order to identify each subject's optimum dose. (revised per Amendment 02) Subjects will remain on their optimum dose once it is achieved during the Titration Period. (revised per Amendment 01)

Table 1 Dosing Schedule (Global)

(revised per Amendment 01)

Week	Subjects on Concomitant EIAEDs (mg/day)	Subjects NOT on Concomitant EIAEDs (mg/day)
0	4	2
1	6	4
2	8	6
3	10	6
4	10	8
5	12	8
6	12	10
7	14	10
8	14	12
9	16	12
10	16	—

EIAED = enzyme inducing antiepileptic drug.
For subjects not on concomitant EIAEDs, titration above 8 mg/day doses is contingent on subject tolerability.

Table 2 Dosing Schedule (Japan Only)

(revised per Amendment 01)

Week	Subjects on Concomitant EIAEDs (mg/day)	Subjects NOT on Concomitant EIAEDs (mg/day)
0	2	2
1	4	4
2	6	6
3	6	6
4	8	8
5	8	8
6	10	10
7	10	10
8	12	12
9	12	12
10	—	—

EIAED = enzyme inducing antiepileptic drug.
For subjects not on concomitant EIAEDs, titration above 8 mg/day doses is contingent on subject tolerability.

According to the investigator's clinical judgment, subjects experiencing intolerability at any dose may remain at the same dose or have their dose decreased 1 dose level down to the previously tolerated dose. If the subject continues to present significant intolerable AE(s) at the decreased dose and the investigator deems it is necessary, the dose can be decreased further to the next dose level down. Dose decreases can be done via telephone. Subjects whose dose has been decreased can have their dose increased again if tolerability improves; this can be done at the next clinic visit after the investigator has deemed it is appropriate in view of resolution of the AE(s). Multiple dose adjustments will be allowed during the Titration Period. Upon completion of the Titration Period, subjects will enter the Maintenance Period.

- ***Maintenance Period***

During the Maintenance Period of the Core Study (up to 12 week), subjects will continue taking perampanel oral suspension once daily at the dose level they achieved at the end of the Titration Period. Multiple dose adjustment is allowed if a subject is experiencing intolerable AE(s) or a higher dose is deemed to be beneficial. All visits are to be done within ±7 days of the schedule. Each study visit is based on the actual prior visit (eg, Visit 6 is completed 3 weeks ±7 days of Visit 5, Visit 7 is completed 4 weeks ±7 days of Visit 6, Visit 8 is completed 4 weeks ±7 days of Visit 7, Visit 9 is completed 4 weeks ±7 days of Visit 8. (revised per Amendment 02)

During the Titration and Maintenance Periods, all dose adjustments will be done via 1 dose level up or down. Those who cannot tolerate a minimum of 2 mg dose must discontinue from the study.

Extension A

Details on treatments administered during Extension A are provided in Appendix 1. (revised per Amendment 03)

Extension B

Details on treatments administered during Extension B are provided in Appendix 2. (revised per Amendment 03)

9.4.2 Identity of Investigational Product(s)

Perampanel oral suspension will consist of the active ingredient, perampanel, and assorted excipients (all of which are considered appropriate for use in a pediatric population) suspended in a water-based medium. The resulting suspension is opaque and practically white. The formulation of perampanel 0.5 mg/mL oral suspension will be provided by Eisai according to current Good Manufacturing Practices.

Perampanel is a Schedule III Controlled Drug Substance in the US. Investigators in the US must have valid Drug Enforcement Administration (DEA) registrations and adequate storage

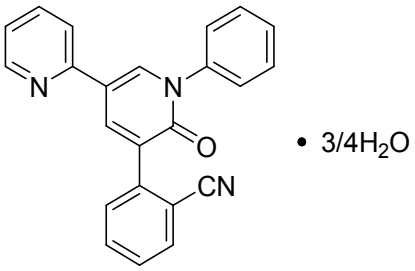
facilities to handle Schedule III controlled substances as required per DEA regulations. All shipments to US sites will comply with the DEA regulations.

Perampanel oral suspension will be provided by Eisai to an Eisai-approved vendor in 400 mL polyethylene terephthalate (PET) bottles containing 340 mL of oral suspension. The approved vendor will label the bottles and ship them to local country depots or the study sites.

A detailed pharmacy manual will be provided to each investigational site. The PET bottles for dispensing the test drug will be, if necessary, fitted with appropriately sized press-in bottle adaptors to aid in accurate aliquotting. Dosing devices (eg, oral syringes) will also be provided for subject use.

9.4.2.1 Chemical Name, Structural Formula of E2007

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



9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

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

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions and, where required per local controlled substance requirements, kept in a locked cabinet. Temperature monitoring is required at the storage location to ensure that the study drug is maintained

within an established temperature range. The investigator or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

This is an open-label, single-arm study. All subjects who provide signed informed consent to participate in this study and satisfy all eligibility requirements (see Section 9.3) will receive 0.5 mg/mL perampanel suspension. There is no randomization in this study.

9.4.4 Selection of Doses in the Study

See Section 7.3 for selection of doses in the study.

9.4.5 Selection and Timing of Dose for Each Subject

Perampanel will be administered orally and daily. Dosing should occur at bedtime.

9.4.6 Blinding

The study will not be blinded.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication CRF or Non-Pharmacological Procedures CRF. The investigator will record on the AE CRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition CRF.

Other than carbamazepine, oxcarbazepine, phenytoin, and eslicarbazepine, concomitant use of medications known to be inducers of cytochrome (CYP) 3A including, but not limited to: rifampin, troglitazone, St John's Wort, efavirenz, nevirapine, glucocorticoids (other than topical usage), modafinil, pioglitazone, and rifabutin will not be permitted and are to be discontinued within 28 days before Visit 1. VNS implanted less than 5 months before Visit 1 or changes in parameter less than 4 weeks before Visit 1 (or thereafter during the study) will be prohibited.

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

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator until the following documentation has been received by the sponsor:

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

The investigator and the study staff will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

In the US, Federal regulations require that registrants notify the DEA Field Division Office in their area, in writing, of the theft or significant loss of any controlled substance within 1 business day of discovery of such loss or theft. The registrant shall also complete and submit to the Field Division Office in their area, DEA Form 106, "Report of Theft or Loss of Controlled Substances" regarding the theft or loss. Additionally, registrants may have local or state level reporting requirements to conform with.

Under no circumstances will the investigator allow the study drug to be used other than as directed by this protocol. Study drug will not be dispensed to any individual who is not enrolled in the study. The subject's parent/guardian will be dispensed the study drugs.

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

The study drug and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Products Regulatory Agency [MHRA]). As applicable, all unused study drug and empty and partially empty containers from used study drug are to be returned to the investigator by the subject and, together with unused study drug that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drug and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drug to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drug that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drug may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drug is approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

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

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

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

9.5.1.2 Baseline Assessments

9.5.1.2.1 Medical History and Physical Examinations

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

Physical examinations (comprehensive or symptom directed) will be performed as designated in the Schedule of Procedures/Assessments (Table 4). A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination, which will consist of assessment of mental status, sensory systems, cranial nerves, motor function, deep tendon reflexes, and cerebellar functions. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the AEs CRF.

