REVISION HISTORY

Previous Protocol Version and Date: v5.0, 08 Jan 2020 **Current Protocol Version: v6.0 (Amendment 02)** **Date of Revisions: 09 Apr 2020**		
Change	**Rationale**	**Affected Protocol Section(s)**
For non-EIAED subjects, target perampanel dose is lowered to 4 mg/day. Depending upon individual clinical response and tolerability, non-EIAED subjects could still have their perampanel dose up-titrated to 6 mg/day. Clarified that the maximum dose allowed will not change.	To reflect European Medicines Agency/Paediatric Committee (EMA/PDCO) final opinion (EMEA-000467-PIP01-08-M13 PIP Modification) dated 18 MAR 2020.	• Synopsis – Study Design • Synopsis – Sample Size Rationale • Synopsis – Study Treatment(s) • Section 9.1.2.1 • Section 9.4.1 • Section 9.4.4 • Table 1
Clarified, in the text, the age range of study population	Editorial update for consistency with language in the final Paediatric Investigation Plan (PIP) PIP Modification #13	• Title Page • Synopsis – Study Protocol Title • Synopsis – Objectives • Synopsis – Study Design • Protocol Signature Page • Investigator Signature Page • Section 8.1 • Section 8.2 • Section 8.3
Updated the Protocol Signature Page	Study personnel change	• Protocol Signature Page

Previous Protocol Version and Date: v4.0, 07 Feb 2017 **Current Protocol Version: v5.0 (Amendment 02)** **Date of Revisions: 08 Jan 2020**		
Change	**Rationale**	**Affected Protocol Section(s)**
Added a cohort of subjects from 2 to less than 4 years of age and specified total number of subjects required when pooled across multiple studies Updated the relevant text throughout the protocol to reflect the inclusion of 2 to less than 4 years age cohort	To fulfill regulatory requirement	• Title Page • Synopsis – Study Protocol Title • Synopsis – Study Design • Synopsis – Objectives and Statistical Methods • Synopsis – Number of Subjects • Synopsis – Inclusion Criteria • Synopsis – Sample Size Rationale • Synopsis – Statistical Methods • Section 7 • Section 7.2 • Section 8.1 • Section 8.2 • Section 8.3 • Section 9.1 • Section 9.2 • Section 9.3 • Section 9.3.1 • Section 9.5.1.4 • Section 9.7.1.1 • Section 9.7.3 • Protocol Signature Page • Investigator Signature Page
Updated introduction	To update approved indications of Fycompa, and reflect academic/regulatory acceptance of adult-to-pediatric efficacy extrapolation in lieu of controlled clinical trials	• Section 7
Made editorial changes to study endpoints	For correctness	• Synopsis – Statistical Methods • Section 9.7.1.1
Increased overall study duration	To allow additional time for recruitment	• Synopsis – Study Period and Phase of Development

Previous Protocol Version and Date: v4.0, 07 Feb 2017 **Current Protocol Version: v5.0 (Amendment 02)** **Date of Revisions: 08 Jan 2020**		
Change	**Rationale**	**Affected Protocol Section(s)**
Deleted Clinical Global Impression of Severity (CGI-S) from exploratory objectives and endpoints	To correct error	• Synopsis – Exploratory objective • Section 8.3
Increased the allowed number of concomitant anti-epileptic drugs (AEDs) from 3 to 4	To reflect clinical reality that refractory patients are on more than 3 concomitant AEDs	• Synopsis – Study Design • Synopsis – Inclusion Criteria • Synopsis – Concomitant Drug/Therapy • Section 9.1 • Section 9.3.1 • Section 9.4.7
Lowered the target dose to 6 mg/day for non-enzyme-inducing anti-epileptic drug (non-EIAED) and to 8 mg/day for EIAED subjects Specified conditions for further up-titrations to maximum allowed doses up to 12 mg/day for non-EIAED and 16 mg/day for EIAED subjects	Precautionary measure to ensure subject's safety	• Synopsis – Study Design • Synopsis – Study Treatment(s) • Section 9.1.2.1 • Section 9.2 • Section 9.4.1 • Section 9.4.4 • Table 1 • Table 2
Updated the discussion of study design	To improve readability and clarity	• Section 9.2
Modified the period during which concomitant AED doses must have remained stable for eligibility determination	To minimize wait period while ensuring the adequate washout is achieved before initiating study treatment	• Synopsis – Inclusion Criteria • Section 9.3.1
Modified the period during which concomitant central nervous system (CNS) drugs must have remained stable, and specified that these drugs are prohibited throughout the course of the study	To minimize wait period, as applicable, while ensuring the adequate washout is achieved before initiating study treatment	• Synopsis – Exclusion Criteria • Synopsis – Concomitant Drug/Therapy • Section 9.3.2 • Section 9.4.7.2
Modified exclusion criterion related to prior or concomitant use of felbamate and vigabatrin and specified that these drugs are prohibited throughout the course of the study	For clarification	• Synopsis – Concomitant Drug/Therapy • Synopsis – Exclusion Criteria • Section 9.3.2 • Section 9.4.7.2

Previous Protocol Version and Date: v4.0, 07 Feb 2017 **Current Protocol Version: v5.0 (Amendment 02)** **Date of Revisions: 08 Jan 2020**		
Change	**Rationale**	**Affected Protocol Section(s)**
Modified the exclusion criterion related to prior use of perampanel	For clarification	• Synopsis – Exclusion Criteria • Section 9.3.2
Specified that concomitant use of cannabidiol (CBD) products is allowed	For clarification	• Synopsis – Concomitant Drug/Therapy • Section 9.4.7
Modified concomitant therapy section to allow dose adjustments of concomitant AEDs (non-enzyme inducing AEDs only) during the Core study. AED addition or deletion will remain prohibited during the Core Study.	To reflect clinical practice in the management of patients with epilepsy.	• Synopsis – Concomitant Drug/Therapy • Section 9.4.7
Specified that the subjects who immediately switch to commercially available perampanel after the last dose of study drug at the end of Core Study or Extension Phase need not undergo Follow-up Period/Visit	For clarification	• Synopsis – Study Design • Synopsis – Study Treatment(s) • Synopsis – Duration of Treatment • Section 9.1 • Section 9.1.2 • Section 9.1.2.3 • Section 9.4.1 • Table 4 • Table 5 • Table 6 • Table 7 • Appendix 3
Added description of sample size calculations for the 2 to less than 4 years of age group	To provide rationale for sample size	• Synopsis – Sample Size Rationale • Section 9.7.2
Lipid and blood glucose tests are to be collected under fasting conditions, whenever practically feasible, at all-time points	Mandatory fasting may not be practical in particular in pediatric subjects	• Table 4 footnote • Table 5 footnote • Table 6 footnote • Table 7 footnote
Clarified baseline seizure frequency data for efficacy endpoint analyses	For clarification	• Synopsis – Statistical Methods • Section 9.7.1.1 • Section 9.7.1.6 • Appendix 3

Previous Protocol Version and Date: v4.0, 07 Feb 2017 **Current Protocol Version: v5.0 (Amendment 02)** **Date of Revisions: 08 Jan 2020**		
Change	**Rationale**	**Affected Protocol Section(s)**
Added early pharmacokinetic (PK) sampling time points at predose and 1 to 5 hours postdose for subjects of 2 to less than 4 years of age and adjusted dosing instructions around PK visits during Maintenance Period. Also updated total blood volumes to be taken as applicable	To support characterization of perampanel PK, especially during absorption and early distribution phases	• Synopsis –Assessments • Section 9.5.1.4 • Table 4 • Table 5 • Appendix 2
Added a statement that the dose-normalized derived exposure parameters will be summarized for age groups	For clarification	• Synopsis – Statistical Methods • Section 9.7.1.7
Updated the PROTOCOL SIGNATURE PAGE	Added current study director, medical monitor, study statistician, and clinical pharmacologist	• PROTOCOL SIGNATURE PAGE

Previous Protocol Version and Date: v3.0, 12 May 2016 **Current Protocol Version: v4.0 (Amendment 01)** **Date of Revisions: 07 Feb 2017**		
Change	**Rationale**	**Affected Protocol Section(s)**
Changed the gestational age from 41 to 36 weeks in inclusion criterion 1	Correction	• Synopsis – Inclusion Criteria • Section 9.3.1
Removed 4-week time frame of last seizure occurrence prior to Visit 1 from inclusion criterion 5	Changed to increase enrolment	• Synopsis – Inclusion Criteria • Section 9.3.1
Changed seizure surgery restriction from "before Visit 1" to "within 1 year of Visit 1" in exclusion criterion 4	Changed to increase enrolment	• Synopsis – Exclusion Criteria • Section 9.3.2
Updated the PROTOCOL SIGNATURE PAGE	Added current statistician and study director	• PROTOCOL SIGNATURE PAGE

Previous Protocol Version and Date: v2.0, 06 Nov 2015 **Current Protocol Version: v3.0** **Date of Revisions: 12 May 2016**		
Change	**Rationale**	**Affected Protocol Section(s)**
Specify that perampanel oral suspension is an adjunctive therapy	For accuracy	• Synopsis – Objectives • Section 8.2 • Section 8.3
Revise planned number of subjects in specified age categories	Per approved PIP, to ensure adequate representation of all relevant age groups	• Synopsis – Study Design • Synopsis -- Number of Subjects • Section 9.1 • Section 9.2 • Section 9.3
Allow for possible sample size increase from 16 to 24 subjects	To ensure adequate evaluable PK data	• Synopsis—Study Design • Synopsis – Statistical Methods • Section 9.4.1 • Section 9.7.2
Revise duration of access to oral suspension to allow for duration of study treatment beyond 52 week	For flexibility	• Synopsis, Study Design • Section 9.1
Clarify that dosing will occur before bedtime	For consistency of dose administration across subjects	• Synopsis – Study Treatment(s) • Section 9.4.5
Specify that MTD will be based on individual tolerability	For safety of subjects	• Synopsis—Study Treatment(s)
Re-word safety endpoint	Per approved PIP	• Synopsis – Statistical Methods
Add Clinical Global Impression (CGI) to assessments	As advised by PDCO	• Synopsis – Statistical Methods • Synopsis -- Objectives • Section 8.3 • Section 9.5.1.3 • Table 4 • Table 5 • Section 9.7.1.1 • Section 9.7.1.6 • Appendix 3 • Table 6 • Table 7
Specify intrinsic and extrinsic factors to be used for population PK analyses	As advised by PDCO	• Synopsis – Statistical Methods • Section 9.7.1.7

Provide further details of population PK analysis including 2-compartment PK model	As advised by PDCO	• Synopsis – Statistical Methods • Section 9.7.1.7
Add SAE to safety assessments	For consistency	• Synopsis – Statistical Methods
Clarify that PK comparisons will include adult subjects	For consistency	• Synopsis – Statistical Methods • Section 9.7.2
Delete IxRS from description of study procedures	The IxRS is not needed for this study.	• Section 4 • Section 9.4.2 • Table 4 • Table 5 • Section 11.3 • Appendix 3 • Table 6 • Table 7
Delete description of titration to higher doses in EIAED subjects	For consistency with study plan.	• Table 1 • Table 2
Delete statement that a pharmacy manual will be provided	There will be no pharmacy manual. Instructions will be sent to the study site.	• Section 9.4.2 • Appendix 3
Delete band from laboratory tests to be conducted	It is considered unnecessary to include this laboratory test.	• Table 3
Change visit window to ±6 instead of ±7 days	Ensure that the shelf life of the investigational product is not exceeded.	• Section 9.3.3 • Section 9.5.5 • Table 4 • Table 5 • Table 6 • Table 7
Modify abnormal QTcF criteria	For clarity and consistency	Section 9.7.1.8 Appendix 3
Editorial and formatting corrections	For consistency and quality	Various locations

Previous Protocol Version and Date: v1.0, 28 Apr 2014 **Current Protocol Version: v2.0** **Date of Revisions: 06 Nov 2015**		
Change	**Rationale**	**Affected Protocol Section(s)**
Revised dosing schedule to flat dosing, at a starting dose of 0.5 mg/day, and to allow for titrations up to 12 mg/day for non-EIAED subjects and 16 mg/day for EIAED subjects	As supported by the Study 232 PK and safety data	• Synopsis – ◦ Study Design ◦ Study Treatments ◦ Duration of Treatment ◦ Sample Size Rationale • Section 9.1 • Section 9.1.2 • Section 9.2 • Figure 1 • Section 9.1.2.1 • Section 9.4.1 • Table 1, Table 2 • Table 4 • Table 5 • Appendix 3
Updated information for relevant studies of perampanel (ie, Study 048, Study 235 and Study 232)	To provide current study status, information on the bioavailability of the oral suspension, outcome of pharmacokinetic analyses, and the supporting rationale for dosing in Study 238	• Section 7.1 • Section 7.2 • Section 9.4.4 • Section 9.7.2
Revised testing for glucose and lipid panel to require fasting at baseline and end of treatment or early termination	In response to FDA request per persistent signal for weight gain and elevated triglycerides	• Table 3, Table 4, and Table 5 • Appendix 3
Revised how investigational product will be provided to the sites and subjects	Due to flat dosing,	• Section 9.4.2 • Appendix 3
Removed the requirement for the CGI-C assessment	Due to the small n in this study and the fact that this assessment has not demonstrated meaningful results in prior studies	• Synopsis – Assessments • Synopsis – Statistical Methods • Section 9.5.1.3 • Table 4 • Section 9.7.1.1 • Section 9.7.1.8 • Section 10 • Appendix 3

Previous Protocol Version and Date: v1.0, 28 Apr 2014 **Current Protocol Version: v2.0** **Date of Revisions: 06 Nov 2015**		
Change	**Rationale**	**Affected Protocol Section(s)**
Revised number of expected sites for participation	Based upon preliminary feasibility	• Synopsis – Sites • Section 6 • Section 9.3
Updated various components of statistical analysis, and the standard safety reporting language, and corrected formatting and general inconsistencies	To comply with the current Eisai template for protocols, the Eisai Style Guide, and for general consistency throughout the protocol	• Various

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2007-G000-238
Study Protocol Title:	An Open-Label Study With an Extension Phase to Evaluate the Pharmacokinetics of Perampanel (E2007) Oral Suspension When Given as an Adjunctive Therapy in Subjects From 1 Month to Less Than 4 Years of Age With Epilepsy (revised per Amendment 02)
Sponsor:	Eisai Inc. 155 Tice Boulevard Woodcliff Lake, New Jersey 07677 US Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK
Investigational Product Name:	Perampanel
Indication:	Epilepsy
Phase:	2
Approval Date:	v1.0 28 Apr 2014 v2.0 06 Nov 2015 v3.0 12 May 2016 v4.0 07 Feb 2017 (Amendment 01) v5.0 08 Jan 2020 (Amendment 02) v6.0 09 Apr 2020
IND Number:	112515
EudraCT Number:	2013-005391-17
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.

E2007 (perampanel)

Name of Active Ingredient

2-(2-Oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl) benzonitrile hydrate 4:3

Study Protocol Title

An Open-Label Study With an Extension Phase to Evaluate the Pharmacokinetics of Perampanel (E2007) Oral Suspension When Given as an Adjunctive Therapy in Subjects From 1 Month to Less Than 4 Years of Age With Epilepsy (revised per Amendment 02)

Sites

Approximately 15 sites in North America (NA) and the European Union (EU)

Study Period and Phase of Development

Total study duration: Approximately 56 months (revised per Amendment 02)

Phase 2

Objectives

Primary Objective

- To evaluate the pharmacokinetics (PK) of perampanel during the Maintenance Period of the Core Study following oral suspension administration given as an adjunctive therapy in pediatric subjects from 1 month to less than 4 years of age with epilepsy (revised per Amendment 02)

Secondary Objectives

- To evaluate the short- and long-term safety and tolerability of perampanel oral suspension given as an adjunctive therapy in subjects from 1 month to less than 4 years of age with epilepsy (revised per Amendment 02)
- To evaluate the long-term effect of perampanel oral suspension, given as an adjunctive therapy, on growth from baseline to end of treatment in pediatric subjects from 1 month to less than 4 years of age with epilepsy (revised per Amendment 02)

Exploratory Objective

- To explore the short- and long-term efficacy of perampanel oral suspension given as an adjunctive therapy in subjects from 1month to less than 4 years of age with epilepsy as assessed by: (revised per Amendment 02)
  - Percent change in 28-day seizure frequency during the Titration + Maintenance Periods compared to baseline and during the Extension Phase compared to baseline
  - Proportion of subjects with a 50% decrease in 28-day seizure frequency during the Maintenance Period compared to baseline and during the Extension Phase compared to baseline
  - Proportion of subjects who are seizure-free during the Maintenance Period and during the Extension Phase
  - Clinical Global Impression (CGI) of change (CGI-C) (revised per Amendment 02)

Study Design

This will be a multicenter, open-label study with an extension phase that will enroll 16 to 24 pediatric subjects 1 to less than 24 months of age and at least to a maximum of 26 pediatric subjects from 2 to less than 4 years of age with epilepsy. (revised per Amendment 02)

All subjects must be taking 1 to a maximum of 4 anti-epileptic drugs (AEDs) to participate in the study. For at least 6 but not more than 8 of the subjects in the age group of 1 to less than 24 months and for 13 subjects in the age group of 2 to less than 4 years (across studies), only 1 enzyme-inducing AED (ie, EIAEDs; carbamazepine [CBZ], oxcarbazepine [OXC], phenytoin [PHT], or eslicarbazepine [ESL]) out of the maximum of 4 AEDs will be allowed. These subjects will be referred to as EIAED subjects. The remaining subjects cannot be taking any EIAEDs and will be referred to as non-EIAED subjects. (revised per Amendment 02)

For the age group of 1 to less than 24 months, the Sponsor will ensure a reasonable representation of subject age (ie, at least 6 subjects in the age range ≥1 to ≤6 months, at least 5 subjects in the age range >6 to ≤12 months, at least 5 subjects in the age range >12 to <24 months). (revised per Amendment 02)

For the age group of 2 to less than 4 years, the required number of subjects (total of 26) can be pooled across multiple studies for PK and safety assessments. Therefore, the target number of subjects to be enrolled in this age group ranges from a minimum of 1 to a maximum of 26 subjects. Enrollment of subjects aged 2 to less than 4 years into this study may be stopped upon notification of sponsor when the total number has been reached across clinical studies, or when enrollment in the 1 to less than 24 months age group in this study has completed (ie, the original purpose of this study has been met). (revised per Amendment 02)

This study will consist of 3 phases: Pretreatment and Treatment (Core Study), and Extension. The Pretreatment Phase will last up to 2 weeks, during which subjects will be assessed for their eligibility to participate in the study. The Treatment Phase will consist of 3 periods: Titration (12-16 weeks), Maintenance (4 weeks), and Follow-up (4 weeks; only for those subjects who complete the Maintenance Period but do not continue into the Extension Phase). The Extension Phase will consist of 2 periods: Maintenance (32-36 weeks) and Follow-up (4 weeks). (revised per Amendment 02)

The maximum total duration of treatment for each subject will be 52 weeks and the maximum total duration of the study for each subject will be 58 weeks (2 weeks Pretreatment+52 weeks of treatment+4 weeks Follow-up). (revised per Amendment 02)

Subjects who complete the Extension Phase and who, in the opinion of the investigator, will likely continue to demonstrate a positive benefit-to-risk ratio from treatment with perampanel may be enrolled into an extended access program (EAP) for perampanel if EAP is implemented for this age group in the country where the subject resides. (revised per Amendment 02)

Pretreatment Phase (Core Study)

At the first visit of the Pretreatment Phase, 4 weeks of prescreening (ie, before Visit 1) seizure frequency data will be collected for each subject as part of their medical history. Upon successful completion of the Pretreatment Phase, eligible subjects will enter the Treatment Phase.