9.5.1.2.2 Epilepsy Medical history

In addition to standard medical history, epilepsy history will be documented for each subject at the Screening/Baseline Visit. For subjects ≥4 years but <12 years of age, lifetime AED history will be collected.

9.5.1.3 Efficacy Assessments

Efficacy will be assessed by seizure counts and types as recorded on the diary. Diaries will be dispensed to all subjects at each visit as described in Table 4. The diary is to be completed daily, by the parent/guardian. All seizures will be recorded. At each visit the parent/guardian will be instructed by the site personnel as to how to complete the diary and reminded that they must return the diary at their next scheduled clinic visit and at the Early Discontinuation and Follow-up Visits (if applicable). To ensure correct seizure classification, the medically qualified investigator should review the diary with the parent/guardian at all visits. Parents/guardians must be counseled if diary compliance is not satisfactory (ie, missed three or more consecutive daily diary entries).

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 Pharmacokinetic Assessments

Plasma concentrations of perampanel will be determined via collection of blood samples during the Maintenance Phase using a sparse sampling technique at specified visits for subsequent population PK analysis.

Participation in the PK assessment portion of the protocol will be mandatory for all sites with appropriately trained staff and adequate equipment for procuring and processing the specimens. (revised per Amendment 01) Blood samples (1 mL each) will be collected at specified time points for all subjects (Table 4). (revised per Amendment 01) Information for the collection, handling, and shipping procedures of the samples will be described in a manual provided to the sites.

Samples from all subjects receiving active treatment will be analyzed. Plasma concentrations of analytes will be quantified by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) methodology using a previously validated assay.

Additional blood for PK analysis will be drawn where possible at the 1st report of a serious adverse event (SAE) or severe unexpected AE and at its resolution. (revised per Amendment 01)

9.5.1.4.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker, Assessments

Not Applicable.

9.5.1.5 Safety Assessments

Safety will be assessed by monitoring and recording all AEs and SAEs, regular monitoring of hematology, blood chemistry, and urine values, periodic measurement of vital signs and ECGs, and performance of physical and neurological examinations, as detailed in Table 4.

Growth and development will be assessed by weight, height, thyroid, and insulin-like growth factor-1 (IGF-1). Cognitive testing ABNAS, behavioral questionnaires (CBCL), and visuomotor skills testing using the LGPT will be administered.

An assessment of suicidal ideation and behavior using the C-SSRS will be performed throughout the study for subjects aged 6 years and older at the time of consent/assent. Suicidal ideation and behavior will be monitored in subjects less than 6 years at the time of consent/assent based upon clinical impression. An EEG will be performed over a minimum of 1-hour up to a 2-hour period in an awake and sleep state.

9.5.1.5.1 Adverse Events and Events Associated With Special Situations

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

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not considered related to the IP (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease

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

All AEs observed during the study will be reported on the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit and for 28 days following study drug discontinuation. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition CRF. SAEs will be collected for 28 days after the last dose.

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

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

It is the responsibility of the investigator to review the results of the C-SSRS in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.7 for a description of the C-SSRS).

All AEs must be followed for 28 days after the subject's last dose, or until resolution, whichever comes 1st. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

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

Assessing Severity of Adverse Events

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

Mild Discomfort noticed, but no disruption of normal daily activity

Moderate Discomfort sufficient to reduce or affect normal daily activity

Severe Incapacitating, with inability to work or to perform normal daily activity

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

Assessing Relationship to Study Treatment

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

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

Classification of Causality

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

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

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

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

9.5.1.5.2 Serious Adverse Events and Events Associated With Special Situations

A SAE is any untoward medical occurrence that at any dose:

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

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

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 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 "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

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

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the 1st report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 3. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 4) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study (Core Study).

Table 3 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils) (revised per Amendment 01)
Chemistry	
Electrolytes	Chloride, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, calcium, cholesterol, globulin, glucose[a], lactate dehydrogenase, phosphorus, total protein, triglycerides[a], uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs, Urine drug screen[b] (revised per Amendment 01)

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

a: Fasting samples to be taken at baseline and at end of treatment or early discontinuation, with fasting window (interval) between 2 and 4 hours.

b: To be performed only at baseline. (revised per Amendment 01)

Clinical laboratory tests during the Core Study and Extension A will be performed by a central laboratory. (revised per Amendment 03) All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory.

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

9.5.1.5.4 Vital Signs and Weight Measurements

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

9.5.1.5.5 Physical Examinations

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 4). Documentation of the physical examination will be

included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the AEs CRF.

9.5.1.5.6 ELECTROCARDIOGRAMS

ECGs will be obtained as designated in the Schedule of Procedures/Assessments (Table 4).

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

9.5.1.5.7 OTHER SAFETY ASSESSMENTS

C-SSRS

An assessment of suicidality using the C-SSRS will be performed for subjects aged 6 years and older at the time of consent/assent at Screening/Baseline, Day 1 postdosing, every visit, including after the last dose of study drug, and at the Termination Visit, as designated in the Schedule of Procedures/Assessments (Table 4).

Pregnancy Test

A serum β-hCG test will be performed for female subjects age 8 years old and above, or of child-bearing potential, only. A sample of blood will be taken at screening; at all other time points a urine pregnancy test will be performed as specified in the Schedule of Procedures/Assessments (Table 4). If urine can not be obtained for pregnancy testing after screening, a serum pregnancy test will be performed. (revised per Amendment 01)

EEG

An EEG will be performed over a minimum of 1-hour and up to a 2-hour period in awake and sleeping states at the visits designated in Table 4.

ABNAS

The ABNAS assessment measures 5 aspects of cognitive function: fatigue, memory, concentration, motor speed, and reading, using a 4-point scale. The assessment is a measure of patient-perceived cognitive effects of AEDs.

This instrument aimed at assessing patient perceived drug-related cognitive impairment. It will be assessed at designated time points as specified in the Schedule of Procedures/Assessments (Table 4).

CBCL

The CBCL is a questionnaire to assess behavioral and emotional problems in children as reported by the primary caregiver. It is standardized to evaluate maladaptive behavioral and

emotional problems in ages 2 to 18 years. It will be assessed at designated time points as specified in the Schedule of Procedures/Assessments (Table 4).

LGPT

The LGPT is a manipulative dexterity test requiring complex visual-motor coordination and will be assessed at designated time points as specified in the Schedule of Procedures/Assessments (Table 4).

9.5.1.6 Other Assessments

EQ-5D-Y

A health related quality of life questionnaire (EQ-5D-Y) will be administered. For patients with mental disabilities and patients ages 4 to 7, caregivers, or parents will complete the proxy EQ-5D-Y. For ages 8 to 11 with no mental disabilities, patients will self-complete the EQ-5D-Y. Patients ages 8 to 11 with physical disabilities but no mental disabilities may have the EQ-5D-Y read to them and their responses recorded by a caregiver, parent, or study coordinator. EQ-5D-Y will be administered at the visits designated in Table 4.

CGI

The CGI, Clinical Global Impression of Severity (CGIS), and CGIC will be administered at the visits designated in Table 4. Telephone interviews with the subjects and/or caregiver will be conducted to ensure that subjects are completing their seizure diaries regularly and to assess AEs, study drug compliance, and concomitant medications, including AEDs.

Details for all assessments in the Extension A and Extension B can be found in Appendix 1 and Appendix 2, respectively. (revised per Amendment 03)

9.5.2 Schedule of Procedures/Assessments – Core Study

9.5.2.1 Schedule of Procedures/Assessments

Table 4 presents the schedule of procedures/assessments for the Core Study.

Table 4 Schedule of Procedures/Assessments in Study E2007-G000-311: Core Study

Phase	Pre-Treatment	Treatment Phase										
	Screening/Baseline	Titration[a]				Maintenance[b]				Follow-up[b,c]		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**		**Early Discontinuation[d]**	**Unscheduled**
Week	**From up to -4 weeks ±3 days to Week 0 (outside of Japan)** **-4 weeks ±3 days to Week 0 (Japan only)** (revised per Amendment 02)	**0**	**2**	**5**	**8**	**11**	**15**	**19**	**23**	**27**		
Procedures/Assessments												
Demography	X											
Informed consent/assent	X											
Inclusion/exclusion criteria	X	X										
Medical history	X											
Epilepsy medical history	X											
Prior/concomitant medication(s)	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant AED(s)	X	X	X	X	X	X	X	X	X	X	X	X
Neurological examination[e]	X								X	X	X	
Physical examination[e]	X								X	X	X	
Vitals[f] and weight[g]	X	X	X	X	X	X	X	X	X	X	X	X
Height[g]		X							X		X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Study drug compliance			X	X	X	X	X	X	X		X	X
Dispense study drug		X	X	X	X	X	X	X	X[h]			X[i]
Retrieve unused study drug			X	X	X	X	X	X	X		X	X[i]
Dispense subject's diary	X	X	X	X	X	X	X	X	X[h]			X
Retrieve and review diary		X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests[j]	X[k]					X			X[k]	X	X	X

Table 4 Schedule of Procedures/Assessments in Study E2007-G000-311: Core Study

Phase	Pre-Treatment	Treatment Phase										
	Screening/Baseline	Titration[a]				Maintenance[b]				Follow-up[b,c]		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**		**Early Discontinuation[d]**	**Unscheduled**
Week	**From up to -4 weeks ±3 days to Week 0 (outside of Japan)** **-4 weeks ±3 days to Week 0 (Japan only)** (revised per Amendment 02)	**0**	**2**	**5**	**8**	**11**	**15**	**19**	**23**	**27**		
Procedures/Assessments												
Thyroid (TSH, fT3, fT4) and IGF-1 testing	X								X		X	
Serum β-hCG (or hCG) test[l]	X											
Urine pregnancy test[l]		X	X	X	X	X	X	X	X	X	X	X
C-SSRS[m]	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[n]	X								X	X	X	X[o]
EEG[p]	X								X		X	X[o]
Perampanel PK sampling (plasma)[q,r]							X	X	X		X	X
Telephone call[s]		X	X	X	X	X	X	X				
ABNAS[t]	X[u]	X					X		X		X[v]	
Lafayette Grooved Pegboard Test	X[u]	X					X		X		X[v]	
Child Behavior Checklist		X							X		X	
EQ-5D-Y		X							X		X	
Clinical Global Impression		X							X		X	
Disposition		X							X		X	
IxRS	X	X	X	X	X	X	X	X	X	X	X	X

ABNAS = A-B neuropsychological assessment schedule, AE = adverse event, AED(s) = antiepileptic drug(s), β-hCG = beta-human chorionic gonadotropin (or hCG = human chorionic gonadotropin), C-SSRS = Columbia-Suicide Severity Rating Scale, eCRF = electronic case report form, EQ-5D-Y = EuroQol 5 Dimensions-Youth, fT3 = free triiodothyronine, fT4 = free thyroxine, IGF-1 = insulin-like growth factor-1, IxRS = interactive and response system, PK = pharmacokinetics, TSH = thyroid-stimulating hormone.

Table 4 Schedule of Procedures/Assessments in Study E2007-G000-311: Core Study

Phase	**Pre-Treatment**	**Treatment Phase**										
	Screening/Baseline	**Titration[a]**				**Maintenance[b]**				**Follow-up[b,c]**		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**		**Early Discontinuation[d]**	**Unscheduled**
Week	**From up to -4 weeks ±3 days to Week 0 (outside of Japan)** **-4 weeks ±3 days to Week 0 (Japan only)** (revised per Amendment 02)	**0**	**2**	**5**	**8**	**11**	**15**	**19**	**23**	**27**		
Procedures/Assessments												

a: All visits to be done within ±3 days of the schedule. Each study visit is based on the actual prior visit (eg, Visit 3 is completed 2 weeks ±3 days of Visit 2, Visit 4 is completed 3 weeks ±3 days of Visit 3, Visit 5 is completed 3 weeks ±3 days of Visit 4). (revised per Amendment 02)

b: Visit to be done within ±7 days of the schedule. Each study visit is based on the actual prior visit (eg, Visit 6 is completed 3 weeks ±7 days of Visit 5, Visit 7 is completed 4 weeks ±7 days of Visit 6, Visit 8 is completed 4 weeks ±7 days of Visit 7, Visit 9 is completed 4 weeks ±7 days of Visit 8). (revised per Amendments 02 and 03)

c: The Follow-up Visit only applies to those subjects who complete the Core Study (or who discontinue the study early), but do not roll-over into Extension A and is to occur 4 weeks (±7 days) after Visit 9 or last dose of study drug.

d: These assessments will be conducted for subjects who discontinue the study early for any reason after Visit 2.

e: Physical and neurological examinations will only be performed at Visit 1 and Visit 9 and at the Follow-up Visit, and at the Early Discontinuation Visit (if applicable). For all other clinic visits during the study, the physical and the neurological exams will only be performed when there is a complaint from the subject. Clinically significant abnormal findings from the physical or the neurological examinations will be reported as AEs.

f: Blood pressure and pulse will be taken.

g: Weight and Height (without shoes) will be measured. Three measurements should be taken at each visit. Each measurement should be recorded as a separate entry on the Vital Sign eCRF.

h: Only for those subjects who continue into Extension A.

i: Unused study drug to be retrieved and study drug dispensed only for subjects requiring dose increases at Unscheduled Visits.

j: Clinical laboratory tests include hematology, blood chemistry including lipid panel, and urinalysis.

k: Fasting lipid and glucose samples to be taken at baseline and at end of treatment or early discontinuation, with fasting window (interval) between 2 and 4 hours.

l: Female subjects age 8 years old and above, or of childbearing potential, only. If urine can not be obtained for pregnancy testing after screening, a serum pregnancy test will be performed. (revised per Amendment 01)

m: Only for subjects aged 6 years and older at the time of consent/assent.

n: If subject has a normal ECG baseline reading, but during any visit thereafter, the QT is measured as greater than 450 ms, 3 consecutive ECGs separated by 5 to 10 minutes will be performed to confirm the abnormality.

o: During Unscheduled Visits, ECG or EEG will only be done if the results from the previous visit were deemed clinically significant by the investigator.

p: EEG will be performed at awake and sleep state for all subjects.

q: One blood sample (approximately 1 mL) for determination of perampanel plasma concentrations will be collected at any time during each of the specified visits.