Treatment Phase (Core Study)

During the Treatment Phase, subjects will be dosed with perampanel oral suspension as follows:

- *Titration Period:* Subjects will start perampanel treatment at a dose of 0.50 mg/day and follow dose titration schemes up to 4 mg/day (non-EIAED subjects) or 8 mg/day (EIAED subjects). Depending on individual subject's clinical response and tolerability, non-EIAED subjects could still have the perampanel dose up-titrated to 6 mg/day. Perampanel dose should not be further up-titrated beyond 6 mg/day (non-EIAED subjects) or 8 mg/day (EIAED subjects) unless there is a medical need (for example, a subject who tolerated perampanel well but have not reached optimal seizure control). Before dose up-titrations beyond 6 mg/day (non-EIAED subjects) or 8 mg/day (EIAED subjects) and whenever practically feasible, it is recommended to take a blood sample for the measurement of plasma perampanel level as a precautionary measure. The date and time of the last perampanel dose

administration, as well as the date and time of PK blood draw, for these unscheduled PK sample collection will be recorded. Up-titrations of perampanel dose within the range of 0.5 to 6 mg/day will be at 1-week intervals; and at doses greater than 6 mg/day will be at 2-week intervals (see Study Treatment(s) section). Dose titrations must not exceed 12 mg/day (non-EIAED subjects) or 16 mg/day (EIAED subjects). The decision to up-titrate perampanel dose will be at the investigator's discretion, based on individual subject's clinical response and/or tolerability to achieve optimal dose for a given subject. Once the optimal dose has been achieved, the subject's dose will be maintained stable for the remaining Titration Period or at least 2 weeks before entering the Maintenance Period. (revised per Amendment 02)

- *Maintenance Period:* During the Maintenance Period, subjects will continue taking perampanel oral suspension at the dose level they achieved at the end of the Titration Period. The maximum total daily dose a subject will be allowed is 12 mg for non-EIAED subjects and 16 mg for EIAED subjects. (revised per Amendment 02)
- *Follow-Up Period:* Subjects will not receive study drug during this period. Subjects who do not continue into the Extension Phase after completing the Maintenance Period, or those who discontinue early from the study will be required to complete the Follow-up Period after their last dose in the Treatment Phase. Subjects who switch to commercially available perampanel or who enter into EAP upon completion of study treatment need not to undergo Follow-up Visit; however, sites will conduct a telephone contact 28 (+6) days after the last dose of study drug to follow adverse events (AEs) and report any serious adverse events (SAEs) that occur within 28 days of the last study drug administration. (revised per Amendment 02)

After every 4th subject in the age group 1 to less than 24 months completes the Maintenance Period, an interim analysis (safety, tolerability, and PK) will be conducted whereby dose-normalized exposure will be compared to that observed in other studies in subjects between ≥2 and <18 years of age. If the exposure of the subjects is significantly different from that observed in subjects ages ≥2 to <12 years from other clinical studies or that are predicted from PK modeling and simulation, or if non-linear PK is observed, the sample size will be increased to at least 24 subjects with evaluable PK data, and the target dose or dosing regimen of those subjects may be modified via protocol amendment, depending on the PK of the previous subjects. PK data collected in older age cohort (2 to less than 4 years) will also be examined in the interim PK analyses. (revised per Amendment 02)

Preliminary PK analysis was performed based on data obtained from 7 subjects (>6 to <24 months of age; 6 subjects without concomitant EIAED and 1 subject on concomitant EIAED) in this study and pooled with existing data from 2336 subjects (aged 2 to 77 years). Preliminary PK findings suggest that oral clearance in subjects aged less than 24 months without concomitant EIAED appears to be approximately 40% of that in subjects aged ≥ 2 years. It is predicted that a daily dose of 6 mg or 8 mg in subjects aged less than 24 months without or with concomitant EIAED, respectively, will result in comparable exposure to that in subjects aged >2 years receiving a daily dose of 12 mg (non-EIAED subjects) or 16 mg (EIAED subjects), respectively. However, European Medicines Agency/Paediatric Committee (EMA/PDCO) recommended that perampanel dose should be titrated up to a target dose of 4 mg/day for non-EIAED subjects (EMEA-000467-PIP01-08-M13), which could be further titrated up to 6 mg/day depending on individual subject's clinical response and tolerability. Therefore, the target dose in this study is revised to 4 mg/day (non-EIAED subjects) and 8 mg/day (EIAED subjects) in subjects less than 24 months of age, while the maximum dose allowed remains as 12 mg/day and 16 mg/day for non-EIAED and EIAED subjects, respectively. (revised per Amendment 02)

In subjects 2 to less than 4 years of age, there were very limited PK data (n=4) to allow adequate evaluation of effect of age on perampanel PK. Therefore, the same target dose and dose titration approach will be followed for non-EIAED and EIAED subjects aged 2 to less than 4 years as described above for 1 to less than 24 months subjects. (revised per Amendment 02)

Extension Phase

Subjects who have completed the last visit of the Core Study Maintenance Period will be eligible to participate in the Extension Phase of this study. For these subjects, the last visit of the Maintenance Period in the Treatment

Phase will be considered the first visit of the Extension Phase.

- *Maintenance Period:* Subjects will continue taking perampanel oral suspension, at the dose level achieved at the end of the Treatment Phase. The maximum total daily dose a subject will be allowed is 12 mg for non-EIAED subjects or 16 mg for EIAED subjects.
- *Follow-Up Period:* No study drug will be administered during Follow-up Period. All subjects will be required to complete the Follow-up Period after their last dose in the Extension Phase, except for subjects who switch to commercially available perampanel or who enter into EAP upon completion of study treatment. For these subjects, sites will conduct a telephone contact 28 (+6) days after the last dose of study drug to follow AEs and report any SAEs that occur within 28 days of the last study drug administration. (revised per Amendment 02)

Data Monitoring Committee

An independent data monitoring committee (DMC) will be constructed to monitor the safety data of this study.

Number of Subjects

1 month to <24 months of age: At least 16 subjects with evaluable PK data, of which at least 6 subjects are in the age range ≥1 to ≤6 months, at least 5 subjects are in the age range >6 to ≤12 months, and at least 5 subjects are in the age range >12 to <24 months. The target number of subjects with EIAED are at least 6 but not more than 8 subjects across these 3 age subgroups. (revised per Amendment 02)

2 years to <4 years of age: A total of 26 subjects (13 EIAED and 13 non-EIAED) to be enrolled and pooled across clinical studies of perampanel with PK data. Therefore, the target number of subjects to be enrolled in this age group in this study ranges from a minimum of 1 to a maximum of 26 subjects. (revised per Amendment 02)

Inclusion Criteria

Pretreatment and Treatment Phases (Core Study)

1. Male or female, from 1 month to less than 4 years of age (and of at least 36 weeks gestational age) at the time of consent (revised per Amendments 01 and 02)
2. Have a minimum weight of 4 kg (8.8 lb)
3. Have a diagnosis of epilepsy with any type of seizure according to the International League Against Epilepsy's (ILAE) Classification of Epileptic Seizures (1981). Diagnosis should have been established at least 2 weeks (≤6 months of age) or 4 weeks (> 6 months of age) before Visit 1, by clinical history and an electroencephalogram (EEG) that is consistent with epilepsy; normal interictal EEGs will be allowed provided that the subject meets the other diagnosis criterion (ie, clinical history)
4. Have had brain imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) before Visit 1 that ruled out a progressive cause of epilepsy
5. Have had 1 or more seizure(s) before Visit 1 (revised per Amendment 01)
6. Are currently being treated with a stable dose (ie, unchanged for at least 5 half-lives) of 1 to a maximum of 4 AEDs. (At least 6, but not more than 8 subjects, in the age group of 1 to less than 24 months, and up to 13 subjects in the age group of 2 to less than 4 years, will be taking 1 enzyme-inducing AED [ie, EIAEDs; CBZ, OXC, PHT, or ESL] out of the maximum of 4 AEDs allowed. The remaining subjects cannot be taking any EIAEDs.) (revised per Amendment 02)
7. Have been on their current concomitant AED(s) with a stable dose for at least 2 weeks or 5 half-lives, whichever is longer, before Visit 1 (revised per Amendment 02)
8. Must have discontinued all restricted medications (eg, medications known to be inducers of cytochrome P450 3A) at least 2 weeks or 5 half-lives (whichever is longer) before Visit 1 (revised per Amendment 02)

Extension Phase

1. Have completed the last visit of the Maintenance Period of the Core Study

Exclusion Criteria

Pretreatment and Treatment Phases (Core Study)

1. Have a history of status epilepticus that required hospitalization during the 3 months before Visit 1
2. Have seizures due to treatable medical conditions, such as those arising due to metabolic disturbances, toxic exposure, or an active infection
3. Have epilepsy secondary to progressive central nervous system (CNS) disease or any other progressive neurodegenerative disease, including tumors
4. Have had epilepsy surgery within 1 year of Visit 1 (revised per Amendment 01)
5. Are scheduled and/or confirmed to have epilepsy surgery within 6 months after Visit 1
6. Used intermittent rescue benzodiazepines (ie, 1 to 2 doses over a 24-hour period considered one-time rescue) 2 or more times in the 2 weeks before Visit 1
7. Current use of felbamate, or any evidence of ongoing hepatic or bone marrow dysfunction associated with prior felbamate treatment. (Prior use of felbamate must be discontinued at least 8 weeks before Visit 1.) (revised per Amendment 02)
8. Current use of vigabatrin or any evidence of clinically significant vision abnormality associated with prior vigabatrin treatment. (Prior use of vigabatrin must be discontinued at least 2 weeks before Visit 1.) (revised per Amendment 02)
9. On ketogenic diet regimen that has not been stable for at least 4 weeks before Visit 1
10. Concomitant use of other drugs known to influence the CNS (other than AEDs for epilepsy), where the dose has not been stabilized for at least 5 half-lives or 2 weeks, whichever is longer, before Visit 1 (revised per Amendment 02)
11. Have any concomitant illnesses/co-morbidities that could severely affect the subject's safety or study conduct
12. Have 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 study conduct
13. Have clinically significant laboratory abnormalities or any clinically acute or chronic disease
14. Have 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 ULN
15. Have clinical evidence of significant active hematological disease; WBC count $\leq$2500/µL (2.50 x 10^9/L) or an absolute neutrophil count $\leq$1000/µL (1.00 x 10^9/L)
16. Have conditions that may interfere with their participation in the study and/or with the PK of study drug
17. 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
18. Have recently (within 30 days before Visit 1) been exposed to perampanel in a clinical study or by prescription, and/or previous discontinuation from perampanel treatment due to adverse events related to perampanel (revised per Amendment 02)
19. Have a clinically significant electrocardiogram (ECG) abnormality, including prolonged corrected QT interval (QTc) defined as > 450 msec
20. Have had multiple drug allergies or a severe drug reaction to an AED(s), including dermatological (eg, Stevens-Johnson syndrome), hematological, or organ toxicity reactions

Study Treatment(s)

Test drug

Perampanel will be provided as 0.5 mg/mL oral suspension stock. Dosing should occur once daily before bedtime in the evening, unless otherwise specified.

Study treatments are to be administered as follows:

Pretreatment and Treatment Phase (Core Study)

Pretreatment Phase: Subjects will not receive study drug during this phase.

Treatment Phase:

- Titration Period (12-16 weeks): Subjects will start perampanel treatment at a dose of 0.50 mg/day and follow dose titration schemes up to 4 mg/day (non-EIAED subjects) or 8 mg/day (EIAED subjects). Depending on individual subject's clinical response and tolerability, non-EIAED subjects could still have the perampanel dose up-titrated to 6 mg/day. Perampanel dose should not be further up-titrated beyond 6 mg/day (non-EIAED subjects) or 8 mg/day (EIAED subjects) unless there is a medical need (for example, a subject who tolerated perampanel well but have not reached optimal seizure control). Before dose up-titrations beyond 6 mg/day (non-EIAED subjects) or 8 mg/day (EIAED subjects) and whenever practically feasible, it is recommended to take a blood sample for the measurement of plasma perampanel level as a precautionary measure. The date and time of the last perampanel dose administration, as well as the date and time of PK blood draw, for these unscheduled PK sample collection will be recorded. Up-titrations of perampanel dose within the range of 0.5 to 6 mg/day will be at 1-week intervals; and at doses greater than 6 mg/day will be at 2-week intervals (see Study Treatment(s) section) Dose titrations must not exceed 12 mg/day (non-EIAED subjects) or 16 mg/day (EIAED subjects)). The decision to up-titrate perampanel dose will be at the investigator's discretion, based on individual subject's clinical response and/or tolerability to achieve optimal dose for a given subject. Once the optimal dose has been achieved, the subject's dose will be maintained stable for the remaining Titration Period or at least 2 weeks before entering the Maintenance Period. (revised per Amendment 02)

  According to the investigator's clinical judgment subjects experiencing intolerability at any dose may remain at the same dose or have their dose decreased one 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 must be done at the next clinic visit after the investigator has deemed it is appropriate in view of the resolution of the AE(s). Multiple dose adjustments will be allowed during the Titration Period. Every effort should be made to have subjects achieve their optimal dose, not to exceed a maximum dose of 12 mg/day (non-EIAED subjects) or 16 mg/day (EIAED subjects) during the Titration Period. (revised per Amendment 02)

- Maintenance Period (4 weeks): During this period, subjects will continue taking perampanel oral suspension at the dose level they achieved at the end of the Titration Period.

  Adjustment of the dose level during the Maintenance Period should be discouraged; however, according to the investigator's clinical judgment, subjects experiencing intolerable AE(s) will be allowed to have their dose decreased to the previously tolerated dose. During the Maintenance Period, subjects whose dose has been decreased cannot have their dose increased again. A subject may not decrease their dose more than once during Maintenance Period unless there is a significant medical reason and with approval from the Medical Monitor.

  During the entire Titration and Maintenance Periods, all dose adjustments will be done via 1 dose titration level up or down (relevant to where the subject is within the study). Subjects who do not tolerate a dose of 0.50 mg/day will be discontinued from the study. The maximum total daily dose a subject will be allowed is 12 mg (non-EIAED subjects) or 16 mg (EIAED subjects).

Dosing Modifications

After every 4th subject in the age group 1 to less than 24 months completes the Maintenance Period, an interim analysis (safety, tolerability, and PK) will be conducted and reviewed by the Eisai study team to decide if dosing modifications are required for additional subjects who enroll in the study. If the exposure of the subjects is significantly different from that observed in subjects ages ≥2 to <12 years from other clinical studies or that are predicted from PK modeling and simulation, or if non-linear PK is observed, the target dose or dosing regimen of those subjects may be modified via a protocol amendment, depending on the PK of the previous subjects. PK data collected in older age cohort (2 to less than 4 years) will also be examined in the interim PK analyses. (revised per Amendment 02)

- Follow-Up Period (4 weeks): Subjects will not receive study drug during this period.

Subjects Not Receiving Concomitant EIAEDs (ie, non-EIAED Subjects) (revised per Amendment 02)

For all non-EIAED subjects (up to 6 mg/day):

Treatment Phase/Titration Period	Visit	Daily Dose
Week 0 (starting dose)	Visit 2	0.50 mg
Week 1 (Titration #1)	-	1 mg
Week 2 (Titration #2)	Visit 3	2 mg
Week 3 (Titration #3)	-	4 mg[a]
Week 4 (Titration #4)	Visit 4	6 mg[b]
For non-EIAED subjects who may require further up-titrations of perampanel doses[c]:		
Week 6 (Titration #5)	-	8 mg[d]
Week 8 (Titration #6)	Visit 5	10 mg
Week 10 (Titration #7)	-	12 mg
Week 12 (no titration)	Visit 6	Last dose achieved at Week 10[d]
Treatment Phase/Maintenance Period	Last dose achieved in the Titration Period	

a. Subjects who have shown good clinical response and tolerability at perampanel daily dosing of up to 4 mg will continue to receive the same dose throughout the remaining of Titration Period. (revised per Amendment 02)

b. Up-titration to 6 mg/day in non-EIAED subjects will be allowed if a higher dose (6 mg/day) is deemed by the investigator to provide a better clinical benefit and provided that the subject tolerates perampanel well. Subjects who have shown good clinical response and tolerability at perampanel 6 mg/day will continue to receive the same dose throughout the remaining of the Titration Period. (revised per Amendment 02)

c. At the discretion of the investigator; only if medically necessary (eg, inadequate seizure control) and provided that the subject has shown good tolerability at 6 mg/day. (revised per Amendment 02)

d. Site to contact the parent/guardian during the scheduled telephone interview approximately midpoint between Visit 4 and Visit 5 to assess if further dose titration (to 8 mg/day) is medically necessary. The subject must return to the clinic for an unscheduled visit for any dose increase. (revised per Amendment 02)

e. Visit is considered the end of the Titration Period and start of the Maintenance Period.

Subjects Receiving Concomitant EIAEDs (ie, EIAED Subjects) (revised per Amendment 02)

Treatment Phase/Titration Period	Visit	Daily Dose
For all EIAED subjects (up to 8 mg/day)		
Week 0 (starting dose)	Visit 2	0.50 mg
Week 1 (Titration #1)	-	1 mg
Week 2 (Titration #2)	Visit 3	2 mg
Week 3 (Titration #3)	-	4 mg
Week 4 (Titration #4)	Visit 4	6 mg
Week 6 (Titration #5)	-	8 mg[a]
For EIAED subjects who may require further titrations of perampanel:[b]		
Week 8 (Titration #6)	Visit 5	10 mg
Week 10 (Titration #7)	-	12 mg
Week 12 (Titration #8)	Visit 6	14 mg
Week 14 (Titration #9)	-	16 mg
Week 16 (no titration)	Visit 7	Last dose achieved at Week 14[c]
Treatment Phase/Maintenance Period	Last dose achieved in the Titration Period	

a. Subjects who have shown good clinical response and tolerability at perampanel daily dosing of up to 8 mg will continue to receive the same dose throughout the remaining of Titration Period. (revised per Amendment 02)

b. At the discretion of the investigator; only if medically necessary (eg, inadequate seizure control) and provided that the subject has shown good tolerability at 8 mg/day. (revised per Amendment 02)

c. Visit is considered the end of the Titration Period and start of the Maintenance Period.