Table 4 Schedule of Procedures/Assessments in Study E2007-G000-311: Core Study

Phase	Pre-Treatment	Treatment Phase										
	Screening/Baseline	Titration[a]				Maintenance[b]				Follow-up[b,c]		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**		**Early Discontinuation[d]**	**Unscheduled**
Week	**From up to -4 weeks ±3 days to Week 0 (outside of Japan)** **-4 weeks ±3 days to Week 0 (Japan only)** (revised per Amendment 02)	**0**	**2**	**5**	**8**	**11**	**15**	**19**	**23**	**27**		
Procedures/Assessments												

r: Additional blood (approximately 1 mL/sample) will be drawn at the 1st report (where possible) of a serious adverse event or severe unexpected AE and at its resolution. (revised per Amendment 01)

s: Telephone interviews with the subjects and/or caregiver will be conducted 1 week after Visit 2, Visit 3, Visit 4, Visit 5, Visit 6; and at the midpoint (±3 days) between each visit from Visit 7, Visit 8 and Visit 9 to ensure that subjects are completing their seizure diaries regularly and to assess AEs, study drug compliance, and concomitant medications, including AEDs. Subjects whose dose was decreased before the scheduled telephone interview will be strongly encouraged to return to the clinic (instead of the scheduled telephone interview) for further consultation with regard to study drug administration. The site will contact IxRS to receive further dispensing instructions. Subjects will then return for their regularly scheduled visit.

t: ABNAS to assess patient-perceived cognitive effects of AED treatment, measuring 5 aspects of cognitive function: fatigue, memory, concentration, motor speed, and reading, using a 4-point scale.

u: To be administered twice at Visit 1 (for training purposes only).

v: Subjects who discontinue after Week 12 must have assessments performed at the Early Discontinuation Visit.

Table 5 and Table 6 present the Schedule of Procedures/Assessments for Extension A and Extension B of the study, respectively. (revised per Amendment 03)

9.5.2.2 Description of Procedures/Assessments Schedule

The schedule of procedures/assessments for the Core Study, Extension A, and Extension B of the study are presented in Table 4, Table 5, and Table 6, respectively. (revised per Amendment 03)

A brief description of the C-SSRS is provided in Section 9.5.1.5.7.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of Phase 3 studies of epilepsy in pediatric subjects.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, radiologic studies, and assessment of AEs, are standard evaluations to ensure subject safety.

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

9.5.4.1 Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.

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

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

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

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

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

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

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

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported

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

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

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

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

9.5.4.3 Reporting of Events Associated With Special Situations

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

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

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose

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

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

9.5.4.3.2 Reporting of Study-Specific Events

Not applicable.

9.5.4.4 Expedited Reporting

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

9.5.4.5 Breaking the Blind

Not applicable.

9.5.4.6 Regulatory Reporting of Adverse Events

AEs will be reported by the sponsor or a 3rd party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

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

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 4 and Table 5).

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

Subjects who discontinue early from the study will be discontinued for one of these primary reasons: AE(s), lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

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

9.5.6 Abuse or Diversion of Study Drug

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

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

9.5.7 Confirmation of Medical Care by Another Physician

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

9.6 Data Quality Assurance

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

9.6.1 Data Collection

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

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 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 3rd parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

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

9.7 Statistical Methods

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

9.7.1 Statistical and Analytical Plans

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

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

Safety and tolerability, which include incidence of treatment-emergent adverse events (TEAEs) and SAEs, laboratory parameters, vital signs, and ECG parameters, of perampanel oral suspension in children (ages 4 to <7 years and ≥7 years to <12 years) with POS or PGTC

9.7.1.1.2 SECONDARY ENDPOINTS

The following endpoints will be analyzed:

1. The relationship between plasma levels of perampanel and efficacy endpoints (ie, change in average seizure frequency over 28 days, responder probability, and the proportion of subjects who are seizure-free in the Maintenance Period of the Core Study) separately for each seizure type
2. The relationship between plasma levels of perampanel and cognition endpoints including change from baseline in ABNAS, CBCL, and LGPT. In addition, depending

on the AE data, the relationship between plasma levels of perampanel and select AEs will be assessed.

3. Change from baseline at Week 23 and Week 52 in ABNAS, CBCL, and LGPT
4. Changes from baseline at Week 23 and Week 52 in growth and development parameters (height, weight, thyroid, and IGF-1)
5. Change from baseline in EEG and the frequency of EEG abnormalities during awake and sleep state
6. Proportion of subjects (aged 6 or older at time of consent/assent) with any treatment-emergent reports of suicidal ideation and behavior on the C-SSRS and intensity of these behaviors assessed using C-SSRS scores
7. The median percent change in seizure frequency per 28 days during Treatment Phase (Titration Period and Maintenance Period) of the Core Study, and during the long-term treatment (up to 52 weeks) relative to the Pretreatment Phase. Seizure frequency will be based on the number of seizures per 28 days, calculated as the number of seizures over the entire time interval divided by the number of days in the interval and multiplied by 28.
8. Proportion of responders (25% responders defined as a decrease in 28-day seizure frequency of equal or greater than 25% compared to baseline seizure frequency; 50% responders defined as a decrease in 28-day seizure frequency of equal or greater than 50% compared to baseline seizure frequency; 75% responders defined as a decrease in 28-day seizure frequency of equal or greater than 75% compared to baseline seizure frequency) during Maintenance Period of Core Study, and during the long term treatment (up to 52 weeks)
9. Proportion of subjects who are seizure-free during Maintenance Period of Core Study, and during the long-term treatment (up to 52 weeks)
10. CGI of Change

9.7.1.1.3 EXPLORATORY ENDPOINT

Change from baseline at Week 23 and Week 52 in EQ-5D-Y.

9.7.1.2 Definitions of Analysis Sets

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

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

PK Analysis Set is the group of subjects receiving perampanel and with at least 1 quantifiable perampanel concentration at one of the visits during the Maintenance Period of the Core Study and with adequately documented dosing history.

PK/PD Analysis Set is the group of subjects receiving perampanel who have seizure frequency, cognition, or AE data with documented dosing history. Subjects receiving perampanel should have at least 1 quantifiable perampanel concentration at one of the visits during the Maintenance Period of the Core Study as per the PK Analysis Set.

9.7.1.3 Subject Disposition

Reasons for discontinuation will be recorded for all entered subjects. The frequencies of occurrence of each reason for discontinuation will be summarized. The data will be described using incidence rate (number of subjects and percentage).

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, weight, height, and body mass index (BMI); categorical variables include sex, age group, race, and ethnicity.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by Anatomical Therapeutic Chemical (ATC) class and WHO DD preferred term (PT). Prior medications will be defined as medications that stopped before the 1st dose of study drug. Concomitant medications will be defined as medications that (1) started before the 1st dose of study drug and were continuing at the time of the 1st dose of study drug, or (2) started on or after the date of the 1st dose of study drug 4 weeks after the subject's last dose. All medications will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

The percent change in seizure frequency per 28 days will be summarized using descriptive statistics (n, mean, median, minimum and maximum) by age cohorts (4 to <7 years, ≥7 to <12 years), by disease cohorts (POS, PGTC, and GTC), and by the presence or absence of concomitant EIAED in the FAS.

The proportion of subjects who are seizure-free and the proportion of responders based on decrease from baseline in 28-day seizure frequency of equal or greater than 25%, equal or greater than 50%, and equal or greater than 75% will be summarized using frequency count (number and percentage) by age cohorts (4 to <7 years, ≥7 to <12 years), by disease cohorts (POS, PGTC, and GTC), and by the presence or absence of concomitant EIAED in the FAS.

The CGIC will be summarized using frequency count (number and percentage) by age cohorts (4 to <7 years, ≥7 to <12 years), by disease cohorts (POS, PGTC, and GTC), and by the presence or absence of concomitant EIAED in the FAS.

For purposes of registration in Japan, perampanel will be determined to be efficacious if, in subjects enrolled in Japan, the upper limit of the 95% CI for the median percent change in POS frequency per 28 days is below the pre-specified threshold. This prespecified threshold consists of the median percent reduction in seizure frequency (ie, 10.5%) in subjects who received placebo during the Randomization Phase of Study E2007-J000-335. For example, if the 95% CI limits for the median percent reduction in seizure frequency are 65.0% and 25.0%, respectively, success would be declared because the upper bound of the CI falls below the prespecified threshold.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Pharmacokinetic Analysis

Population PK analysis will be performed to characterize the PK of perampanel by pooling the concentration data with other studies, including 19 Phase 1 studies, 2 Phase 2 studies (232 and 235), and 5 Phase 3 studies (304, 305, 306, 332, and 335). A 2-compartment PK model will be fit to the data and the effect of intrinsic and extrinsic factors, including body weight and age, on the PK of perampanel will be evaluated. The post-hoc estimates of both maximum observed concentration (C_{max}) and area under the curve (AUC) from the final PK model will be derived for all subjects. In addition, average steady-state drug concentration (Css,av) will be calculated. Subsequently, the dose-normalized derived exposure parameters will be summarized descriptively by age group (≤4 years, >4 to ≤8 years, >8 to <12 years, ≥12 to <18 years, and ≥18 years) for subjects with and without inducing AEDs, and also presented in box-plots.

Pharmacokinetic/Pharmacodynamic Analyses

Population PK/PD analysis will be conducted for the relationship between model-predicted average exposure to perampanel at steady-state (Css,av) vs responder rate and percent reduction in seizure frequency during the Maintenance Phase. In addition, the relationship between Css,av and the cognition endpoints and most frequent AEs will be explored graphically. Any emergent relationship will be subjected to population PK/PD modeling. The effect of intrinsic and extrinsic factors (ie, most common concomitant AEDs, demographics) on the PK/PD relationship will be evaluated. Two separate analyses will be performed, one for POS, where data from subjects with POS from Study 311 will be pooled with data from POS subjects from Studies 304, 305, 306, and 335, and another for PGTC, where data from subjects with PGTC from Study 311 will be pooled with data from PGTC subjects from Study 332.

9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Pharmacodynamic Analysis

PD endpoints to be evaluated as part of PK/PD analyses include endpoints for efficacy cognition, and selected safety parameters.

9.7.1.8 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data will be summarized on an "as treated" basis using descriptive statistics (eg, n, mean, SD, median, minimum, maximum for continuous variables; n [%] for categorical variables) by age cohorts (4 to <7 years, ≥7 to <12 years), by disease cohorts (POS, PGTC, and GTC), and by the presence or absence of concomitant EIAEDs. Safety variables include TEAEs, clinical laboratory parameters, vital signs, 12-lead ECG results, C-SSRS, growth parameters, CBCL, LGPT, and EEG. Study Day 1 for all safety analyses will be defined as the date of the 1st dose of study drug.

9.7.1.8.1 EXTENT OF EXPOSURE

The duration of treatment (Titration Period and Maintenance Period of the Core Study) will be calculated as the number of days between the date the subject receives their 1st treatment dose and the date the subject receives the last dose of treatment. These values will be used to summarize the extent of exposure to study medication.

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). AEs will be coded to the MedDRA (version 18.1 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

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

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

The TEAEs will be summarized using the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than

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

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

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study treatment.

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

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT. A subject data listing of all SAEs will be provided.

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

The incidence of TEAEs of special interest defined by standardized MedDRA queries (SMQs) will also be summarized.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit using descriptive statistics. 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. For each laboratory parameter, shift from baseline (LNH) to each postbaseline visit and at the end of treatment will be presented. Similar shift tables from baseline (LNH) to the highest/lowest postbaseline value will also be presented.

Appendix 3 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAV). Except for phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. The number and percentage of subjects with TEMAVs will be presented; each subject will be counted once in the laboratory parameter high and low categories, as applicable. Markedly abnormal laboratory values will be flagged in the subject data listings.

For ALT and AST analysis, the number of subjects with greater than 3 times, but less than 5 times the ULN and the number of subjects with greater than 5 times the ULN will be summarized. For bilirubin, a summary of the number of subjects with serum concentrations greater than 2 times the ULN will be created.

9.7.1.8.4 VITAL SIGNS

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

9.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit.

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

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTc Bazett and QTc Fridericia during the treatment period will be summarized. Clinically borderline or abnormal ECG results in QTc Bazett and QTc Fridericia will be categorized as follows:

Absolute QTc interval prolongation:

- QTc interval 430-450 ms
- QTc interval>450 ms
- QTc interval>500 ms

Change from baseline in QTc interval:

- QTc interval increases from baseline 30-60 ms
- QTc interval increases from baseline>60 ms

9.7.1.8.6 OTHER SAFETY ANALYSES

The change from baseline in ABNAS, CBCL, and LGPT will be summarized.

The change from baseline in growth (height, weight, thyroid, and IGF-1) will be summarized.

The change from baseline in EEG parameters and the frequency of EEG abnormalities will be summarized.

Proportion of subjects with any treatment-emergent report of suicidal ideation and behavior and intensity of these behaviors will be summarized.

9.7.1.9 Other Analyses

The change from baseline in EQ-5D-Y, and Global Assessment of Change and its severity will be summarized by age and disease cohorts, and by the presence or absence of concomitant EIAED, using descriptive statistics.

9.7.2 Determination of Sample Size

A sample size of at least 160 subjects (with up to 40 subjects with PGTC and the balance with POS), is deemed sufficient for safety evaluation in this age group (age 4 to <12 years). (revised per Amendment 02) This sample size matches the total number of adolescents who were enrolled in the 4 global Phase 3 efficacy and safety studies that support the POS and PGTC indications.