Extension Phase

- Maintenance Period (32-36 weeks): Subjects will continue taking perampanel oral suspension, at the dose level achieved at the end of the Treatment Phase. The maximum total daily dose a subject will be allowed is 12 mg (non-EIAED subjects) or 16 mg (EIAED subjects) .

  Dose adjustment during this phase is allowed if necessary, per the investigator's clinical judgment. Subjects must return to the clinic for an unscheduled visit for any dose increase. However, dose decreases can be done via telephone.

  All dose adjustments during this phase will be done by going one dose level up or down. Subjects who do not tolerate a dose of 0.50 mg/day will be discontinued from the study.

- Follow-Up Period (4 weeks): Subjects will not receive study drug during this period.

Comparator Drug (if applicable)

Not applicable.

Duration of Treatment

The maximum total duration of treatment for each subject will be 52 weeks and the maximum total duration of the study for each subject will be 58 weeks (52 weeks treatment + 2 weeks Pretreatment+ 4 week Follow-up).

- **Pretreatment Phase (Core Study):** up to 2 weeks
- **Treatment Phase (Core Study):** 16 to 20 weeks (12-16-week Titration + 4-week Maintenance) + 4-week Follow-Up for those not entering the Extension Phase, those who discontinue early from the study, or those who do not switch to commercially available perampanel or enter into EAP after study completion (revised per Amendment 02)
- **Extension Phase:** 36 to 40 weeks (32-36-week Maintenance + 4-week Follow-up)

Concomitant Drug/Therapy

Subjects will be taking 1 to a maximum of 4 marketed AEDs (see inclusion criteria 6 and 7 and exclusion criteria 6 through 8 for further details). Changes of baseline AEDs (addition, deletion, or adjustment in dose) will not be allowed during 5 half-lives or during the 2 weeks, whichever is longer, before Visit 1. During the Core study, dose adjustments will be allowed only for non-EIAEDs. Dose adjustments of EIAEDs and addition/deletion of any concomitant AEDs are not allowed during the Core study. Use of cannabidiol (CBD) products is allowed and is counted as 1 of the 4 maximum allowed concomitant AEDs. CBD dose and product must have remained stable for at least 2 weeks before Visit 1 and is to remain the same throughout the course of the Core Study. (revised per Amendment 02)

The following medications will not be permitted (revised per Amendment 02):

- Medications known to be inducers of cytochrome P450 3A (CYP3A) (other than CBZ, OXC, PHT, or ESL) including, but not limited to: rifampin, troglitazone, St John's Wort, efavirenz, nevirapine, barbiturates (except for use as an AED), glucocorticoids (other than topical usage), modafinil, pioglitazone, and rifabutin within 2 weeks or 5 half-lives, whichever is longer, before Visit 1 and throughout the course of the study [Core and Extension])
- Felbamate (within 8 weeks before Visit 1 and throughout the course of the study [Core and Extension])
- Vigabatrin(within 2 weeks before Visit 1 and throughout the course of the study [Core and Extension])

In case of an emergency, subjects may receive other AEDs, including diazepam as well as other appropriate AEDs as rescue medications, to treat status epilepticus, uncontrolled seizures, or seizure clusters.

For any drug known to influence the CNS (other than AEDs for epilepsy), the dose should be kept stable for 2 weeks or 5 half-lives, whichever is longer, before Visit 1 and throughout the course of the study (Core and Extension). (revised per Amendment 02)

Subjects are not permitted to participate in another study involving administration of an investigational drug or device for the full duration of this study (ie, up to and including the Follow-up Visit).

Assessments

Efficacy Assessments

Efficacy will be assessed by seizure counts and types as recorded on a study specific seizure diary, and by CGI-C.

Pharmacokinetic Assessments (Core Study only)

Blood samples (1.0 mL) for plasma will be collected from all subjects at prespecified visits for the determination of perampanel plasma concentrations. On the day of PK sampling, subjects will attend the clinic any time during the day to provide blood sampling for PK analysis and to enable close monitoring of the subjects for safety and tolerability. The resulting plasma sample will be aliquoted into 2 Microtainer® tubes.

For subjects aged 1 to less than 24 months, dosing should occur once daily before bedtime in the evening. The dosing date and time of the last 3 doses before each PK visit will be recorded. (revised per Amendment 02)

For subjects aged 2 to less than 4 years, dosing should occur once daily before bedtime in the evening, including

the evening before the PK visit during Titration Period (Visit 5 for non-EIAED subjects, or Visit 6 for EIAED subjects). The dosing date and time of the last 3 doses before Titration Period PK visit will be recorded. Note: For PK visits during Maintenance Period (ie, Visits 7 and 8 for non-EIAED subjects, or Visits 8 and 9 for EIAED subjects), as 2 PK samples (1 predose and 1 early postdose [within 1 to 5 hours after dosing]) are to be collected, the following steps are to be followed (revised per Amendment 02):

- Study drug administration in the evening immediately before the PK visits during Maintenance Period will be withheld. All other AEDs should be administered per the subject's usual AED regimen.
- During each of the Maintenance Period PK visits, collect predose PK sample. Then administer study drug on site, followed by early postdose PK sample collection (within 1 to 5 hours after dose administration).
- Bedtime dosing will resume beginning in the evening of the Maintenance Period PK visits.
- The dosing date and time of the study drug dose administered on-site during each Maintenance Period PK visit, as well as the last 2 doses before will be recorded.

Pharmacodynamic Assessments

Not applicable.

Pharmacogenomic/Pharmacogenetic Assessments

Not applicable.

Safety Assessments

Safety will be assessed by monitoring and recording of all AEs and SAEs, clinical labs (ie, hematology and blood chemistry), vital signs, ECGs, medical history, and physical and neurological examinations. In addition, growth will be assessed for this age population by measurement of height, weight, head circumference, thyroid function and insulin-like growth factor-1 (IGF-1) testing.

Other Assessments

Not applicable

Bioanalytical Methods

Plasma concentrations of perampanel will be quantified using a validated liquid chromatography mass spectrometry (LC-MS/MS) analytical method.

Statistical Methods

Study Endpoints

Primary Endpoint

- PK of perampanel during the Maintenance Period of the Core Study (revised per Amendment 02)

Secondary Endpoints

- Safety and tolerability during the Core Study and the Extension Phase, which include incidence of treatment-emergent adverse events (TEAEs) and SAEs, laboratory parameters, vital signs, and ECG parameters, and growth parameters height, weight, head circumference, thyroid function,and IGF-1 levels) (revised per Amendment 02)

Exploratory Endpoints

The efficacy endpoints are:

- Seizure frequency: Percent change in 28-day seizure frequency during the Treatment Phaseand during the Extension Phase, compared to baseline (revised per Amendment 02)
- Responder rate: Proportion of subjects with a 50% or greater reduction in 28-day seizure frequency during the Maintenance Period and during the Extension Phase, compared to baseline (revised per Amendment 02)
- Seizure-free rate: Proportion of subjects who are seizure-free during the Maintenance Period and

during the Extension Phase

- CGI-C at the end of the Core Study and the Extension Phase

Analyses

Analysis Sets

The Pharmacokinetic Analysis Set is the group of subjects with at least 1 PK assessment of perampanel during the Maintenance Period and who have a documented dosing history.

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 study drug and had any seizure frequency data during the 2 weeks of Pretreatment Phase plus 4 weeks before Pretreatment Phase and during the Treatment Phase.

Efficacy Analyses

Exploration of efficacy will be performed on the FAS. Summary statistics will be displayed for all efficacy parameters.

Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic/ Pharmacogenetic Analyses

Pharmacokinetic Analyses

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

A population PK approach will be used to characterize the PK of perampanel. The effect of intrinsic and extrinsic factors (age, body weight, gender, race, ALT, AST, creatinine clearance and concomitant therapy with carbamazepine, oxcarbazepine, phenytoin, phenobarbital, valproic acid, lamotrigine, topiramate, primidone, zonisamide, levetiracetam and primidone) on perampanel PK will be evaluated. A 2-compartment disposition PK model with linear elimination will be parameterized for absorption rate, oral clearance, and apparent central and peripheral volumes of distribution. Derived exposure parameters such as the steady state peak concentration ($C_{max,ss}$), area under concentration vs time curve at steady state (AUC_{ss}), and average steady-state drug concentration (Css,av) will be calculated using the individual posterior estimates of PK parameters from the final PK model. Descriptive statistics of the individual model-predicted PK parameters (including but not limited to $C_{max,ss}$) will be provided.

Due to the small sample size, population PK analysis will be performed using NONMEM with first-order conditional estimation with interaction on data from this study pooled with existing rich data from 19 Phase 1 studies and spare data from 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 fitted 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 AUC from the final PK mode will be derived for all subjects. Subsequently, dose-normalized derived exposure parameters will be summarized descriptively by age group (≤6 months, > 6 to ≤ 12 months, >12 to < 24 months, ≥24 months to ≤4 years, >4 to ≤ 8 years, >8 to <12 years, ≥12 to <18 years and ≥18 years) and also presented in box-plots, stratified by subjects taking and not taking EIAEDs. Additionally, dose-normalized derived exposure parameters will be summarized descriptively for the following age groups: 1 to 24 months, 2 to ≤ 4 years, >4 to ≤ 8 years, >8 to <12 years, ≥12 to <18 years and ≥18 years), and also presented in box-plots, stratified by subjects with EIAED and non-EIAEDs. (revised per Amendment 02)

The final PK model will be qualified using visual predictive checks and validated using bootstrap analysis.

Pharmacodynamic and Pharmacogenomic/ Pharmacogenetic Analyses

Not applicable.

Safety Analyses

Evaluation of safety will be performed on the Safety Analysis Set. Assessments that will be evaluated include AEs, SAEs, clinical laboratory results, vital signs, and 12-lead ECGs. Treatment-emergent AEs will be summarized by presenting the incidence of TEAEs and the overall incidence by age group and EIAED and non-EIAED groups. The incidence of out-of-normal-range laboratory safety tests variables will be summarized along with change from baseline in laboratory safety test variables and vital sign measurements. Descriptive summary statistics of the laboratory, vital signs, and ECG parameters will also be evaluated.

Descriptive summary statistics of changes from baseline in growth (ie, height/length, head circumference, weight) will be evaluated. These data may also be compared with normative scores to assess clinical relevance.

Changes from baseline for thyroid function and IGF-1 testing will be summarized.

Other Analyses

Not applicable.

Interim Analyses

An interim analysis (safety, tolerability, and PK) will be performed as follows:

- After every 4th subject in the age group 1 to less than 24 months completes the Maintenance Period where dose-normalized exposure will be compared to that observed in other studies in subjects between ≥2 and <18 years of age for evidence of systematic deviations potentially warranting dose adjustment in this age group or for other subjects enrolled in the study. PK data collected in older age cohort (2 to less than 4 years) will also be examined in the interim PK analyses. (revised per Amendment 02)
- All data from the Pretreatment and Treatment Phases will be analyzed when all subjects have completed the Maintenance Period. In addition, a final analysis of data from the Pretreatment, Treatment, and Extension Phases will be analyzed when all subjects have completed the Extension Phase. (revised per Amendment 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.

Sample Size Rationale

Similar to Study 232, Study 238 will use population PK modeling to characterize PK in pediatric subjects 1 to less than 24 months and 2 to less than 4 years of age, and compare these data to PK in adolescent and adult subjects. In a prior study (Study 232), data were obtained in 42 subjects ≥ 2 to <12 years of age, with approximate equal numbers enrolled in the age ranges of ≥2 to ≤6 and ≥7 to <12 years. (revised per Amendment 02)

Given the narrower age range planned for Study 238 compared with Study 232, and the fact that the PK data from this study will be pooled with the data from subjects in ≥2 to <12 years of age, it is proposed that PK data obtained in at least 16 subjects ≥ 1 to <24 months of age would be adequate to characterize the PK in this age group. The sample size will be increased to at least 24 subjects if dose-normalized (to 8 mg) exposure in the Maintenance Period from the first 16 subjects in this study is not comparable to existing data in subjects aged ≥2 to 18 years. (revised per Amendment 02)

In order to compare the PK of pediatric subjects aged 2 to less than 4 years of age with the PK of pediatric subjects aged >4 years of age, a total of 26 subjects with 13 EIAED and 13 non-EIAED subjects will be enrolled and pooled across clinical studies of perampanel with PK assessment. This estimate of the required sample size assumes the inter-subject variability of 46.8% (CPMS-E2007-015-v1), equivalent to a coefficient of variation (CV) on the log scale of 0.445, that provides a sufficient number of subjects to target a 95% confidence interval within 60% and 140% of the point estimate for the geometric mean clearance of

perampanel (equal to 0.638 L/h; determined using population PK modeling) with at least 80% power. (revised per Amendment 02)

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
AED	anti-epileptic drug
ALT	alanine aminotransferase
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
$AUC_{0–72}$	area under the curve baseline to 72 hours
AUC_{last}	area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration
AUC_{ss}	area under the curve at steady state
BP	blood pressure
CA	Competent Authority
CBZ	carbamazepine
CFR	Code of Federal Regulations
CGI	Clinical Global Impression
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CHMP	Committee for Medicinal Products for Human Use
CL/F	apparent clearance
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximum observed concenration
$C_{max,ss}$	Msximum observed concentration at steady state
CNS	central nervous system
CPMP	Committee for Proprietary Medicinal Products
CRA	Clinical Research Associate
CRF	case report form
CRO	contract research organization
Css,av	average steady-state drug concentration
CT	computed tomography
CTCAE	Based on Common Terminology Criteria for Adverse Events
CV	curriculum vitae
CYP	cytochrome P450
CYP3A	cytochrome P450 3A
DBS	dried blood spot
DEA	Drug Enforcement Administration

Abbreviation	Term
DMC	independent Data Monitoring Committee
ECG	electrocardiogram
EEG	electroencephalogram
EMA	European Medicines Agency
ESL	eslicarbazepine
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
fT3	free triiodothyronine
fT4	free thyroxine
GCP	Good Clinical Practice
GGT	γ-glutamyl transpeptidase
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGF-1	insulin-like growth factor-1
ILAE	International League Against Epilepsy
IND	Investigational New Drug
IRB	Institutional Review Board
LC-MS/MS	liquid chromatography mass spectrometry
LLT	lower level term
LNH	low/normal/high
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NA	North America
OXC	oxcarbazepine
PD	pharmacodynamics
PDCO	Paediatric Committee
PET	polyethylene terephthalate
PGTCS	primary generalized tonic-clonic seizures
PHT	phenytoin
PI	principal investigator
PiBA	press in bottle adaptors
PIP	Paediatric Investigation Plan
PK	pharmacokinetics

Abbreviation	Term
POS	partial-onset seizures
PT	preferred term
QD	once daily
QTc	time from the beginning of the QRS complex to the end of the T wave, corrected for heart rate
QTcF	QT interval data corrected using Fridericia's formula (QT/RR1/3)
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SI	Système International
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
t_{max}	time to reach maximum concentrations following drug administration
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
UDP	uridine-5'-diphosphate
ULN	upper limits of normal
US	United States
V/F	apparent volume of distribution
WBC	white blood cell
WHO	World Health Organization
WHO DD	World Health Organization Drug Dictionary

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with ICH E6 (Good Clinical Practice [GCP]), Section 3, and the European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC, and the United States (US) Code of Federal Regulations (CRF), Title 21 CFR Part 56. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in Clinical Research Associate [CRA(s)], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (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 (CA) 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 CA 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 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 (CPMP), International Conference on Harmonisation of Pharmaceuticals for Human Use
- 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 Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All Suspected Unexpected Serious Adverse Reactions (SUSAR[s]) will be reported, as required, to the Competent Authorities of all involved EU member states.

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 parent/guardian 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 guardian/legally authorized representative) should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject (or guardian/legally authorized 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 guardian/legally authorized representative), and after the subject (or guardian/legally authorized representative) has verbally 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 (or guardian/legally authorized representative) 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.

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 parent/guardian/legally authorized representative must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject (or guardian/legally authorized representative) should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness

to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 15 investigational sites in North America (NA) and the EU.

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) are listed in the Regulatory Binder provided to each site.

7 INTRODUCTION

Perampanel (E2007) is an orally active, noncompetitive, and highly selective α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptor antagonist with potential for therapeutic use in patients with various neurological diseases. Perampanel is approved in the US for the treatment (including monotherapy) of partial-onset seizures (POS) with or without secondarily generalized seizures in patients with epilepsy aged 4 years and older, and as adjunctive therapy of primary generalized tonic-clonic seizures (PGTCS) in patients with epilepsy aged 12 years and older. Perampanel is also approved in the EU as an adjunctive treatment of POS and PGTCS in patients with epilepsy aged 12 years and older. This study aims to provide pharmacokinetics (PK) and safety data of perampanel in pediatric subjects from age ≥1 to <24 months and from age 2 to less than 4 years. (revised per Amendment 02)

Epilepsy is a common neurological problem in (Hauser, 1992; Hauser, 1994, Bourgeois, 1995). Generalized seizures predominate in the first years of life, but by age 5 years, POS are also common (Hauser, 1992). Despite recent advances in drug treatment, one of every 4 patients with epilepsy does not achieve long-term seizure freedom (Northam, 2005) and suffers from intractable seizures, while many others experience significant treatment-related side effects (Fountain, 2007). Selection of an anti-epileptic drug (AED) for the treatment of pediatric patients with epilepsy has been particularly difficult because of the lack of clinical studies in this population especially in younger pediatrics (age <4 years) (Piña-Garza, 2005; Ouellet, 2001). (revised per Amendment 02)

Given the inherent challenges in performing clinical studies in children, extrapolation of efficacy from adult to pediatric subjects (24 months and above) with partial onset seizures has been accepted as an alternative to randomized, double-blind, placebo-controlled Phase 3 studies in children, as reflected in the September 2019 FDA Guidance "Drugs for Treatment of Partial Onset Seizures: Full Extrapolation of Efficacy from Adults to Pediatric subjects 24 months of Age and Older". To support extrapolation, adequately designed PK and tolerability study(ies) with sufficient sample size are required to demonstrate similar exposure (blood/plasma levels of active drugs and, as applicable, metabolites) and to evaluate safety profile following drug administration in pediatric subjects aged 24 months and above. This efficacy extrapolation approach, however, does not apply to subjects under 24 months of age. For this population, well-designed clinical trials are required to determine efficacy, safety and tolerability, PK, and appropriate dosages (Northam, 2005). (revised per Amendment 02)

7.1 Study Rationale

European Union legislation on pediatric medicines came into effect in Jan 2007. This legislation defines the obligations for the conduct of clinical trials in pediatric populations to address problems of inadequate dosage information, non-availability of therapeutic advances, dose formulations, and routes of administration in pediatric populations. The legislation is expected to stimulate research and result in increased numbers of pediatric clinical trials

overseen by the new Paediatric Committee (PDCO) within the European Medicines Agency (EMA).