For purposes of registration in Japan, it has been determined that a sample size of 65 subjects enrolled in Japan will provide 80% power to exclude the possibility that there would be a reduction smaller than that observed in the placebo arm of Study E2007-J000-335 (ie, 10.5%). Details are provided in the SAP.

9.7.3 Interim Analysis

(revised per Amendments 01 and 02)

An independent data monitoring committee (DMC) will be constructed to monitor the safety data. The responsibilities, membership, and purpose of the DMC, the timing of the meeting(s), and an outline of the plan for review of the safety data will be documented in the DMC Charter.

Analyses for regional submissions may be performed during the course of the study. (revised per Amendment 02)

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

Cancer Therapy Evaluation Program, CTCAE version 4.0 [published 28 May 2009 (v4.03: June 14, 2010)]. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_201006-1 4_QuickReference_8.5x11.pdf.

Columbia-Suicide Severity Rating Scale (C-SSRS). Columbia University. Available from: http://www.cssrs.columbia.edu/scales_cssrs.html

Pellock JM, Carman WJ, Thyagarajan V, Daniels T, Morris DL, D'Cruz O. Efficacy of antiepileptic drugs in adults predicts efficacy in children: a systematic review. Neurology. 2012;79:1482-89.

11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

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

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

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

11.3 Monitoring Procedures

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

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

- Clinic, office, or hospital charts

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

11.4 Recording of Data

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

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

The Site and PI shall reasonably cooperate with Sponsor to answer critical queries related to the study data generated by the Site and PI that may arise after the completion of the study. The Site and PI will, upon reasonable notice and during normal business hours, be available to provide information requested by Sponsor or its designees regarding such critical queries. (revised per Amendment 01)

11.5 Identification of Source Data

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

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator or the designated representative is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572), ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the IP.

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

11.7 Auditing Procedures and Inspection

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

11.8 Handling of Study Drug

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

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

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The Site and PI shall at least 90 days prior to submitting or presenting a publication to any third party, provide to Sponsor a copy of such publication, and allow Sponsor to comment on it within this period. The Site and PI shall remove any confidential information or other proprietary information, requested by Sponsor, prior to submitting or presenting a publication and shall incorporate reasonable comments made by the Sponsor into the publication. (revised per Amendment 01)

The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

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

11.10 Disclosure and Confidentiality

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

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

11.11 Discontinuation of Study

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

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

11.12 Subject Insurance and Indemnity

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

11.13 Data Monitoring Committee

An independent DMC will be constructed to monitor the safety data. The responsibilities, membership, and purpose of the DMC, the timing of the meeting(s), and an outline of the plan for review of the safety data will be documented in the DMC Charter.

12 APPENDICES

Appendix 1 Extension Phase (Extension A)

Study Design and Plan

Extension A will consist of a Maintenance Period (up to 29 weeks) and a Follow-up Period (up to 4 weeks; only for those subjects not entering into Extension B). (revised per Amendments 02, 03, and 04)

All subjects who complete all scheduled visits up to and including Visit 9 in the Treatment Phase will be eligible to participate in Extension A of the study. (revised per Amendment 03)

During the Maintenance Period of Extension A, all subjects will continue with their optimal perampanel dose (ie, that dose level that they completed on during the Core Study). (revised per Amendment 03) Multiple dose adjustment is allowed if a subject is experiencing intolerable AE(s) or a higher dose is deemed beneficial. The maximum dose is up to 12 mg/day for non-EIAED subjects or up to 16 mg/day for EIAED subjects, except that subjects enrolled in Japan may not receive doses higher than 12 mg/day regardless of EIAED status. Addition, deletion, and dose changes to the concomitant AEDs are allowed during Extension Maintenance Period. Conversion to monotherapy on perampanel is also permitted at the discretion of the investigator, if it is considered appropriate to control the seizures.

The study Follow-up Visit should be conducted 4 weeks (±7 days) after the last dose of study drug for all subjects, except for subjects in Japan or in countries where an EAP cannot be implemented, who are entering into Extension B. (revised per Amendments 03 and 04)

Study Drug Supplies

Perampanel is a Schedule III Controlled Drug Substance in the US. Investigators in the US must have valid DEA registrations and adequate storage facilities to handle Schedule III controlled substances as required per DEA regulations. All shipments to US sites will comply with the DEA regulations.

Schedule of Procedures/Assessments

Table 5 presents the Schedule of Procedures/Assessments for the Extension A (up to 33 weeks). (revised per Amendments 02 and 03)

Table 5 Schedule of Procedures/Assessments in Study E2007-G000-311: Extension A (revised per Amendments 03 and 04)

Phase	Extension[a]					
Period	Maintenance			Follow-up[b]		
Visit	10[c]	11	12		Early Discontinuation	Unscheduled
Week	28	40	52	56		
Procedures/Assessments						
Prior/concomitant medication(s)	X	X	X	X	X	X
Prior/concomitant AED(s)	X	X	X	X	X	X
Neurological examination[d]				X		X
Physical examination[d]			X	X		X
Vitals[e] and weight[f]	X	X	X	X	X	X
Height[f]		X	X		X	
Adverse events	X	X	X	X	X	X
IxRS call	X	X		X	X	X
Study drug compliance	X	X	X		X	X
Dispense study drug	X	X				X[g]
Retrieve unused study drug	X	X	X		X	X[g]
Dispense subject's diary	X	X				X
Retrieve and review diary	X	X	X	X	X	X
Clinical laboratory tests[h]		X	X[i]		X	X[j]
Thyroid (TSH, fT3, fT4) and IGF-1 testing			X		X	
Urine pregnancy test[k]	X	X	X	X	X	X
C-SSRS[l]	X	X	X	X	X	X
12-lead ECG[m]			X		X	X[n]
EEG[o]			X		X	X[n]
Telephone call[p]	X	X	X			
ABNAS[q]			X		X	
Lafayette Grooved Pegboard Test			X		X	
CBCL			X		X	
EQ-5D-Y			X		X	
Clinical Global Impression			X		X	
Disposition			X		X	

ABNAS = A-B neuropsychological assessment schedule, AE = adverse event, AED(s) = antiepileptic drug(s), CBCL = Child Behavior Checklist, C-SSRS = Columbia-Suicide Severity Rating Scale, eCRF = electronic case report form, EQ-5D-Y = EuroQol 5 Dimensions-Youth, fT3 = free triiodothyronine, fT4 = free thyroxine, IGF-1 = insulin-like growth factor-1, IxRS = interactive and response system, QTc = corrected QT interval, TSH = thyroid-stimulating hormone.

a: All visits to be done within ±6 days of the schedule. (revised per Amendment 02)

b: Follow-up Visit should be conducted 4 weeks (±7 days) after the last dose of study drug for all subjects, except for those subjects entering into Extension B. (revised per Amendment 04) .

c: Subjects should roll-over into Extension A immediately after completion of the Treatment Phase of the Core Study. Additional assessments to be done for subjects who choose to roll-over into Extension A.

d: For any other clinic visits during the study, the physical and the neurological exams will only be performed when there is a complaint from the subject. Clinically significant abnormal findings from the physical or the neurological examinations will be reported as adverse events.

e: Blood pressure and pulse.

f: Weight and Height (without shoes) will be measured. Three measurements should be taken. Each measurement should be recorded as a separate entry on the Vital Sign eCRF.

g: Unused study drug to be retrieved and study drug dispensed only for subject requiring dose increases at Unscheduled Visits.

h: Clinical laboratory tests include hematology, blood chemistry including lipid panel, and urinalysis.

i: Clinical laboratory test will be collected under fasting conditions.

j: Performed if only an abnormality was noted at previous visit.

k: Female subjects age 8 years old and above, or of child-bearing potential, only.

l: Only for subjects aged 6 years and older at the time of consent/assent.

m: If during any visit the QTc was measured as greater than 450 ms, 3 consecutive ECGs separated by 5 to 10 minutes will be performed to confirm the abnormality.

n: During the unscheduled visits, ECG or EEG will only be done if the results from the previous visit were deemed clinically significant by the investigator.

o: EEG will be performed in awake and sleep state in all subjects.

p: Telephone interviews with the subjects and/or caregiver will be conducted 2 weeks (±3 days) after Visit 10 through 12, to ensure that subjects are completing their seizure diaries regularly and assess AEs, study drug compliance and concomitant medications, including AEDs. Subjects whose dose was decreased before the scheduled telephone interview will be strongly encouraged to return to the clinic (instead of the scheduled telephone interview) for further consultation with regard to study drug administration. The site will contact IxRS to receive further dispensing instructions. Subjects will then return for their regularly scheduled visits.

q: ABNAS to assess patient-perceived cognitive effects of AED treatment, measuring 5 aspects of cognitive function: fatigue, memory, concentration, motor speed, and reading, using a 4-point scale.

Statistical Analyses

Statistical analyses will be performed by the sponsor or designee after the study is completed, the database is locked and released, and a snapshot of the database is obtained and released. Analyses for regional submissions may be performed during the course of the study. (revised per Amendment 02) Statistical analyses will be performed using SAS software or other validated statistical software, as required. Details of the statistical analyses will be included in a separate SAP.

Analysis Sets

Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least one postdose safety assessment in Extension A. (revised per Amendment 03)

FAS is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose seizure measurement in Extension A. (revised per Amendment 03)

Efficacy Analyses

The percent change in seizure frequency per 28 days will be summarized using descriptive statistics (n, mean, median, minimum, and maximum) by age cohorts (4 to <7 years, ≥7 to <12 years), by disease cohorts (POS, PGTC, and GTC), and by the presence or absence of concomitant EIAED in the FAS.

The proportion of subjects who are seizure-free and the proportion of responders based on the decrease from baseline in 28-day seizure frequency of equal or greater than 25%, equal or greater than 50%, and equal or greater than 75% will be summarized using frequency count (number and percentage) by age cohorts (4 to <7 years, ≥7 to <12 years), by disease cohorts (POS, PGTC, and GTC), and by the presence or absence of concomitant EIAED in the FAS.

The CGIC will be summarized using frequency count (number and percentage) by age cohorts (4 to <7 years, ≥7 to <12 years), by disease cohorts (POS, PGTC, and GTC), and by the presence or absence of concomitant EIAED in the FAS.

Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data that will be evaluated include TEAEs, clinical laboratory parameters, vital signs, 12-lead ECG results, C-SSRS, growth parameters, CBCL, LGPT, and EEGs. Safety analyses will be performed similarly to the Core Study analyses and all analyses will be on the perampanel treatment duration (Core Study and Extension A). (revised per Amendment 03)

Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using MedDRA. Adverse events will be coded to the MedDRA (version 18.1 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary SOC are also captured in the database.

A TEAE is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

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

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

Adverse events will be summarized using the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with

TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (related or not related).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study treatment.

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

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT. A subject data listing of all SAEs will be provided.

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

The incidence of TEAEs of special interest defined by SMQs will also be summarized.

Laboratory Values

Laboratory results will be summarized using SI units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit using descriptive statistics. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a LNH classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. For each laboratory parameter, shift from baseline (LNH) to each postbaseline visit and at the end of treatment will be presented. Similar shift tables from baseline (LNH) to the highest/and lowest postbaseline value will also be presented

Appendix 3 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with TEMAVs. Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. The number and percentage of subjects with TEMAVs will be presented; each subject will be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable. Markedly abnormal laboratory values will be flagged in the subject data listings.

For ALT and AST analysis, the number of subjects with greater than 3 times, but less than 5 times the ULN and the number of subjects with greater than 5 times the ULN will be

summarized. For bilirubin, a summary of the number of subjects with serum concentrations greater than 2 times the ULN will be created.

Vital Signs

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

ECG

ECG parameters and changes from baseline will be presented by visit.

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

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTc Bazett and QTc Fridericia during the treatment period will be summarized. Clinically borderline or abnormal ECG results in QTc Bazett and QTc Fridericia will be categorized as follows:

Absolute QTc interval prolongation:

- QTc interval 430-450 ms
- QTc interval>450 ms
- QTc interval>500 ms

Change from baseline in QTc interval:

- QTC interval increases from baseline 30-60 ms
- QTC interval increases from baseline>60 ms

Other Safety Analyses

The change from baseline in ABNAS, CBCL, and LGPT will be summarized.

The change from baseline in growth (height, weight, thyroid, and IGF-1) will be summarized.

The change from baseline in EEG parameters and the frequency of EEG abnormalities will be summarized.

Proportion of subjects with any treatment-emergent report of suicidal ideation and behavior and intensity of these behaviors will be summarized.

Other Analyses

The change from baseline in EQ-5D-Y will be summarized by age and disease cohorts, and by the presence or absence of concomitant EIAED, using descriptive statistics.

Appendix 2 Extension Phase B (revised per Amendment 04)

Extension B is only for subjects in Japan or countries where an EAP cannot be implemented, after having completed Extension A. (revised per Amendments 03 and 04)

Study Design and Plan

Extension B will consist of a Treatment Period and a Follow-up Period (up to 4 weeks). Treatment will continue as long as clinically appropriate according to the judgment of the investigator. In Japan, treatment of subjects in the Extension B will be completed when the subject reaches 12 years of age or when perampanel is commercially available in Japan for treatment of POS in pediatric subjects (4 to less than 12 years of age). In countries where an EAP cannot be implemented, participation in Extension B will continue as long as clinically appropriate according to the judgment of the investigator, until the subject reaches 12 years of age or perampanel oral suspension is commercially available. (revised per Amendment 04)

Subjects eligible for Extension B shall be subjects in Japan or in countries where an EAP cannot be implemented, after having completed Extension A of this study, are less than 12 years of age at the time of entering Extension B, and who in the opinion of the investigator continue to benefit from treatment with perampanel. (revised per Amendment 04)

Subjects will enter Extension B with their optimal perampanel dose (ie, the same dose of perampanel that they were maintained on at the end of Extension A). During the course of the Extension B, doses of perampanel and concomitant AEDs can be adjusted (concomitant AEDs can be used in accordance with the approved dosage and indication) based on clinical judgment.