The main directive of the PDCO is to assess the content of Paediatric Investigation Plans (PIPs) and adopt opinions on them in accordance with Regulation (EC) 1901/2006 as amended. This includes the assessment of applications and assessing data generated in accordance with agreed PIPs and adopting opinions on the quality, safety or efficacy of any medicine for use in the pediatric population (at the request of the Committee for Medicinal Products for Human Use (CHMP) or a CA). The original PIP for perampanel was approved by PDCO on 19 Mar 2010. Study E2007-G000-238 is part of the approved PIP to which Eisai is committed to perform as part of the pediatric program.

Pediatric study requirements in the United States are legislated under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), which requires that all applications for new active ingredients, new indications, new dosage forms, new dosing regimens or new routes of administration contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless the requirement is waived, deferred, or inapplicable. As part of the approval for perampanel tablets in the US under NDA 202834 as adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older, the FDA granted a deferral of pediatric studies of perampanel for ages 1 month to less than 12 years. Study E2007-G000-238 is part of a series of deferred pediatric studies that are required postmarketing studies under section 505B(a) of the Federal Food, Drug and Cosmetic Act.

Study E2007-G000-238 has been approved by PDCO; it is required by FDA and will be the first study to be conducted in the pediatric population of age ≥1 to <24 months with perampanel. In this youngest age group, the study will evaluate the PK and will generate preliminary safety and efficacy of perampanel following the administration of an oral suspension. Below is a summary of 2 studies of perampanel that have been initiated in the pediatric age group:

- Study E2007-G000-235 (Study 235), was the first stand-alone pediatric study for perampanel, recruited an adolescent population similar to those examined in the Phase 3 studies with the same dose range (ie, 2 to 12 mg/day). The primary objective of this study was to evaluate the effect of perampanel on cognition. In addition to cognition, growth and development will also be evaluated including sexual maturation. Although no such safety issues have been identified in relation to perampanel to date, Study 235 has been designed according to the European CHMP guideline (CPMP/EWP/566/98 Rev. 2) on the need for data "to detect the potential effect on learning, intelligence, growth, endocrine function, and puberty". The study has been completed. The study met its primary objective and there was no statistically significant or clinically relevant overall cognitive impairment detected in the study with perampanel compared to placebo.
- Study E2007-G000-232 (Study 232), in a pediatric population of ages ≥2 to <12 years has completed. The primary objective of this study was to evaluate the

pharmacokinetics (PK) of perampanel following oral suspension administration given as an adjunctive therapy in pediatric subjects age ≥2 to <12 years with epilepsy.

Perampanel oral suspension (0.5 mg/mL) will be used in Study 238. This formulation was used in Study 232. The bioequivalence between the oral suspension formulation and the tablet formulation was evaluated in Study E2007-A001-048 under fed and fasted conditions. The results of the study in conjunction with steady state PK simulations of the data confirmed that the oral suspension formulation is bioequivalent to the tablet formulation, and can be used interchangeably with the tablet formulation. From a safety point of view, both the oral suspension and tablet formulations were well-tolerated

In support of pediatric development and minimizing the blood volume necessary to complete appropriate PK analyses, fully validated dried blood spot (DBS) sampling method was used for analysis of perampanel concentrations in Study 232. However, sites in this study encountered sampling challenges with resultant loss of samples. For this study, a small-volume plasma assay requiring only 1-mL blood volume per time point will be used. (revised per Amendment 02)

Eslicarbazepine (ESL) is structurally and functionally related to oxcarbazepine (OXC) (Rogawski, 2004) and was approved for use by the EMA in April 2009. In vitro, ESL is a weak inducer of CYP3A4 and UDP-glucuronyl transferases. In vivo, ESL showed an inducing effect on the metabolism of medicinal products that are mainly eliminated by metabolism through CYP3A4 (Zebinix® SmPC). Therefore, ESL is being included in this study as an enzyme-inducing AED (ie, EIAED) to facilitate enrollment of subjects into this subgroup.

7.2 Dosing Rationale

A key objective of AED dosing with perampanel in pediatrics is to identify appropriate doses such that plasma levels fall within a concentration range associated with the therapeutic effect and acceptable safety previously demonstrated in adults. Stabilizing plasma drug levels can be more difficult in infants and toddlers than in adolescents or adults because of variability in absorption and drug metabolism (Ramsey, 2007). For example, compared to adolescents and adults, during the first year of life infants have reduced hepatic metabolism that by the end of their first year progresses to substantially greater hepatic metabolism, which can have important implications for dosing (Pellock, 1998).

Perampanel is almost completely absorbed from the gastrointestinal tract and is mostly eliminated in the feces (about 70%) following metabolism primarily via the cytochrome (CYP) P450 3A4 pathway in the liver. The possibility exists that the PK profile of perampanel may differ between infants and toddlers compared with, adolescents and adults, thus requiring age-specific dosage regimens. Study 238 is designed to evaluate the optimal maintenance dose and the dosing regimens to achieve plasma concentrations in infants and toddlers aged 1 month to less than 4 years comparable to those in adolescents and adults.

The clinical development plan for perampanel included Phase 3 studies (Studies E2007 G000-304, -305 and -306); in addition to enrollment of adults, these studies included adolescent

subjects ≥12 to <18 years of age. Treatment with perampanel for doses ranging from 4 to 12 mg/day in these Phase 3 studies was significantly more effective than adjunctive treatment with placebo in improving seizure control in subjects ≥12 years of age with refractory POS. The studies also demonstrated a positive safety and tolerability profile in this population.

A population PK analysis was completed on data from 74 adolescent (≥12 to <18 years of age) subjects only and from 770 adolescent and adult subjects combined from Studies 304, 305 and 306. Perampanel clearance increased in the presence of co-administered carbamazepine (CBZ), OXC, and phenytoin (PHT) by approximately 3-fold, 2-fold, and 2-fold respectively. Perampanel clearance was not affected by baseline seizure frequency, the time during the study, dose administered, race, age, renal or liver conditions (estimated from creatinine clearance or liver function tests respectively) and concomitant AEDs lamotrigine, levetiracetam, topiramate, valproic acid, zonisamide, primidone, clobazam, and phenobarbital. A small effect of gender and body mass was found but these were not considered clinically important. Findings from a recent population PK analysis on data from 78 adolescents from Study 235 pooled with the data from the 74 adolescents from Studies 304, 305, and 306, were in full agreement with those from the previous analysis.

A corresponding population PK/pharmacodynamic (PD) analysis for the relationship between exposure and seizure frequency was also completed on data from 105 adolescent subjects only and 1109 adolescent and adult subjects combined from Studies 304, 305, and 306. On the natural logarithm scale, a significant decrease in seizure frequency of 0.000569 for an increase of 1 ng/mL in perampanel concentration was found. There were no differences in response to perampanel resulting from gender, race, age, and co-administration of any AEDs. An additional population PK/PD responder analysis on data from the same 105 adolescent subjects only and from 1109 adolescent and adult subjects combined showed that the proportion of responders increases with the concentration of perampanel. Again, findings from a recent population PK/PD analysis on data from 110 adolescents from Study 235 pooled with the data from the 105 adolescents from Studies 304, 305, and 306 were in full agreement with those from the previous analysis.

Overall, perampanel PK was shown to be similar in adolescents and adults, was not affected in clinically important ways by body weight, age, gender, race, body mass (across the range of adolescents and adults), and not affected by co-administration of AEDs other than inducing CYP3A concomitant CBZ, OXC, and PHT.

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 ≥2 to ≤6 years and 22 were aged ≥7 to <12 years. A total of 28 subjects were not receiving any of the EIAEDs (CBX, OXC, or PHT) and 14 subjects were receiving one of these EIAEDs. As noted above, 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. Whole blood perampanel concentration values from Study 232

analyzed using the DBS technique were converted to plasma concentrations, and for comparison purposes both plasma perampanel concentrations. The results of the analysis demonstrated that perampanel PK was linear as there was no dose or time-dependency to apparent 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 clearance) 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 (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/body) administered in these. The results of the analysis suggested that flat dosing approach will be more appropriate in subjects within that age range.

Considering the ontogenic profile of CYP3A enzyme in pediatrics, especially between 1 to less than 24 months old, and due to the unknown safety profile in this population, a lower starting dose of 0.5 mg/day was selected, with titrations to a dose of 12 mg/day (non-EIAED subjects) or 16 mg (EIAED subjects). To date, sparse PK data is available from 3 pediatric subjects between age of 4.5 months to 20 months receiving perampanel as part of a Named Patient IND. These subjects were dosed with perampanel up to 8 mg/day at steady state. The plasma concentration data in the 3 individuals although close to upper end of the range, were still within the 2-fold relative to the exposures observed in 2 to <12 year old subjects. Based on these findings, the likelihood of starting dose of 0.5 mg achieving unexpectedly high plasma exposures in the proposed age population is considered to be low. Furthermore, noting the wide variability in hepatic metabolism via CYP3A in pediatric subjects less than 24 months of age, the risk of unexpected plasma exposures in number of pediatric subjects is further minimized by planned interim PK analysis in the first 4 subjects completing the PK portion of Study 238. These data (dose-normalized to 8 mg) will be compared with data from and adolescents (≥2 to <18 years of age) from previous studies for evidence of systematic deviations potentially warranting dose adjustment in this age group.

8 STUDY OBJECTIVES

8.1 Primary Objectives

The primary objective of the study is to evaluate the PK of perampanel during the Maintenance Period of the Core Study following oral suspension administration given as an adjunctive therapy in pediatric subjects from 1 month to less than 4 years of age with epilepsy. (revised per Amendment 02)

8.2 Secondary Objective(s)

The secondary objectives of the study are:

- To evaluate the short- and long-term safety and tolerability of perampanel oral suspension, given as an adjunctive therapy, in subjects from 1 month to less than 4 years of age with epilepsy (revised per Amendment 02)
- To evaluate the long-term effect of perampanel oral suspension, given as an adjunctive therapy, on growth from baseline to end of treatment in pediatric subjects from 1 month to less than 4 years of age with epilepsy (revised per Amendment 02)

8.3 Exploratory Objective(s)

The exploratory study objective is to explore the short- and long-term efficacy of perampanel oral suspension, given as an adjunctive therapy, in subjects from 1 month to less than 4 years of age with epilepsy as assessed by: (revised per Amendment 02)

- Percent change in 28-day seizure frequency during the Titration + Maintenance Periods compared to baseline and during the Extension Phase compared to baseline
- Proportion of subjects with a 50% decrease in 28-day seizure frequency during the Maintenance Period compared to baseline and during the Extension Phase compared to baseline
- Proportion of subjects who are seizure-free during the Maintenance Period and during the Extension Phase
- Clinical Global Impression (CGI)of change (CGI-C)

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This will be a multicenter, open-label study with an Extension Phase that will enroll 16 to 24 pediatric subjects 1 to less than 24 months of age and at least to a maximum of 26 pediatric subjects from 2 to less than 4 years of age with epilepsy. (revised per Amendment 02)

All subjects must be taking 1 to a maximum of 4 AEDs to participate in the study. For at least 6 but not more than 8 of the subjects in the age group of 1 to less than 24 months and for 13 subjects in the age group of 2 to less than 4 years (across studies), only 1 EIAED (ie, CBZ, OXC, PHT, or ESL) out of the maximum of 4 AEDs will be allowed. These subjects will be referred to as EIAED subjects. The remaining subjects cannot be taking any EIAEDs and will be referred to as non-EIAED subjects. (revised per Amendment 02)

For the age group of 1 to less than 24 months, the Sponsor will ensure a reasonable representation of subject age (ie, at least 6 subjects in the age range ≥1 to ≤6 months, at least 5 subjects in the age range >6 to ≤12 months, and at least 5 subjects in the age range >12 to <24 months). (revised per Amendment 02)

For the age group of 2 to less than 4 years, the required number of subjects (total of 26) can be pooled across multiple studies for PK and safety assessments in pediatric subjects of 2 to less than 4 years of age. Therefore, the target number of subjects to be enrolled in this age group in this study ranges from a minimum of 1 to a maximum of 26 subjects. Enrollment of subjects aged 2 to less than 4 years into this study may be stopped upon notification of sponsor when the total number has been reached across clinical studies, or when enrollment in the 1 to less than 24 months age group in this study has completed (ie, the original purpose of this study has been met). (revised per Amendment 02)

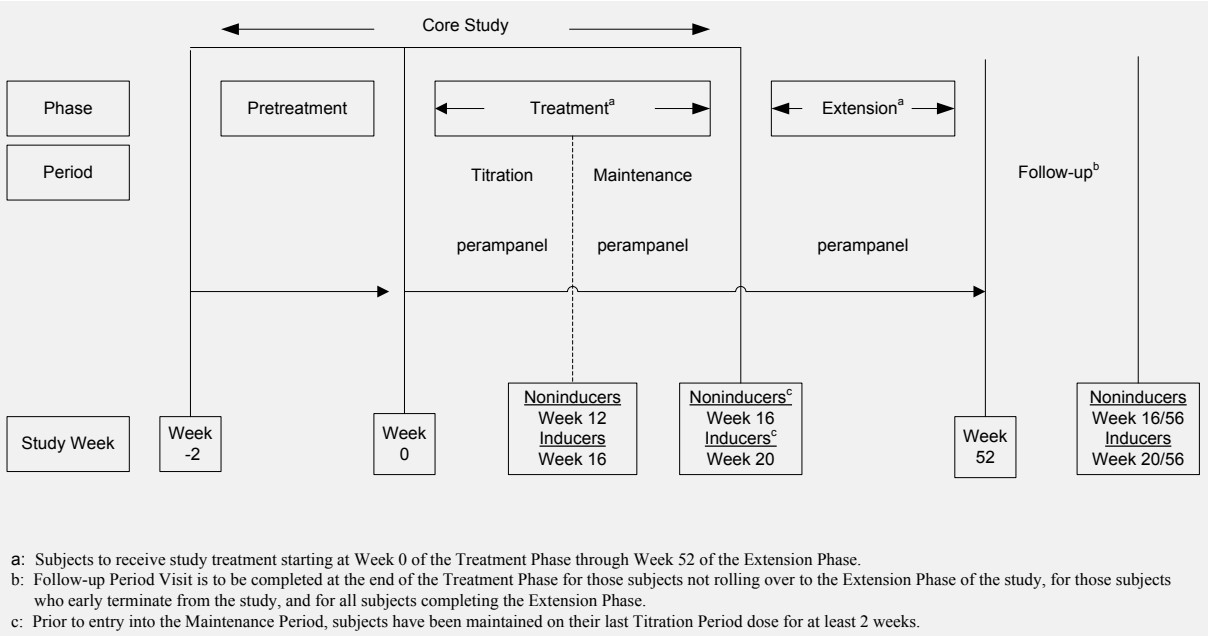
This study will consist of 3 phases: Pretreatment and Treatment (Core Study), and Extension. The Pretreatment Phase will last up to 2 weeks, during which subjects will be assessed for their eligibility to participate in the study. The Treatment Phase will consist of 3 periods: Titration (12-16 weeks), Maintenance (4 weeks), and Follow-up (4 weeks; only for those subjects who complete the Maintenance Period but do not continue into the Extension Phase). The Extension Phase will consist of 2 periods: Maintenance (32-36 weeks) and Follow-up (4 weeks). (revised per Amendment 02)

The end of the study will be the date of the last study visit for the last subject.

The maximum total duration of treatment for each subject will be 52 weeks and the maximum total duration of the study for each subject will be 58 weeks (2 weeks Pretreatment+52 weeks of treatment+4 week Follow-up). (revised per Amendment 02)

Subjects who complete the Extension Phase and who, in the opinion of the investigator, will likely continue to demonstrate a positive benefit-to-risk ratio from treatment with perampanel may be enrolled into an extended access program (EAP) for perampanel if EAP is implemented for this age group in the country where the subject resides. (revised per Amendment 02)

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



a: Subjects to receive study treatment starting at Week 0 of the Treatment Phase through Week 52 of the Extension Phase.
b: Follow-up Period Visit is to be completed at the end of the Treatment Phase for those subjects not rolling over to the Extension Phase of the study, for those subjects who early terminate from the study, and for all subjects completing the Extension Phase.
c: Prior to entry into the Maintenance Period, subjects have been maintained on their last Titration Period dose for at least 2 weeks.

Figure 1 Study Design for Study E2007-G000-238

9.1.1 Pretreatment Phase

At the first visit of the Pretreatment Phase, 4 weeks of prescreening (ie, before Visit 1) seizure frequency data will be collected for each subject as part of their medical history. Upon successful completion of the Pretreatment Phase, eligible subjects will enter the Treatment Phase.

9.1.2 Treatment Phase

The Treatment Phase will consist of 3 periods: Titration (12-16 weeks), Maintenance (4 weeks), and Follow-up (4 weeks; only for those subjects who complete the Maintenance Period but do not continue into the Extension Phase, or those who discontinue early from the study). (revised per Amendment 02)

9.1.2.1 Titration Period

During the Titration Period, subjects will start perampanel treatment at a dose of 0.50 mg/day and follow dose titration schemes (Table 1 and Table 2) up to 4 mg/day (non-EIAED subjects) or 8 mg/day (EIAED subjects). Depending on individual subject's clinical response and tolerability, non-EIAED subjects could still have the perampanel dose up-titrated to 6 mg/day. Perampanel dose should not be further up-titrated beyond 6 mg/day (non-EIAED subjects) or 8 mg/day (EIAED subjects) unless there is a medical need (for example, a subject who tolerated perampanel well but have not reached optimal seizure control). Before dose up-titrations beyond 6 mg/day (non-EIAED subjects) or 8 mg/day (EIAED subjects) and whenever practically feasible, it is recommended to take a blood sample for the measurement of plasma perampanel level as a precautionary measure. The date and time of the last perampanel dose administration, as well as the date and time of PK blood draw, for these unscheduled PK sample collection will be recorded. Up-titrations of perampanel dose within the range of 0.5 to 6 mg/day will be at 1-week intervals; and at doses greater than 6 mg/day will be at 2-week intervals (see Study Treatment(s) section). Dose titrations must not exceed 12 mg/day (non-EIAED subjects) or 16 mg/day (EIAED subjects); see Study Treatment(s) section). The decision to up-titrate perampanel dose will be at the investigator's discretion, based on individual subject's clinical response and/or tolerability to achieve optimal dose for a given subject. Once the optimal dose has been achieved, the subject's dose will be maintained stable for the remaining Titration Period or at least 2 weeks before entering the Maintenance Period. (revised per Amendment 02).