In Japan, the maximum dose of perampanel is 12 mg/day. (revised per Amendment 04)

In countries where an EAP cannot be implemented, the maximum dose of perampanel is 12 mg/day in subjects not taking any concomitant EIAEDs, or 16 mg/day in subjects taking a concomitant EIAED. (revised per Amendment 04)

Tolerability at a minimum perampanel dose of 2 mg/day is required to continue in the program. Subjects who do not tolerate the minimum perampanel dose of 2 mg/day during the study will be discontinued from the study. (revised per Amendment 04)

Conversion to monotherapy on perampanel is also permitted at the discretion of the investigator, if it is considered appropriate to control the seizures.

The visit intervals in Extension B will be every 12 weeks. All visits to be done within ±6 days of the schedule.

During Extension B, when a subject reaches 12 years of age, the subject would have to switch to the commercial perampanel product promptly, and an End of Study Visit should be conducted. If the subject does not switch to the commercial perampanel product promptly, study drug treatment will be discontinued. A Discontinuation Visit should be conducted, and a Follow-up Visit should be conducted 4 weeks (±7 days) later. (revised per Amendment 03)

In Japan, when perampanel is commercially available for treatment of POS in pediatric subjects (4 to less than 12 years of age), all subjects will have to switch to perampanel commercial product promptly, and an End of Study Visit should be conducted. If the subject does not switch to commercial product promptly, study drug treatment will be discontinued. A Discontinuation Visit should be conducted for that subject, and a Follow-up Visit should be conducted 4 weeks (±7 days) later. (revised per Amendments 03 and 04)

In countries where an EAP cannot be implemented, participation in Extension B will continue as long as clinically appropriate according to the judgment of the investigator, until the subject reaches 12 years of age or perampanel oral suspension is commercially available. (revised per Amendment 04)

The investigator may discontinue the subject from the study at any time for safety or administrative reasons. When the decision is made to discontinue to subject from the study, a Discontinuation Visit and a Follow-up Visit 4 weeks (±7 days) later should be conducted for that subject. (revised per Amendment 03)

Subjects who discontinue or choose not to switch to the commercial product, once perampanel is commercially available will require a Follow-up Visit which will be conducted 4 weeks (±7 days) after the Discontinuation Visit. (revised per Amendment 04)

Subjects who switch to the commercial product, once perampanel is commercially available will require an End of Study Visit. A Follow-up Visit will not be required for subjects who switched to the commercial product and attended an End of Study Visit. (revised per Amendment 04)

The sponsor reserves the right to terminate the program at any time.

Study Drug Supplies

Perampanel will be supplied as 0.5 mg/mL oral suspension.

Schedule of Procedures/Assessments

Table 6 presents the Schedule of Procedures/Assessments for the Extension B. During Extension B, laboratory tests will be performed by the local laboratory.

Assessments

Safety Assessments

Safety will be assessed by monitoring of AEs, withdrawal from treatment, clinical laboratory tests, vital signs, and weight.

Other Assessments

Concomitant medication usage will be monitored.

Statistical Analyses

Analysis Sets

Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment in Extension B.

Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data that will be evaluated include TEAEs, clinical laboratory parameters and vital signs.

Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using MedDRA. Adverse events will be coded to the MedDRA (version 18.1 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary SOC are also captured in the database.

A TEAE is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

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

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

Adverse events will be summarized using the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (related or not related).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study treatment.

Laboratory Values

Laboratory results will be summarized using SI units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on treatment value) will be summarized by visit using descriptive statistics. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Vital Signs

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

Table 6 Schedule of Procedures/Assessments in Study E2007-G000-311: Extension B (revised per Amendments 03 and 04

Phase	**Extension**					
Period	**Treatment**					
Visit/Timing	**At Initial Assessment[a] (Day 1, Week 1)**	**Scheduled Visit[b] (Every 12 weeks)**	**Unscheduled Visit[c]**	**End of Study**	**Discontinuation Visit[d]**	**Follow-Up[e] (4 Weeks After Discontinuation Visit)**
Procedures/Assessments						
Review risk/benefit of continued therapy with perampanel and verify age eligibility	X	X	X			
Concomitant medications and Concomitant AED(s)	X[f]	X	X	X	X	X
Study drug compliance	X[f]	X	X	X	X	
Vital signs	X[f]	X	X	X	X	X
Weight	X[f]	X	X[g]	X	X	X
Clinical laboratory evaluations	X[f]	X	X[g]	X	X	X
Urine pregnancy test[h]	X[f]	X	X[g]	X	X	X
Dispense study drug	X	X	X[i]			
Retrieve unused study drug		X	X[i]	X	X	
Adverse events	X[f]	X	X	X	X	X

AED = antiepileptic drug, POS = partial-onset seizures.

a: Perform on the final visit of Extension A Maintenance Period (ie, Visit 12).

b: Visit window ±6 days.

c: At the unscheduled visit, selected assessments will be performed based on investigator's judgment of subject's condition.

d: Once a subject reaches 12 years of age or perampanel is commercially available, the subject would have to switch to the commercial product promptly. If a subject does not switch to the commercial product promptly, a Discontinuation Visit and a Follow-up Visit 4 weeks (±7 days) later should be conducted for the subject.

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

Table 6 Schedule of Procedures/Assessments in Study E2007-G000-311: Extension B (revised per Amendments 03 and 04

Phase	Extension					
Period	Treatment					
Visit/Timing	At Initial Assessment[a] (Day 1, Week 1)	Scheduled Visit[b] (Every 12 weeks)	Unscheduled Visit[c]	End of Study	Discontinuation Visit[d]	Follow-Up[e] (4 Weeks After Discontinuation Visit)

f: Refer to the data recorded during the final visit of Extension A Maintenance Period (ie, Visit 12).

g: At the discretion of the investigator.

h: Female subjects age 8 years old and above, or of childbearing potential, only.

i: Dispense study drug or Retrieve unused study drug should be done, if necessary.

Appendix 3 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

Sponsor's Grading for Laboratory Values

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

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	E2007-G000-311
Study Protocol Title:	An Open-Label, Multicenter Study with an Extension Phase to Evaluate the Safety, Tolerability, and Exposure-Efficacy Relationship of Perampanel Oral Suspension when Administered as an Adjunctive Therapy in Pediatric Subjects (Age 4 to less than 12 years) with Inadequately Controlled Partial-Onset Seizures or Primary Generalized Tonic-Clonic Seizures
Investigational Product Name:	E2007/perampanel
IND Number:	112515
EudraCT Number:	2014-002167-16

SIGNATURES

Authors:

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INVESTIGATOR SIGNATURE PAGE

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Investigational Product Name:	E2007/perampanel
IND Number:	112515
EudraCT Number:	2014-002167-16

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with ICH and all applicable local GCP guidelines, including the Declaration of Helsinki.

<Name of institution>

Medical Institution

<Name, degree(s)>

Investigator	Signature	Date