9.1.2.2 Maintenance Period

During the Maintenance Period, subjects will continue taking perampanel oral suspension at the dose level they achieved at the end of the Titration Period.

9.1.2.3 Follow-Up Period

Subjects who do not continue into the Extension Phase after completing the Maintenance Period, or those who discontinue early from the study will be required to complete the Follow-up Period after their last dose in the Treatment Phase. During this period, subjects will not receive study drug. Subjects who switch to commercially available perampanel or who enter into EAP upon completion of study treatment would not need to under Follow-up Visit; however, sites will conduct a telephone contact 28 (+6) days after the last dose of study drug to follow adverse events (AEs) and report any serious adverse events (SAEs) that occur within 28 days of the last study drug administration. (revised per Amendment 02)

9.1.3 Extension Phase

Subjects who have completed the last visit of the Core Study Maintenance Period will be eligible to participate in the Extension Phase of this study. For these subjects, upon completion of the last visit of the Maintenance Period they will be considered as participating in the Extension Phase.

See Appendix 3 for a full description of the Extension Phase.

9.2 Discussion of Study Design, Including Choice of Control Groups

This current study (E2007-G000-238) is part of the continuing development of perampanel in pediatric subjects. The purpose of the current study is to fulfill both the European and US regulatory requirements for the development of AEDs in pediatric age groups.

The primary objective of the study is to assess PK in order to determine appropriate dosing regimens of perampanel in pediatric subjects younger than 24 months of age. Accordingly, this study is designed as open-label, single-arm, uncontrolled study with no placebo or active-control treatment groups. (revised per Amendment 02)

Considering the ontogenic development of CYP3A (the enzyme responsible for perampanel metabolism) during the first 24 months of life, perampanel PK may be affected as the levels of CYP3A is changing. To better characterize perampanel PK over the time course of CYP3A maturation, this study will seek to ensure adequate age representation among subjects (ie, at least 6 subjects are in the age range 1 to ≤6 months, at least 5 subjects are in the age range >6 to ≤12 months, and at least 5 subjects are in the age range >12 to <24 months). Additionally, due to the limited PK data collected for perampanel in the age group of 2 to <4 years, this study is amended to expand enrollment to include subjects aged 2 to less than 4 years. (revised per Amendment 02)

In this study, all subjects will be receiving perampanel as an adjunctive treatment. As with dosing regimens studied in Phase 3 studies in adolescents and adults, gradual increase in dose (dose titrations) to reach therapeutic dose levels will be employed. Clinical response and tolerability will be used as the criteria to make decision whether to escalate dose at each titration step and to define the optimal dose for individual subject. The dose titration scheme and maximum doses (12 mg/kg [non-EIAED subjects] and 16 mg/kg [EIAED subjects]) have been evaluated in a Phase 3 study (E2007-G000-311) in 180 pediatric subjects (4 to <12 years) with refractory POS with or without secondarily generalized seizures or with PGTCS, and was found to be generally safe and well tolerated. (revised per Amendment 02)

Given the vulnerability associated with the young age of this study population and the lack of safety and PK information in this young age group, precautionary safety measures will be employed: (1) Slightly longer titration intervals (ie, 1-week intervals up to 6 mg/day and then 2-week intervals from 6 mg/day to maximum dose of 12 mg/day [non-EIAED subjects] or 16 mg/day [EIAED subjects]), compared to those in the adolescent/adult studies; (2) a 4-fold lower starting dose (0.5 mg/day instead of labeled 2 mg/day) will be employed as a precautionary safety measure, and (3) periodic interim PK analysis to examine the appropriateness of the target doses and dose range employed in this study. (revised per Amendment 02)

9.3 Selection of Study Population

For the age group of 1 to less than 24 months, at least 16 pediatric subjects who have been diagnosed with epilepsy, of which at least 6 subjects are in the age range ≥1 to ≤6 months, at least 5 subjects are in the age range >6 to ≤12 months, and at least 5 subjects are in the age range >12 to <24 months. (revised per Amendment 02)

In addition, up to 26 subjects in the age range of 2 to less than 4 years may be enrolled in this study. As these subjects can be pooled across clinical studies of perampanel with PK data, there is no prespecified number of subjects in this age group that must be enrolled in this study. (revised per Amendment 02)

Subjects will be enrolled at approximately 15 sites in NA and the EU. (revised per Amendment 02)

9.3.1 Inclusion Criteria

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

1. Male or female, from 1 month to less than 4 years of age (and of at least 36 weeks gestational age) at the time of consent (revised per Amendments 01 and 02)
2. Have a minimum weight of 4 kg (8.8 lb)
3. Have a diagnosis of epilepsy with any type of seizure according to the ILAE guidelines: International League Against Epilepsy's Classification of Epileptic Seizures (1981). Diagnosis should have been established at least 2 weeks (≤6 months of age) or 4 weeks (>6 months of age) before Visit 1, by clinical history and an electroencephalogram (EEG) that is consistent with epilepsy; normal interictal EEGs will be allowed provided that the subject meets the other diagnosis criterion (ie, clinical history)
4. Have had brain imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) before Visit 1 that ruled out a progressive cause of epilepsy
5. Have had 1 or more seizure(s) before Visit 1 (revised per Amendment 01)
6. Are currently being treated with a stable dose (ie, unchanged for at least 5 half-lives) of 1 to a maximum of 4 AEDs. (At least 6, but not more than 8 subjects, in the age group of 1 to less than 24 months, and up to 13 subjects in the age group of 2 to less than 4 years, will be taking 1 EIAEDs [ie, CBZ, OXC, PHT, or ESL] out of the maximum of 4 AEDs allowed. The remaining subjects cannot be taking any EIAEDs.) (revised per Amendment 02)
7. Have been on their current concomitant AED(s) with a stable dose for at least 2 weeks or 5 half-lives, whichever is longer, before Visit 1 (revised per Amendment 02)
8. Must have discontinued all restricted medications (eg, medications known to be inducers of cytochrome P450 3A) at least 2 weeks or 5 half-lives (whichever is longer) before Visit 1 (revised per Amendment 02)

Inclusion criteria for the Extension Phase are listed in Appendix 3.

9.3.2 Exclusion Criteria

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

1. Have a history of status epilepticus that required hospitalization during the 3 months before Visit 1
2. Have seizures due to treatable medical conditions, such as those arising due to metabolic disturbances, toxic exposure, or an active infection
3. Have epilepsy secondary to progressive central nervous system (CNS) disease or any other progressive neurodegenerative disease, including tumors
4. Have had epilepsy surgery within 1 year of Visit 1 (revised per Amendment 01)
5. Are scheduled and/or confirmed to have epilepsy surgery within 6 months after Visit 1
6. Used intermittent rescue benzodiazepines (ie, 1 to 2 doses over a 24-hour period considered one-time rescue) 2 or more times in the 2 weeks before Visit 1
7. Current use of felbamate, or any evidence of ongoing hepatic or bone marrow dysfunction associated with prior felbamate treatment. (Prior use of felbamate must be discontinued at least 8 weeks before Visit 1.) (revised per Amendment 02)
8. Current use of vigabatrin or any evidence of clinically significant vision abnormality associated with prior vigabatrin treatment. (Prior use of vigabatrin must be discontinued at least 2 weeks before Visit 1.) (revised per Amendment 02)
9. On a ketogenic diet that has not been stable for at least 4 weeks before Visit 1
10. Concomitant use of other drugs known to influence the CNS (other than AEDs for epilepsy), where the dose has not been stabilized for at least 5 half-lives or 2 weeks, whichever is longer, before Visit 1 (revised per Amendment 02)
11. Have any concomitant illnesses/co-morbidities that could severely affect the subject's safety or study conduct
12. Have 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 study conduct
13. Have clinically significant laboratory abnormalities or any clinically acute or chronic disease
14. Have 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 limits of normal (ULN)
15. Have clinical evidence of significant active hematological disease; WBC count $\leq$2500/µL (2.50 x 10^9/L) or an absolute neutrophil count $\leq$1000/µL (1.00 x 10^9/L)

16. Have conditions that may interfere with their participation in the study and/or with the PK of study drug
17. 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
18. Have recently (within 30 days before Visit 1) been exposed to perampanel in a clinical study or by prescription, and/or previous discontinuation from perampanel treatment due to adverse events related to perampanel (revised per Amendment 02)
19. Have a clinically significant electrocardiogram (ECG) abnormality, including prolonged corrected QT interval (QTc) defined as > 450 msec
20. Have had multiple drug allergies or a severe drug reaction to an AED(s), including dermatological (eg, Stevens-Johnson syndrome), hematological, or organ toxicity reactions

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 study drug, an Early Discontinuation Visit will be performed. The subject should also return 4 weeks (±6 days) after the last dose of study drug to complete the Follow-up Visit procedures. The Subject Disposition case report form (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(s)

Test drug for this study will be perampanel, oral suspension, 0.5 mg/mL. Dosing should occur once daily before bedtime in the evening, unless otherwise specified (see Section 9.5.1.4 for more details).

9.4.1 Treatment(s) Administered

Pretreatment Phase:

During the Pretreatment Phase subjects will continue to take their baseline AEDs regimen. No study drug will be administered to subjects during this phase.

Treatment Phase:

- Titration Period (12-16 weeks): Subjects will start perampanel treatment at a dose of 0.50 mg/day and follow dose titration schemes [Table 1 and Table 2], up to 4 mg/day (non-

EIAED subjects) or 8 mg/day (EIAED subjects). Depending on individual subject's clinical response and tolerability, non-EIAED subjects could still have the perampanel dose up-titrated to 6 mg/day. Perampanel dose should not be further up-titrated beyond 6 mg/day (non-EIAED subjects) or 8 mg/day (EIAED subjects) unless there is a medical need (for example, a subject who tolerated perampanel well but have not reached optimal seizure control). Before dose up-titrations beyond 6 mg/day (non-EIAED subjects) or 8 mg/day (EIAED subjects) and whenever practically feasible, it is recommended to take a blood sample for the measurement of plasma perampanel level as a precautionary measure. The date and time of the last perampanel dose administration, as well as the date and time of PK blood draw, for these unscheduled PK sample collection will be recorded. Up-titrations of perampanel dose within the range of 0.5 to 6 mg/day will be at 1-week intervals; and at doses greater than 6 mg/day will be at 2-week intervals (see Study Treatment(s) section). Dose titrations must not exceed 12 mg/day (non-EIAED subjects) or 16 mg/day (EIAED subjects). The decision to up-titrate perampanel dose will be at the investigator's discretion, based on individual subject's clinical response and/or tolerability to achieve optimal dose for a given subject. Once the optimal dose has been achieved, the subject's dose will be maintained stable for the remaining Titration Period or at least 2 weeks before entering the Maintenance Period (revised per Amendment 02)

According to the investigator's clinical judgment subjects experiencing intolerability at any dose may remain at the same dose or have their dose decreased one 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 must be done at the next clinic visit after the investigator has deemed it is appropriate in view of the resolution of the AE(s). Multiple dose adjustments will be allowed during the Titration Period. Every effort should be made to have subjects achieve their optimal dose, not to exceed a maximum dose of 12 mg/day (non-EIAED subjects) or 16 mg/day (EIAED subjects) during the Titration Period. (revised per Amendment 02)

- Maintenance Period (4 weeks): During this period, subjects will continue taking perampanel oral suspension at the dose level they achieved at the end of the Titration Period.

  Adjustment of the dose level during the Maintenance Period should be discouraged; however, according to the investigator's clinical judgment, subjects experiencing intolerable AE(s) will be allowed to have their dose decreased to the previously tolerated dose. During the Maintenance Period, subjects whose dose has been decreased cannot have their dose increased again. A subject may not decrease their dose more than once during Maintenance Period unless there is a significant medical reason and with approval from the Medical Monitor.

  During the entire Titration and Maintenance Periods, all dose adjustments will be done via 1 dose level up or down (Table 1 and Table 2). Subjects who do not tolerate a dose of 0.50 mg/day will be discontinued from the study. The maximum total daily dose a subject will be allowed is 12 mg (non-EIAED subjects) or 16 mg (EIAED subjects).

Dosing Modifications

After every 4th subject in the age group 1 to less than 24 months completes the Maintenance Period, an interim analysis (safety, tolerability, and PK) will be conducted and reviewed by the Eisai study team to decide if dosing modifications are required for additional subjects who enroll in the study. If the exposure of the subjects is significantly different from that observed in subjects ages ≥2 to <12 years from other clinical studies or that are predicted from PK modeling and simulation, or if non-linear PK is observed, the sample size will be increased to at least 24 subjects with evaluable PK data and the target dose or dosing regimen of those subjects may be modified via a protocol amendment, depending on the PK of the previous subjects. PK data collected in older age cohort (2 to less than 4 years) will also be examined in the interim PK analyses. (revised per Amendment 02)

- Follow-Up Period (4 weeks): Subjects will not receive study drug during this period. Subjects who do not continue into the Extension Phase after completing the Maintenance Period, or those who discontinue early from the study will be required to complete the Follow-up Period after their last dose in the Treatment Phase. Subjects who switch to commercially available perampanel or who enter into EAP upon completion of study treatment need not to undergo Follow-up Visit; however, sites will conduct a telephone contact 28 (+6) days after the last dose of study drug to follow AEs and report any SAEs that occur within 28 days of the last study drug administration. (revised per Amendment 02)

Table 1 Non-EIAED Subjects: Dose Adjustments during the Titration and Maintenance Periods (revised per Amendment 02)

For all non-EIAED subjects (up to 6 mg/day):		
Treatment Phase/Titration Period	**Visit**	**Daily Dose**
Week 0 (starting dose)	Visit 2	0.50 mg
Week 1 (Titration #1)	-	1 mg
Week 2 (Titration #2)	Visit 3	2 mg
Week 3 (Titration #3)	-	4 mg[a]
Week 4 (Titration #4)	Visit 4	6 mg[b]
For non-EIAED subjects who may require further titrations of perampanel doses:[c]		
Week 6 (Titration #5)	-	8 mg[d]
Week 8 (Titration #6)	Visit 5	10 mg
Week 10 (Titration #7)	-	12 mg
Week 12 (no titration)	Visit 6	Last dose achieved at Week 10[d]
Treatment Phase/Maintenance Period	Last dose achieved in the Titration Period	

EIAED = enzyme-inducing anti-epileptic drug

Table 1 Non-EIAED Subjects: Dose Adjustments during the Titration and Maintenance Periods (revised per Amendment 02)

For all non-EIAED subjects (up to 6 mg/day):		
Treatment Phase/Titration Period	**Visit**	**Daily Dose**

a. Subjects who have shown good clinical response and tolerability at perampanel daily dosing of up to 4 mg will continue to receive the same dose throughout the remaining of Titration Period. (revised per Amendment 02)

b. Up-titration to 6 mg/day in non-EIAED subjects will be allowed if a higher dose (6 mg/day) is deemed by the investigator to provide a better clinical benefit and provided that the subject tolerates perampanel well. Subjects who have shown good clinical response and tolerability at perampanel 6 mg/day will continue to receive the same dose throughout the remaining of Titration Period (revised per Amendment 02)

c. At the discretion of the investigator; only if medically necessary (eg, inadequate seizure control) and provided that the subject has shown good tolerability at 6 mg/day. (revised per Amendment 02)

d. Site to contact the parent/guardian during the scheduled telephone interview approximately midpoint between Visit 4 and Visit 5 to assess if further dose titration (to 8 mg/day) is medically necessary. The subject must return to the clinic for an unscheduled visit for any dose increase. (revised per Amendment 02)

e. Visit is considered the end of the Titration Period and start of the Maintenance Period.

Table 2 EIAED Subjects: Dose Adjustments during the Titration and Maintenance Periods (revised per Amendment 02)

Treatment Phase/Titration Period	**Visit**	**Daily Dose**
For all EIAED subjects (up to 8 mg/day)		
Week 0 (starting dose)	Visit 2	0.50 mg
Week 1 (Titration #1)	-	1 mg
Week 2 (Titration #2)	Visit 3	2 mg
Week 3 (Titration #3)	-	4 mg
Week 4 (Titration #4)	Visit 4	6 mg
Week 6 (Titration #5)	-	8 mg[a]
For EIAED subjects who may require further titrations of perampanel:[b]		
Week 8 (Titration #6)	Visit 5	10 mg
Week 10 (Titration #7)	-	12 mg
Week 12 (Titration #8)	Visit 6	14 mg
Week 14 (Titration #9)	-	16 mg
Week 16 (no titration)	Visit 7	Last dose achieved at Week 14[c]
Treatment Phase/Maintenance Period	Last dose achieved in the Titration Period	

EIAED = enzyme-inducing anti-epileptic drug

Table 2 EIAED Subjects: Dose Adjustments during the Titration and Maintenance Periods (revised per Amendment 02)

Treatment Phase/Titration Period	Visit	Daily Dose
For all EIAED subjects (up to 8 mg/day)		

a. Subjects who have shown good clinical response and tolerability at perampanel daily dosing of up to 8 mg will continue to receive the same dose throughout the remaining of Titration Period. (revised per Amendment 02)

b. At the discretion of the investigator; only if medically necessary (eg, inadequate seizure control) and provided that the subject has shown good tolerability at 8 mg/day (revised per Amendment 02)

c. Visit is considered the end of the Titration Period and start of the Maintenance Period.

Extension Phase

Details on treatments administered during the Extension Phase are provided in Appendix 3.

Other Dosing Considerations

Down-titration of perampanel upon early discontinuation or completion of the study is not necessary, because the plasma half-life of perampanel is between ~25 (in the presence of EIAED) to 105 (in the absence of EIAED) hours. As such, plasma concentrations decrease gradually following stopping perampanel. If, in the clinical judgment of the investigator, down-titration of perampanel is still deemed necessary, the investigator must discuss the down-titration before the early discontinuation with the Medical Monitor.

9.4.2 Identity of Investigational Product

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 United States.

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, place the bottles, suitably sized dosing devices (ie, oral syringes), and appropriately sized bottle adapters for accurate aliquotting (ie, PiBAs) into a tamper-evident sealed carton, and ship them to the study sites.

During the Core Study visits, parents/guardians will be provided with a bottle or bottles of suspension that can be redispensed or replaced at the next visit. Each bottle provided will be in a tamper-evident sealed carton that will also contain oral syringes and PiBAs. Detailed instructions on increments in dosage during the Titration Period will be provided to the subjects/guardians by the site investigator.

Details for the identity of the investigational product for the Extension Phase can be found in Appendix 3.

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)

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

Test drug will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. Perampanel is a Schedule III Controlled Drug Substance in the United States and will be labeled as such for US sites.

9.4.2.4 Storage Conditions

Where applicable, test drug will be stored and labeled in accordance with the US FDA Drug Enforcement Administration (DEA) Regulations for Scheduled III - V Drugs.

Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator 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. There is no randomization in this study.

9.4.4 Selection of Doses in the Study

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 a wide range of body weights (ie, 12.2 to 90.9 kg) analyzed to date, 20 were aged ≥2 to ≤7 years and 22 were aged ≥7 to <12 years. A total of 28 subjects were not receiving any of the EIAEDs (ie, CBX, OXC, or PHT) and 14 subjects were receiving one of these EIAEDs. As noted above, subjects in Study 232 were administered perampanel oral suspension (0.5 mg/mL) according to a weight-based regimen compared to tablets in Studies 304, 305, and 306. Whole blood perampanel concentration values from Study 232 analyzed using the DBS technique were converted to plasma concentrations, and for comparison purposes both plasma perampanel concentrations. The results of the analysis demonstrated that perampanel PK was linear as there was no dose or time-dependency to CL/F. The CL/F was not significantly affected by age, body weight, gender, race, hepatic function markers (ALT or AST), renal function marker (creatinine clearance) 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/body) administered in pediatric subjects. The results of the analysis suggested that a flat dosing approach will be more appropriate in subjects within that age range.

Considering the ontogenic profile with CYP3A enzyme in pediatrics, especially between 1 to less than 24 months of age, and due to the unknown safety profile in this population, a lower starting dose of 0.5 mg/day was selected for this study, with titrations to a maximum dose of 12 mg/day (non-EIAED subjects) or 16 mg/day (EIAED subjects). To date, sparse PK data is available from 3 pediatric subjects between age of 4.5 months to 20 months receiving perampanel through a Named Patient IND. These subjects were dosed perampanel up to 8 mg/day at steady state. The plasma concentration data in the 3 individuals although close to upper end of the range, were still within the 2-fold relative to the exposures observed in 2 to <12 year old subjects. Based on these findings, the likelihood of starting dose of 0.5 mg achieving unexpectedly high plasma exposures in the proposed age population is considered to be low.

Furthermore, noting the wide variability in hepatic metabolism via CYP3A in pediatric subjects less than 24 months of age, the risk of unexpected plasma exposures in number of pediatric subjects is further minimized by planned interim analysis (safety, tolerability, and PK) after every 4th subject completes the Maintenance Period. Dose-normalized exposures will be compared to that observed in other studies in subjects between ≥2 and <18 years of age for evidence of systematic deviations potentially warranting dose adjustment in this age group or for other subjects enrolled in the study.

Preliminary PK analysis was performed based on data obtained from 7 subjects (>6 to <24 months of age; 6 subjects without concomitant EIAED and 1 subject on concomitant EIAED) in this study and pooled with existing data from 2336 subjects (aged 2 to 77 years). Preliminary PK findings suggest that oral clearance in subjects aged less than 24 months without concomitant EIAED appears to be approximately 40% of that in subjects aged

≥2 years. It is predicted that a daily dose of 6 mg or 8 mg in subjects aged less than 24 months without or with concomitant EIAED, respectively, will result in comparable exposure to that in subjects aged >2 years receiving a daily dose of 12 mg (non-EIAED subjects) or 16 mg (EIAED subjects), respectively. However, European Medicines Agency/Paediatric Committee (EMA/PDCO) recommended that perampanel dose should be titrated up to a target dose of 4 mg/day for non-EIAED subjects (EMEA-000467-PIP01-08-M13), which could be further titrated up to 6 mg/day depending on individual subject's clinical response and tolerability. Therefore, the target dose in this study is revised to 4 mg/day (non-EIAED subjects) and 8 mg/day (EIAED subjects) in subjects less than 24 months of age, while the maximum dose allowed remains as 12 mg/day and 16 mg/day for non-EIAED and EIAED subjects, respectively. Perampanel dosage should not be further up-titrated, unless there is a medical need (for example, a subject who tolerated perampanel well but have not reached optimal seizure control). At any time in the study, perampanel dose must not to exceed 12 mg/day (non-EIAED subjects) or 16 mg/day (EIAED subjects). (revised per Amendment 02)

In subjects 2 to <4 years of age, there were very limited PK data (n=4) to allow adequate evaluation of effect of age on perampanel PK. Therefore, the same target dose and dose titration approach will be followed for non-EIAED and EIAED subjects aged 2 to less than 4 years as described above for 1 to less than 24 months subjects. (revised per Amendment 02)

9.4.5 Selection and Timing of Dose for Each Subject

Subjects will be instructed to take the study drug, by mouth, and before bedtime in the evening.

9.4.6 Blinding

This is an open-label, single-arm study. There is no blinding.

9.4.7 Prior and Concomitant Therapy

Any medication (including over the counter medications, or herbals) or therapy administered (including AEDs) during the course of the study (starting at the date of informed consent and those taken within 4 weeks of Visit 1) will be recorded on the Prior and Concomitant Therapy CRF and/or Nonpharmacologic Therapy/Procedure CRF. The investigator will record any AE on the Adverse Events CRF for which the concomitant medication/therapy was administered.

Subjects will be taking 1 to a maximum of 4 marketed AEDs (see inclusion criteria 6 and 7 and exclusion criteria 6 through 8 for further details). Changes of baseline AEDs (addition, deletion, or adjustment in dose) will not be allowed during 5 half-lives or during the 2 weeks, whichever is longer, before Visit 1. During the Core study, dose adjustments will be allowed only for non-EIAEDs. Dose adjustments of EIAEDs, and addition/deletion of any concomitant AEDs are not allowed during the Core study. Use of CBD products is allowed and is counted as 1 of the 4 maximum allowed concomitant AEDs. CBD dose and product must have remained stable for at least 2 weeks before Visit 1 and is to remain the same throughout the course of the Core Study. (revised per Amendment 02)

9.4.7.1 Drug-Drug Interactions

Not applicable.

9.4.7.2 Prohibited Concomitant Therapies and Drugs

The following medications will not be permitted (revised per Amendment 02):

- Medications known to be inducers of cytochrome P450 3A (CYP3A) (other than CBZ, OXC, PHT, or ESL) including, but not limited to: rifampin, troglitazone, St John's Wort, efavirenz, nevirapine, barbiturates (except for use as an AED), glucocorticoids (other than topical usage), modafinil, pioglitazone, and rifabutin within 2 weeks or 5 half-lives, whichever is longer, before Visit 1 and throughout the course of the study [Core and Extension])

- Felbamate (within 8 weeks before Visit 1 and throughout the course of the study [Core and Extension])

- Vigabatrin (within 2 weeks before Visit 1 and throughout the course of the study [Core and Extension])

In case of an emergency, subjects may receive other AEDs, including diazepam as well as other appropriate AEDs as rescue medications, to treat status epilepticus, uncontrolled seizures, or seizure clusters (see exclusion criterion 6).

For any drug known to influence the CNS (other than AEDs for epilepsy), the dose should be kept stable for 2 weeks or 5 half-lives, whichever is longer, before Visit 1 and throughout the course of the study (Core and Extension). (revised per Amendment 02)

Subjects are not permitted to participate in another study involving administration of an investigational drug or device for the full duration of this study (ie, up to and including the Follow-up Visit).

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. The CRA 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 Food and Drug Administration (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.

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 one 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 drugs to be used other than as directed by this protocol. The subject's parent/guardian may be dispensed study drugs for pediatric subjects.

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

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

9.5 Study Assessments

9.5.1 Assessments

Details for all assessment in the Extension Phase can be found in Appendix 3.

9.5.1.1 Demography

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

9.5.1.2 Baseline Assessments

MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical history, including and surgical history and current medical conditions, will be recorded. 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 and Table 5). 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. 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 Adverse Events CRF.

EPILEPSY MEDICAL HISTORY

In addition to standard medical history, epilepsy medical history will be documented for each subject.

9.5.1.3 Efficacy Assessments

SEIZURE COUNTS

Efficacy will be assessed by seizure counts and types as recorded on a study specific seizure diary. Diaries will be dispensed to all subjects at each visit as described in Table 4 and Table 5. 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 physician 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).

CLINICAL GLOBAL IMPRESSION OF CHANGE

The CGI will be used to evaluate perceived seizure frequency and severity, the occurrence of AEs, and overall functional status of the subject. The evaluations of CGIS and CGIC both use a 7-point scale. For the CGI-S, 1 = normal, not at all ill and 7 = extremely ill, and for the CGI-C, 1 = very much improved and 7 = very much worse.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

PHARMACOKINETIC ASSESSMENTS

Blood samples (1.0 mL) for plasma will be collected from all subjects at pre-specified visits for the determination of perampanel concentrations, as detailed in Table 4.

For subjects aged 1 to less than 24 months: Dosing should occur once daily before bedtime in the evening (revised per Amendment 02). On the day of the PK sampling, subjects will have to attend the clinic any time during the day to provide blood sampling for PK analysis and to enable close monitoring of the subjects for safety and tolerability. One blood sample (1.0 mL) for the determination of perampanel plasma concentrations will be collected during the specified visits. The resulting plasma sample will be aliquoted into 2 Microtainer tubes. Plasma samples will be analyzed using a validated small-volume plasma assay method.The

date and time of perampanel dosing for 3 days before a PK visit and time of blood PK sampling will be recorded.

For subjects aged 2 to less than 4 years, dosing should occur once daily before bedtime in the evening, including the evening before the PK visit during Titration Period (Visit 5 for non-EIAED subjects, or Visit 6 for EIAED subjects). The dosing date and time of the last 3 doses before Titiration Period PK visit will be recorded. Note: For PK visits during Maintenance Period (ie, Visits 7 and 8 for non-EIAED subjects, or Visits 8 and 9 for EIAED subjects), as 2 PK samples (1 predose and 1 early postdose [within 1 to 5 hours after dosing]) are to be collected, the following steps are to be followed (revised per Amendment 02):

- Study drug administration in the evening immediately before the PK visits during Maintenance Period will be withheld. All other AEDs should be administered per the subject's usual AED regimen.

- During each of the Maintenance Period PK visits, collect predose PK sample. Then administer study drug on site, followed by early postdose PK sample collection (within 1 to 5 hours after dose administration).

- Bedtime dosing will resume beginning in the evening of the Maintenance Period PK visits.

- The dosing date and time of the study drug dose administered on-site during each Maintenance Period PK visit, as well as the last 2 doses before will be recorded. (revised per Amendment 02)

A population PK approach will be used to characterize the PK of perampanel.

An approximation of the total blood volume that will be drawn from each subject during the study is presented in Appendix 2.

For all PK samples, including the unscheduled PK samples collected, if any, before dose up-titrations beyond 6 mg/day (non-EIAED subjects) or 8 mg/day (EIAED subjects), plasma concentrations of perampanel will be quantified by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) analytical method in sodium heparinized human plasma samples. (revised per Amendment 02)

Blood also will be drawn where possible at the first report of a serious adverse event (SAE) or severe unexpected AE and at its resolution.

A detailed description of collection, handling, and shipping procedures of PK samples will be provided in the Laboratory Manual to be provided to the sites.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Not applicable.

9.5.1.5 Safety Assessments

Safety will be assessed by monitoring and recording of all AEs and SAEs, clinical labs (ie, hematology and blood chemistry), vital signs, ECGs, medical history, and physical and neurological examinations.

Growth will be assessed for this age population by measurement of height, weight, head circumference, thyroid function and insulin-like growth factor-1 (IGF-1) testing.

Details of the timing of all safety assessments are presented in Table 4.

Adverse Events and Events Associated With Special Situations

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is perampanel (E2007).

The criteria for identifying AEs in this study are:

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

All AEs 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 Adverse Event 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 msec and there is an increase of more than 60 msec from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

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

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

ASSESSING SEVERITY OF ADVERSE EVENTS

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

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

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5 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.

Serious Adverse Events and Events Associated With Special Situations

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

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the 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 AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

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

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

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)

- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

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

LABORATORY MEASUREMENTS

Blood collections for clinical laboratory testing, including hematology, and chemistry, are summarized in Table 3. Subjects should be in a supine position during blood collection. In addition, blood samples for the determination of thyroid function (thyroid stimulating hormone [TSH], free triiodothyronine [fT3], free thyroxine [fT4]), and IGF-1 levels will be collected The Schedule of Procedures/Assessments (Table 4) shows the visits and timepoints at which blood for all clinical laboratory tests will be collected in the study (Core Study). An approximation of total blood volume that will be drawn for each subject during the study is presented in Appendix 2. (revised per Amendment 02)

Table 3 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
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, thyroid (TSH, fT3, fT4) and IGF-1 tests

fT3 = free triiodothyronine, fT4 = free thyroxine, IGF = insulin-like growth factor, RBC = red blood cell, TSH = thyroid stimulating hormone, WBC = white blood cell.

a. Samples for glucose and triglycerides will be taken under fasted conditions, whenever practically feasible. (revised per Amendment 02)

Clinical laboratory tests during the study will be performed by a central laboratory. All clinical laboratory tests are to be performed at the central laboratory. At Screening/Baseline (Visit 1), use of local laboratory test results (hematology, clinical chemistry, thyroid function and IGF-1 test), if obtained within 4 weeks before Visit 1, may be allowed in lieu of blood draw for central laboratory analyses, provided that the subject's local laboratory tests were performed at a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. In these cases,

to enable safety evaluation (eg, to assess whether there are treatment-emergent shifts in laboratory values from baseline), all post-baseline labs must be conducted at the same local laboratory using same assays as those used at Screening/Baseline. In other cases where unscheduled laboratory samples need to be taken and immediately analyzed to address a safety concern, blood samples will be split (or 2 samples drawn) to allow for a local laboratory analysis in addition to the central laboratory. Laboratory certification, as well as normal assay range for each of local laboratory tests run, will be collected as available and will be included in the clinical study report for this protocol. (revised per Amendment 02)

For laboratory abnormalities meeting the criteria of SAEs (see Section 9.5.1.5), the site must fax or email the SAE report including the laboratory report (as regionally required) to the sponsor using the SAE form (see Section 9.5.4.1).

VITAL SIGNS WEIGHT, HEIGHT, AND HEAD CIRCUMFERENCE 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 growth parameters including measurement of height, weight (kg), head circumference, will be obtained at the visits designated in the Schedule of Procedures/Assessments (Table 4). Blood pressure and pulse will be measured after the subject has been sitting or supine, for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

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 Adverse Events CRF.

ELECTROCARDIOGRAMS

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

ECGs should preferably be recorded prior to blood draws when both are scheduled at the same visit. However, if for any reason blood draws occur before ECG recording, then the ECG must be recorded at a minimum of 30 minutes after the blood draw. The subject should be relaxed and must be in a supine position at least 5 minutes prior to recording an ECG. The ECG will be reviewed by the investigator (paper or electronic tracing) and will be available for comparison with subsequent ECGs by the investigator.

If the subject has a normal ECG baseline reading, but during any visit thereafter there is any clinically significant ECG abnormality (as determined by the investigator), 3 consecutive ECGs separated by 5 to 10 minutes will be performed to confirm the abnormality at that visit.

ECGs will be transmitted the same day they are taken to the central ECG laboratory for evaluation. The ECG will be interpreted by a Central ECG laboratory cardiologist. The results of this over-read will be transmitted to the investigator. The cardiologist at the central ECG laboratory will be available to consult with the investigator(s) on the interpretation of individual subject ECG recordings, as needed. The corrected interval, as reported to the investigator by the Central ECG laboratory, will be QTc Fridericia (QTcF).

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

OTHER SAFETY ASSESSMENTS

Not applicable.

9.5.2 Schedule of Procedures/Assessments

Table 4 and Table 5 present the schedule of procedures/assessments for the Core Study.

Table 4 Schedule of Procedures/Assessments in Study E2007-G000-238: Core Study – Non-EIAED Subjects

Phase	Pretreatment	Treatment								Early Discontinuation	Unscheduled
Period		Titration					Maintenance		Follow-Up[a]		
Visit	1	2[b]	3[b]	4[c]	5[c]	6[c,d,e]	7[c]	8[c,f]			
Week	-2	0	2	4	8	12	14	16	20		
Days	-14	1	15	29	57	85	99	113	141		
Procedures/Assessments											
Demography	X										
Informed consent/assent	X										
Inclusion/exclusion criteria	X	X									
Medical history	X										
Epilepsy medical history	X										
Prior and concomitant medication(s)	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant AED(s)	X	X	X	X	X	X	X	X	X	X	X
Neurological examination[g]	X							X	X	X	
Physical examination[h]	X							X	X	X	
Vitals and weight	X	X	X	X	X	X	X	X	X	X	X
Height/length[h]	X	X						X		X	
Head circumference	X	X						X		X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug		X	X	X	X	X	X	X[i]			X[j]
Retrieve unused study drug			X	X	X	X	X	X		X	X[j]
Study drug compliance			X	X	X	X	X	X		X	X
Dispense subject's diary	X[k]	X	X	X	X	X	X	X		X	X[l]
Retrieve and review subject diary		X	X	X	X	X	X	X	X	X	X[l]
Clinical laboratory tests[m, n]	X					X		X	X	X	X[o]
Thyroid function (TSH, fT3, fT4) and IGF-1 tests	X							X		X	
12-lead ECG[p]	X			X		X		X	X	X	X[q]
Perampanel PK blood sampling[r]					X		X	X		X	X[l]
Telephone call[s]		X	X	X	X	X	X	X	X		
CGI-C, CGI-S[t]		X						X		X	
Disposition	X	X						X		X	

Table 4 Schedule of Procedures/Assessments in Study E2007-G000-238: Core Study – Non-EIAED Subjects

Phase	Pretreatment	Treatment								Early Discontinuation	Unscheduled
Period		Titration					Maintenance		Follow-Up[a]		
Visit	1	2[b]	3[b]	4[c]	5[c]	6[c,d,e]	7[c]	8[c,f]			
Week	-2	0	2	4	8	12	14	16	20		
Days	-14	1	15	29	57	85	99	113	141		
Procedures/Assessments											

AE = Adverse event, AED = Anti-epileptic drug, CGI-C = Clinical Global Impression of Change, CGI-S = Clinical Global Impression of Severity, CLIA = Clinical Laboratory Improvement Amendments, CRF = case report form, EAP = extended access program, ECG = electrocardiogram, EOT = end of treatment, fT3 = free triiodothyronine, fT4 = free thyroxine, IGF-1 = insulin-like growth factor-1, PK = pharmacokinetics, SAE = serious adverse event,TSH = thyroid-stimulating hormone.

a: To be done within ±6 days of the scheduled visit. Visit applies only to those subjects who complete the Treatment Phase but do not roll-over into the Extension Phase and those subjects who discontinue the study early for any reason after Visit 2 and before Visit 8.

b: To be done within ±2 days of the scheduled visit.

c: Visits should be done within ± 3 days of the scheduled visit. There must be at least 10 days of treatment between Visits 3 and 4, 4 and 5, and 5 and 6.

d: Upon successful completion of Visit 6, subjects will begin the Maintenance Period of the study.

e: No dose titration is allowed at this visit or future visits.

f: Visit 8 will be considered the first visit of the Extension Phase for subjects who choose to continue into the Extension Phase.

g: For clinic visits other than those specified, physical and complete neurological exams, including evaluation of the cranial nerves, motor, sensory, brainstem, cerebellar, and autonomic functions, will only be performed when there is a complaint from the parent/guardian.

h: Two measurements of height/length should be taken. Each measurement should be recorded as a separate entry on the Vital Sign CRF.

i: Only for those subjects who roll-over into the Extension Phase.

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

k: To include the number and type of seizures for the 4 weeks before the Pretreatment Phase.

l: As needed.

m: Lipid and blood glucose tests to be conducted under fasting conditions, whenever practically feasible. (revised per Amendment 02)

n: All clinical laboratory tests are to be performed at the central laboratory. At Screening/Baseline (Visit 1), use of local laboratory test results (hematology, clinical chemistry, thyroid function and IGF-1 test) may be allowed if the subject's local laboratory tests are obtained from a CLIA-certified laboratory within 4 weeks before Visit 1. In these cases, to enable safety evaluation (eg, to assess whether there are treatment-emergent shifts in laboratory values from baseline), all post-baseline labs must be conducted at the same local laboratory using same assays as those used at Screening/Baseline. (revised per Amendment 02)

o: During the unscheduled visits, clinical laboratory tests will only be done if an abnormality was noted at the previous visit or per the discretion of the investigator. (revised per Amendment 02)

p: If the subject has a normal ECG baseline reading, but during any visit thereafter if there is any clinically significant ECG abnormality (as determined by the investigator), 3 consecutive ECGs separated by 5 to 10 minutes will be performed at that visit to confirm the abnormality.

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

r: Blood samples (1.0 mL each) will be collected from all subjects for the determination of perampanel concentrations. The date and time of PK sample collection will be recorded on the CRF, as well as the date and time of the last 3 perampanel doses administered before the PK sample collection. Subjects aged 1 to less than 24 months will have 1 PK sample taken at anytime after the last perampanel dose per PK visit. Subjects aged 2 to less than 4 years will have 2 PK samples taken (1 predose and 1 postdose between 1 and 5 hours after dose administration) per PK visit. See Section 9.5.1.4 for details. After centrifugation, plasma sample harvested will be aliquoted onto 2 Microtainer tubes (1 primary and 1 back-up sample). (revised per Amendment 02)

Table 4 Schedule of Procedures/Assessments in Study E2007-G000-238: Core Study – Non-EIAED Subjects

Phase	Pretreatment	Treatment								Early Discontinuation	Unscheduled
Period		Titration					Maintenance		Follow-Up[a]		
Visit	1	2[b]	3[b]	4[c]	5[c]	6[c,d,e]	7[c]	8[c,f]			
Week	-2	0	2	4	8	12	14	16	20		
Days	-14	1	15	29	57	85	99	113	141		
Procedures/Assessments											

s: Telephone interviews with the parent/guardian will be conducted approximately 1 week after Visit 2 and 3, and approximately at the midpoint between each subsequent visit, 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 strongly be encouraged to return to the clinic (instead of the scheduled telephone interview) for further consultation with regard to study drug administration. Subjects will then return for their regularly scheduled visit. Subjects not continuing into the Extension phase will have a telephone interview at approximately the midpoint between Visit 8 and the Follow-up Visit after finishing the Maintenance Period when drug has been stopped. Subjects that discontinue the study at any time will have a telephone interview at approximately the midpoint between the EOT Visit and the Follow-up Visit. For subjects who will not need to undergo Follow-up Visit (eg, when switching to commercially available Fycompa or entering EAP after the last study drug administration) will have a telephone interview 28 (+6) days after the last study drug administration. AEs/SAEs that occurred within 28 days after the last study drug administration will be reported. (revised per Amendment 02)

t: CGI-S to be administered at Visit 2, CGI-C to be administered at Visit 8 or early discontinuation.

Table 5 Schedule of Procedures/Assessments in Study E2007-G000-238: Core Study - EIAED Subjects

Phase	Pretreatment	Treatment									Early Discontinuation	Unscheduled
Period		Titration						Maintenance		Follow-Up[a]		
Visit	1	2[b]	3[b]	4[c]	5[c]	6[c]	7[c,d,e]	8[c]	9[c,f]			
Week	-2	0	2	4	8	12	16	18	20	24		
Days	-14	1	15	29	57	85	113	127	141	169		
Procedures/Assessments												
Demography	X											
Informed consent/assent	X											
Inclusion/exclusion criteria	X	X										
Medical history	X											
Epilepsy medical history	X											
Prior and concomitant medication(s)	X	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant AED(s)	X	X	X	X	X	X	X	X	X	X	X	X
Neurological examination[g]	X								X	X	X	
Physical examination[h]	X								X	X	X	
Vitals and weight	X	X	X	X	X	X	X	X	X	X	X	X
Height/length[h]	X	X							X		X	
Head circumference	X	X							X		X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug		X	X	X	X	X	X	X	X[i]			X[j]
Retrieve unused study drug			X	X	X	X	X	X	X		X	X[j]
Study drug compliance			X	X	X	X	X	X	X		X	X
Dispense subject's diary	X[k]	X	X	X	X	X	X	X	X		X	X[l]
Retrieve and review subject diary		X	X	X	X	X	X	X	X	X	X	X[l]
Clinical laboratory tests[m,n]	X					X	X		X	X	X	X[o]
Thyroid function (TSH, fT3, fT4) and IGF-1 tests	X								X		X	
12-lead ECG[p]	X			X		X	X		X	X	X	X[p,q]
Perampanel PK blood sampling[r]						X		X	X		X	X[o]
Telephone call[s]		X	X	X	X	X	X	X	X			
CGI-C, CGI-S[t]		X							X		X	

Table 5 Schedule of Procedures/Assessments in Study E2007-G000-238: Core Study - EIAED Subjects

Phase	Pretreatment	Treatment										
Period		Titration						Maintenance		Follow-Up[a]	Early Discontinuation	Unscheduled
Visit	1	2[b]	3[b]	4[c]	5[c]	6[c]	7[c,d,e]	8[c]	9[c,f]			
Week	-2	0	2	4	8	12	16	18	20	24		
Days	-14	1	15	29	57	85	113	127	141	169		
Procedures/Assessments												
Disposition	X	X							X		X	

AE = Adverse event, AED = Anti-epileptic drug, CGIC = Clinical Global Impression of Change, CGI-S = Clinical Global Impression of Severity, CLIA = Clinical Laboratory Improvement Amendments, CRF = case report form, EAP = extended access program, ECG = electrocardiogram, EOT = end of treatment, fT3 = free triiodothyronine, fT4 = free thyroxine, IGF-1 = insulin-like growth factor-1, PK = pharmacokinetics, SAE = serious adverse event, TSH = thyroid-stimulating hormone.

a: To be done within ±6 days of the scheduled visit. Visit applies only to those subjects who complete the Treatment Phase but do not roll-over into the Extension Phase, those who discontinue early from the study for any reason after Visit 2 and before Visit 9. (revised per Amendment 02)
b: To be done within ±2 days of the scheduled visit.
c: Visits should be done within ± 3 days of the scheduled visit. There must be at least 10 days of treatment between Visits 3 and 4, 4 and 5, 5 and 6, and 6 and 7
d: Upon successful completion of Visit 7, subjects will begin the Maintenance Period of the study.
e: No dose titration is allowed at this visit or future visits.
f: Visit 9 will be considered the first visit of the Extension Phase for subjects who choose to continue into the Extension Phase.
g: For clinic visits other than those specified, physical and complete neurological exams, including evaluation of the cranial nerves, motor, sensory, brainstem, cerebellar, and autonomic functions, will only be performed when there is a complaint from the parent/guardian.
h: Two measurements of height/length should be taken. Each measurement should be recorded as a separate entry on the Vital Sign CRF.
i: Only for those subjects who roll-over into the Extension Phase.
j: Unused study drug to be retrieved and study drug dispensed only for subject requiring dose increases at Unscheduled Visits.
k: To include the number and type of seizures for the 4 weeks before the Pretreatment Phase.
l: As needed.
m: Lipid and blood glucose tests must be conducted under fasting conditions, whenever practically feasible. (revised per Amendment 02)
n: All clinical laboratory tests are to be performed at the central laboratory. At Screening/Baseline (Visit 1), use of local laboratory test results (hematology, clinical chemistry, thyroid function and IGF-1 test) may be allowed if the subject's local laboratory tests are obtained from a CLIA-certified laboratory within 4 weeks before Visit 1. In these cases, to enable safety evaluation (eg, to assess whether there are treatment-emergent shifts in laboratory values from baseline), all post-baseline labs must be conducted at the same local laboratory using same assays as those used at Screening/Baseline. (revised per Amendment 02)
o: During the unscheduled visits, clinical laboratory tests will only be done if an abnormality was noted at the previous visit or per the discretion of the investigator.
p: If the subject has a normal ECG baseline reading, but during any visit thereafter if there is any clinically significant ECG abnormality (as determined by the investigator), 3 consecutive ECGs separated by 5 to 10 minutes will be performed at that visit to confirm the abnormality.
q: During the unscheduled visits, ECG will only be done if the results from the previous visit were deemed to be clinically significant by the investigator.

Table 5 Schedule of Procedures/Assessments in Study E2007-G000-238: Core Study - EIAED Subjects

Phase	Pretreatment	Treatment									Early Discontinuation	Unscheduled
Period		Titration						Maintenance		Follow-Up[a]		
Visit	1	2[b]	3[b]	4[c]	5[c]	6[c]	7[c,d,e]	8[c]	9[c,f]			
Week	-2	0	2	4	8	12	16	18	20	24		
Days	-14	1	15	29	57	85	113	127	141	169		
Procedures/Assessments												

r: Blood samples (1.0 mL each) will be collected from all subjects for the determination of perampanel concentrations. The date and time of PK sample collection will be recorded on the CRF, as well as the date and time of the last 3 perampanel doses administered before the PK sample collection. Subjects aged 1 to less than 24 months will have 1 PK sample taken at anytime after the last perampanel dose per PK visit. Subjects aged 2 to less than 4 years will have 2 PK samples taken (1 predose and 1 postdose between 1 and 5 hours after dose administration) per PK visit. See Section 9.5.1.4 for details. After centrifugation, plasma sample harvested will be aliquotted onto 2 Microtainer tubes (1 primary and 1 back-up sample). (revised per Amendment 02)

s: Telephone interviews with the parent/guardian will be conducted approximately 1 week after Visit 2 and Visit 3, and at approximately the midpoint between each subsequent 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 strongly be encouraged to return to the clinic (instead of the scheduled telephone interview) for further consultation with regard to study drug administration. Subjects will then return for their regularly scheduled visit. Subjects not continuing into the Extension phase will have a telephone interview at approximately the midpoint between Visit 9 and the Follow-up Visit after finishing the maintenance period when drug has been stopped. Subjects that discontinue the study at any time will have a telephone interview at approximately the midpoint between the EOT Visit and the Follow-up Visit. For subjects who will not need to undergo Follow-up Visit (eg, when switching to commercially available Fycompa or entering EAP after the last study drug administration), sites will conduct a telephone contact 28 (+6) days after the last dose of study drug to follow AEs and report any SAEs that occur within 28 days of the last study drug administration. (revised per Amendment 02)

t: CGI-S administered at Visit 2, CGIC administered at Visit 9 or early discontinuation. (revised per Amendment 02)

9.5.2.1 Description of Procedures/Assessments Schedule

For a description of the procedures and assessments see Table 4.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in Phase 2 studies of epilepsy in pediatric subjects.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, 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.

Serious adverse events, 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.

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 24 hours 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

Not applicable.

9.5.4.3 Reporting of Events Associated with Special Situations

REPORTING OF ADVERSE EVENTS ASSOCIATED WITH STUDY DRUG OVERDOSE, MISUSE, ABUSE, OR MEDICATION ERROR

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

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol. Intentional and inappropriate use of study drug not in accordance with the prescribed or authorized dose, route of administration, or indication(s) or use of prescription-only study drug without a prescription
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

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

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

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

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

9.5.5 Completion/Discontinuation of Subjects

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. 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 are to return for a Follow-up Visit 4 weeks (±6 days) after the last dose of study drug.

The investigator will promptly explain to the parent/guardian 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, or administrative/other. In addition to the primary reason, the subject may indicate one 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 course of 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.

Adverse events associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects' parent(s)/guardian(s) to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subjects' parent(s)/guardian(s) whether the subject has received medical care from 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 third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

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

9.7 Statistical Methods

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

9.7.1 Statistical and Analytical Plans

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

9.7.1.1 Study Endpoints

PRIMARY ENDPOINT

- PK of perampanel during the Maintenance Period of the Core Study (revised per Amendment 02)

SECONDARY ENDPOINTS

- Safety and tolerability during the Core Study and the Extension Phase, which include incidence of treatment-emergent adverse events (TEAEs) and SAEs, laboratory parameters, vital signs, and ECG parameters, and growth parameters (height, weight, head circumference, thyroid function,and IGF-1 levels) (revised per Amendment 02)

EXPLORATORY ENDPOINTS

The efficacy endpoints are:

- Seizure frequency: Percent change in 28-day seizure frequency during the Treatment Phase and during the Extension Phase, compared to baseline (revised per Amendment 02)
- Responder rate: Proportion of subjects with a 50% or greater reduction in 28-day seizure frequency during the Maintenance Period and during the Extension Phase, compared to baseline (revised per Amendment 02)
- Seizure-free rate: Proportion of subjects who are seizure-free during the Maintenance Period and during the Extension Phase
- CGI-C at the end of the Core Study and the Extension Phase

Details on endpoints for the Extension Phase can be found in Appendix 3.

9.7.1.2 Definitions of Analysis Sets

The Pharmacokinetic Analysis Set is the group of subjects with at least 1 PK assessment of perampanel during the Maintenance Period with a documented dosing history.

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 study drug and had any seizure frequency data during the 2 weeks of Pretreatment Phase plus 4 weeks before the Pretreatment Phase and during the Treatment Phase.

9.7.1.3 Subject Disposition

A disposition or reason 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

The demographics and baseline characteristics of the Safety Analysis Set will be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum) for the continuous variables such as age, and using numbers and percentages for categorical variables which includes sex, age group, and race.

9.7.1.5 Prior and Concomitant Therapy

Prior and concomitant medications will be assigned an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) drug codes. Concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. Concomitant medications by drug and drug class will be tabulated and included in the clinical study report for this protocol.

9.7.1.6 Efficacy Analysis

This study is designed to assess PK and preliminary safety, tolerability and efficacy. No formal statistical analysis will be performed. Summary statistics will be displayed for the following efficacy parameters in the FAS.

Treatment Phase:

- Seizure Frequency: Percentage change in 28-day seizure frequency during the Treatment Phase and the Extension Phase, compared to Baseline. The primary analysis will use data prospectively collected during the 2-week Pretreatment Phase to calculate baseline 28-day seizure frequency. A secondary analysis will use data prospectively collected during the 2-week Pretreatment Phase plus data retrospectively collected during the 4 week period before Visit 1 to calculate baseline 28-day seizure frequency. Seizure frequency per 28 days will be calculated as the number of seizures over the entire time interval divided by the number of days in the interval and multiplied by 28. (revised per Amendment 02)
- Responder Rate: A responder is defined as a subject with atleast 50% decrease in 28-day seizure frequency while on treatment when compared to Baseline. Analyses using the 2 different baseline definitions above will be performed. For subjects who discontinue the

study with less than 8 weeks of seizure data in the Maintenance Period, the last 8 weeks of data after the first dose (or entire treatment duration if <8 weeks of data are available) will be used in lieu of Maintenance Period.

- Seizure-free status: The proportion of subjects who are seizure-free during the Maintenance Period
- CGI-C

Details on efficacy analyses for the Extension Phase can be found in Appendix 3.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

PHARMACOKINETIC ANALYSES

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

A population PK approach will be used to characterize the PK of perampanel. The effect of intrinsic and extrinsic factors (age, body weight, gender, race, ALT, AST, creatinine clearance, and concomitant therapy with carbamazepine, oxcarbazepine, phenytoin, phenobarbital, valproic acid, lamotrigine, topiramate, primidone, zonisamide, levetiracetam and primidone) on perampanel PK will be evaluated. A 2-compartment disposition PK model with linear elimination will be parameterized for absorption rate, oral clearance (CL/F) and apparent central and peripheral volumes of distribution (V_1/F and V_2/F). Derived exposure parameters such as the steady state peak concentration ($C_{max,ss}$), area under concentration vs time curve at steady state (AUC_{ss}), and average steady-state drug concentration ($C_{ss,av}$) will be calculated using the individual posterior estimates of PK parameters from the final PK model. Descriptive statistics of the individual model-predicted PK parameters including but not limited ($C_{max,ss}$ will be provided.

Due to the small sample size, population PK analysis will be performed using NONMEM with first-order conditional estimation with interaction on data from this study pooled with existing rich data from 19 Phase 1 studies and sparse data from two Phase 2 studies (232 and 235), and 5 Phase 3 Studies (304, 305, 306, 332 and 335). A 2-compartment PK model will be fitted 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 AUC from the final PK mode will be derived for all subjects. Subsequently, dose-normalized derived exposure parameters will be summarised descriptively by age group (≤ 6 months, > 6 to ≤ 12 months, >12 to < 24 months, ≥ 24 months to ≤4 years, >4 to ≤ 8 years, > 8 to < 12 years, ≥12 to < 18 years and ≥18 years) and also presented in box-plots, stratified by subjects taking and not taking EIAEDs. Additionally, dose-normalized derived exposure parameters will be summarized descriptively for the following age groups: 1 to 24 months, 2 to ≤ 4 years, >4 to ≤ 8 years, >8 to <12 years, ≥12 to <18 years and ≥18

years), and also presented in box-plots, stratified by subjects with EIAEDs and non-EIAEDs. (revised per Amendment 02)

The final PK model will be qualified using visual predictive checks and validated using bootstrap analysis.

PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Not applicable.

9.7.1.8 Safety Analyses

Evaluation of safety will be performed on the Safety Analysis Set.

EXTENT OF EXPOSURE

Duration of Treatment Phase (Titration Period + Maintenance Period) exposure will be calculated as the number of days between the date the subject received the first dose of study drug and the date the subject received the last dose of study drug in the Treatment Phase.

Overall study compliance rate for each subject will be calculated as the mean compliance rate over all the visits.

ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 16.1 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A 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 by age group and by EIAED and non-EIAED. 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) and 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 treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

Adverse events of special interest will also be summarized by SOC and PT using MedDRA SMQ terms.

A subject data listing will be produced for all deaths, SAEs, and discontinuation due to an AE.

Adverse events will be summarized using the Safety Analysis Set.

LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.7.1.8, 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 and by age group using descriptive statistics. Qualitative parameters listed in Section 9.7.1.8 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

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

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

VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and growth

parameters including measurement of height, weight (kg) changes from baseline, head circumference) will be presented by visit and by age group.

ELECTROCARDIOGRAMS

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

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 QTcF during the treatment period will be summarized. Clinically borderline and abnormal ECG results in QTcF will be categorized as follows:

Absolute QTc interval prolongation:

- QTc interval 430-450 msec
- QTc interval >450 msec
- QTc interval >500 msec

Change from baseline in QTc interval:

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

OTHER SAFETY ANALYSES

Growth

Descriptive summary statistics of changes from baseline in height, weight, and head circumference will be evaluated for each cohort and overall. This data will be compared with normative scores to assess clinical relevance.

Changes from baseline for thyroid function and IGF-1 testing will be summarized.

9.7.2 Determination of Sample Size

Study E2007-G000-238 will use population PK modeling to determine PK in pediatrics ≥1 to <24 months and from 2 to less than 4 years of age and compare these data to PK in adolescents and adults. In Study E2007-G000-232, data were obtained in 42 pediatric subjects ≥2 to <12 years of age, with approximate equal numbers enrolled in the age ranges of ≥2 to ≤6 and ≥7 to <12 years. (revised per Amendment 02)

Given the narrower age range planned for Study 238 compared with Study 232, and the fact that the PK data from this study will be pooled with the data from subjects ≥2 to <12 years of age, it is proposed that PK data obtained in at least 16 subjects ≥1 to <24 months of age would

be adequate to characterize the PK in this age group. The sample size will be increased to at least 24 subjects if dose-normalized (to 8 mg) exposure in the Maintenance Period from the first 16 subjects in this study is not comparable to existing data in subjects aged ≥2 to 18 years.

In order to compare the PK of pediatric subjects aged 2 to <4 years of age with the PK of pediatric subjects aged >4 years of age, a total of 26 subjects with 13 EIAED subjects and 13 non-EIAED subjects will be enrolled and pooled across clinical studies of perampanel with PK assessment. This estimate of the required sample size assumes the inter-subject variability of 46.8% (CPMS-E2007-015-v1), equivalent to a coefficient of variation (CV) on the log scale of 0.445, that provides a sufficient number of subjects to target a 95% confidence interval within 60% and 140% of the point estimate for the geometric mean clearance of perampanel (equal to 0.638 L/h; determined using population PK modeling) with at least 80% power. (revised per Amendment 02)

9.7.3 Interim Analysis

After every 4th subject in the age group 1 to less than 24 months completes the Maintenance Period an interim analysis (safety, tolerability, and PK) will be conducted where dose-normalized exposure will be compared to that observed in other studies in subjects between ≥2 and <18 years of age for evidence of systematic deviations potentially warranting dose adjustment in this age group or for other subjects enrolled in the study. PK data collected in older age cohort (2 to less than 4 years) will also be examined in the interim PK analyses. (revised per Amendment 02)

All data from the Pretreatment and Treatment Phases (Core Study) will be analyzed when all subjects have completed the Maintenance Period. In addition, a final analysis of data from the Pretreatment, Treatment, and Extension Phases will be analyzed when all subjects have completed the Extension Phase.

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.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistician determines that the analysis plan needs to be revised after this study starts, the person in charge of the analysis plan and the study director will examine the validity of the revision and the impact of the revision against the evaluation of this study and determine if the revision should be made. The details of revision will be described in the clinical study report for this protocol.

10 REFERENCE LIST

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Zebinix® Summary of Product Characteristics.

11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

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

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

11.2 Adherence to the Protocol

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

11.3 Monitoring Procedures

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

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

- Clinic, office, or hospital charts

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

11.4 Recording of Data

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

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

11.5 Identification of Source Data

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

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, 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 investigational product.

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

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department may conduct 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.

11.8 Handling of Study Drug

Perampanel is a Schedule III Controlled Drug Substance in the United States.

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

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

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

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

11.10 Disclosure and Confidentiality

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

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

11.11 Discontinuation of Study

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

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

11.12 Subject Insurance and Indemnity

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

12 APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values

	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	<$3.0 – 2.0\times10^9$/L <3000 – 2000/mm^3	<$2.0 – 1.0\times10^9$/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 <$0.8 – 0.5\times10^9$/L	<500 – 200/mm^3 <$0.5 – 0.2\times10^9$/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<$1.5 – 1.0\times10^9$/L <1500 – 1000/mm^3	<$1.0 – 0.5\times10^9$/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	<$75.0 – 50.0\times10^9$/L <75,000 – 50,000/mm^3	<50.0 – 25.0×109/L <50,000 – 25,000/mm^3	<25.0×109/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3.0 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

	Grade 1	Grade 2	Grade 3	Grade 4
				life-threatening consequences; seizures
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), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix 2 Total Blood Volumes (revised per Amendment 02)

Non-EIAED Subjects												
	Minimum Blood Volumes Required (mL)[a]											
	Core Study (Pretreatment Phase + Treatment Phase)								Extension Phase			
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	F/U
Chemistry	0.5					0.5		0.5	0.5	0.5	0.5	0.5
Hematology	0.5					0.5		0.5	0.5	0.5	0.5	0.5
TSH, fT3, fT4	0.5							0.5	0.5		0.5	
IGF-1	0.5							0.5	0.5		0.5	
Perampanel PK					1.0		1.0[b]/2.0[c]	1.0[b]/2.0[c]				
Approximate total blood volume sampled during each visit (mL)	**2.0**				**1.0**	**1.0**	**1.0[b]/2.0[c]**	**3.0[b]/4.0[c]**	**2.0**	**1.0**	**2.0**	**1.0**
Approximate total blood volume per subject (mL)	**~14.0[b] to 16.0[c]**											

fT3 = free triiodothyronine; fT4 = free thyroxine; F/U = follow-up; IGF-1 = insulin-like growth factor-1; PK = pharmacokinetics; TSH = thyroid-stimulating hormone; V = visit.

a: Assumes no retesting.
b: For subjects aged 1 to less than 24 months. (revised per Amendment 02)
c: For subjects aged 2 to less than 4 years. (revised per Amendment 02)

EIAED Subjects													
	Minimum Blood Volumes Required (mL)[a]												
	Core Study (Pretreatment Phase + Treatment Phase)									Extension Phase			
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	F/U
Chemistry	0.5					0.5	0.5		0.5	0.5	0.5	0.5	0.5
Hematology	0.5					0.5	0.5		0.5	0.5	0.5	0.5	0.5
TSH, fT3, fT4	0.5								0.5	0.5		0.5	
IGF-1	0.5								0.5	0.5		0.5	
Perampanel PK						1.0		1.0[b]/2.0[c]	1.0[b]/2.0[c]				
Approximate total blood volume sampled during each visit (mL)	**2.0**					**1.0**	**1.0**	**1.0[b]/2.0[c]**	**3.0[b]/4.0[c]**	**2.0**	**1.0**	**2.0**	**1.0**
Approximate total blood volume per subject (mL)	**~14.0[b] to 16.0[c]**												

fT3 = free triiodothyronine; fT4 = free thyroxine; F/U = follow-up; IGF-1 = insulin-like growth factor-1; PK = pharmacokinetics; TSH = thyroid-stimulating hormone; V = visit.

a: Assumes no retesting.
b: For subjects aged 1 to less than 24 months. (revised per Amendment 02)
c: For subjects aged 2 to less than 4 years. (revised per Amendment 02)

Appendix 3 Extension Phase

Eligibility Criteria

Subjects who meet the following will be eligible to participate in the Extension Phase of this study:

- Have completed the last visit of the Maintenance Period of the Core Study

Study Design and Plan

During the 32-36-week Maintenance Period of the Extension Phase, subjects will continue taking perampanel oral suspension, at the dose level achieved at the end of the Treatment Phase. The maximum total daily dose a subject will be allowed is 12 mg for non-EIAED subjects and 16 mg for EIAED subjects.

Study Drug Supplies

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 Substance in the United States and will be labeled as such for US sites.

Perampanel oral suspension will be provided by Eisai to an Eisai-approved vendor in 400-mL PET bottles containing 340 mL of oral suspension. The approved vendor will label the bottles, place the bottles, suitably sized dosing devices (ie, oral syringes), and appropriately sized bottle adapters for accurate aliquotting (ie, PiBAs) into a tamper-evident sealed carton, and ship them to the study sites. During the Extension Phase, parents/guardians will be provided with a bottle or bottles of suspension that can be redispensed or replaced at the next visit. Each bottle provided will be in a tamper-evident sealed carton that will also contain oral syringes and PiBAs. Instructions regarding routine dosages during the Extension Phase will be provided by the site.

Treatments Administered

- Maintenance Period (32-36 weeks): Subjects will continue taking perampanel oral suspension, at the dose level achieved at the end of the Treatment Phase. The maximum total daily dose a subject will be allowed is 12 mg for non-EIAED subjects or 16 mg for EIAED subjects.

  Dose adjustment during this phase is allowed if necessary, per the investigator's clinical judgment. Subjects must return to the clinic for an unscheduled visit for any dose increase. However, dose decreases can be done via telephone.

All dose adjustments during this phase will be done by going one dose level up or down. Subjects who do not tolerate a dose of 0.5 mg/day will be discontinued from the study.

Changes of concomitant AEDs (addition, deletion or adjustment in dose) will be allowed. However, if changes do occur subjects should be carefully monitored, especially when switching between an EIAED and a non-EIAED.

- Follow-Up Period (4 weeks): No study drug will be administered during Follow-up Period. All subjects will be required to complete the Follow-up Period after their last dose in the Extension Phase, except for subjects who switch to commercially available perampanel or who enter EAP upon completion of study treatment. For these subjects, sites will conduct a telephone contact 28 (+6) days after the last dose of study drug to follow adverse events (AEs) and report any serious adverse events (SAEs) that occur within 28 days of the last study drug administration. (revised per Amendment 02)

The Schedule of Procedures/Assessments for the 36 - 40-week Extension Phase of the study is presented in Table 6 and Table 7.

Table 6 Schedule of Procedures/Assessments in Study E2007-G000-238: Extension Phase – Non-EIAED Subjects

Phase	Extension[a]					
Period	Maintenance			Follow-Up[b]		
Visit	9	10	11		Early Discontinuation	Unscheduled
Week	28	40	52	56		
Days	197	281	365	393		
Procedures/Assessments						
Concomitant medications	X	X	X	X	X	X
Concomitant AEDs	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
Study drug compliance	X	X	X		X	X
Dispense study drug	X	X				X[c]
Retrieve unused study drug	X	X	X		X	X[c]
Dispense subject's diary	X	X	X		X	X[d]
Retrieve and review subject diary	X	X	X	X	X	X[d]
Physical examination[e]	X		X		X	
Neurological examination[e]	X		X		X	
Vitals and weight	X	X	X		X	X
Height/length[f]	X		X		X	
Head circumference	X		X		X	
Clinical laboratory tests[g]	X	X	X[h]	X	X[h]	X[i]
Thyroid function (TSH, fT3, fT4) and IGF-1 tests	X		X		X	
12-lead ECG[j]	X		X		X	X[k]
CGI-C			X		X	
Telephone call[l]	X	X	X			
Disposition			X		X	

AE = Adverse event, AED = Anti-epileptic drug, CGI-C = Clinical Global Impression of Change, CRF = case report form, EAP = extended access program, ECG = electrocardiogram, EOT = End of Treatment, fT3 = free triiodothyronine, fT4 = free thyroxine, IGF-1 = insulin-like growth factor-1, SAE = serious adverse event, TSH = thyroid-stimulating hormone.

a: All visits to be done within ± 6 days of the schedule.

b: The Follow-up Visit (4 weeks ± 6 days after the last dose of study medication) applies to those subjects who complete the entire study and those who discontinue early during the Extension Phase. Subjects who switch to commercially available perampanel or who enter into EAP upon completion of study treatment will not need to undergo Follow-up Visit; however, sites will conduct a telephone contact 28 (+6) days after the last dose of study drug to follow AEs and report any SAEs that occur within 28 days of the last study drug administration. (revised per Amendment 02)

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

d: As needed.

e: For clinic visits other than those specified, physical and complete neurological exams, including evaluation of the cranial nerves, motor, sensory, brainstem, cerebellar, and autonomic functions, will only be performed when there is a complaint from the parent/guardian. Clinically significant abnormal findings from the physical or the neurological examinations must be reported as AEs.

f: Two measurements of height/length should be taken. Each measurement should be recorded as a separate entry on the Vital Sign CRF.

g: Clinical laboratory tests include hematology and blood chemistry.

h: Lipid and blood glucose tests must be conducted under fasting conditions, whenever practically feasible. (revised per Amendment 02)

i: During the unscheduled visits, clinical laboratory tests will only be done if an abnormality was noted at the previous visit or per the discretion of the investigator.

j: If the subject has a normal ECG baseline reading, but during any visit thereafter if there is any clinically significant ECG abnormality (as determined by the investigator), 3 consecutive ECGs separated by 5 to 10 minutes will be performed at that visit to confirm the abnormality.

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

l: Telephone interviews with the parent/guardian will be conducted approximately 6 weeks following Visit 8 through Visit 11 to ensure that subjects are completing their seizure diaries regularly and assess AEs, study drug compliance and concomitant medications, including AEDs and to remind the subjects that they are to complete their seizure diary. 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. Subjects will then return for their regularly scheduled visits. All subjects will have a telephone interview at approximately the midpoint between Visit 11 and the Follow-up Visit when drug has been stopped. Subjects who discontinue the study at any time will have a telephone interview at approximately the midpoint between the EOT Visit and the Follow-up Visit. For subjects who will not need to undergo Follow-up Visit (eg, when switching to commercially available Fycompa or enetering EAP after the last study drug administration), sites will conduct a telephone contact 28 (+6) days after the last dose of study drug to follow AEs and report any SAEs that occur within 28 days of the last study drug administration. (revised per Amendment 02)

Table 7 Schedule of Procedures/Assessments in Study E2007-G000-238: Extension Phase - EIAED Subjects

Phase	Extension[a]					
Period	Maintenance			Follow-Up[b]		
Visit	10	11	12		Early Discontinuation	Unscheduled
Week	32	44	52	56		
Days	225	309	365	393		
Procedures/Assessments						
Concomitant medications	X	X	X	X	X	X
Concomitant AEDs	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
Study drug compliance	X	X	X		X	X
Dispense study drug	X	X				X[c]
Retrieve unused study drug	X	X	X		X	X[c]
Dispense subject's diary	X	X	X		X	X[d]
Retrieve and review subject diary	X	X	X	X	X	X[d]
Physical examination[e]	X		X		X	
Neurological examination[e]	X		X		X	
Vitals and weight	X	X	X		X	X
Height/length[f]	X		X		X	
Head circumference	X		X		X	
Clinical laboratory tests[g]	X	X	X[h]	X	X[h]	X[i]
Thyroid function (TSH, fT3, fT4) and IGF-1 tests	X		X		X	
12-lead ECG[j]	X		X		X	X[k]
CGI-C			X	X	X	
Telephone call[l]	X	X	X			
Disposition			X		X	

AE = Adverse event, AED = Anti-epileptic drug, CGI-C = Clinical Global Impression of Change, CRF = case report form, EAP = extended access program, ECG = electrocardiogram, EOT = End of Treatment, fT3 = free triiodothyronine, fT4 = free thyroxine, IGF-1 = insulin-like growth factor-1, SAE = serious adverse event, TSH = thyroid-stimulating hormone.

a: All visits to be done within ± 6 days of the schedule.

b: The Follow-up Visit (4 weeks ± 6 days after the last dose of study medication) applies to those subjects who complete the entire study and those who discontinue early during the Extension Phase. Subjects who switch to commercially available perampanel or who enter into EAP upon completion of study treatment would not need to undergo Follow-up Visit; however, sites will conduct a telephone contact 28 (+6) days after the last dose of study drug to follow AEs and report any SAEs that occur within 28 days of the last study drug administration. (revised per Amendment 02)

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

d: As needed.

e: For clinic visits other than those specified, physical and complete neurological exams, including evaluation of the cranial nerves, motor, sensory, brainstem, cerebellar, and autonomic functions, will only be performed when there is a complaint from the parent/guardian. Clinically significant abnormal findings from the physical or the neurological examinations must be reported as AEs.

f: Two measurements of height/length should be taken. Each measurement should be recorded as a separate entry on the Vital Sign CRF.

g: Clinical laboratory tests include hematology and blood chemistry.

h: Lipid and blood glucose tests must be conducted under fasting conditions, whenever practically feasible. (revised per Amendment 02).

i: During the unscheduled visits, clinical laboratory tests will only be done if an abnormality was noted at the previous visit or per the discretion of the investigator.

j: If the subject has a normal ECG baseline reading, but during any visit thereafter if there is any clinically significant ECG abnormality (as determined by the investigator), 3 consecutive ECGs separated by 5 to 10 minutes will be performed at that visit to confirm the abnormality.

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

l: Telephone interviews with the parent/guardian will be conducted approximately 6 weeks following Visit 9 through Visit 11 and at approximately the midpoint between Visit 11-12 to ensure that subjects are completing their seizure diaries regularly and assess AEs, study drug compliance and concomitant medications, including AEDs and to remind the subjects that they are to complete their seizure diary. 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. Subjects will then return for their regularly scheduled visits. All subjects will have a telephone interview at approximately the midpoint between Visit 12 and the Follow-up Visit when drug has been stopped. Subjects that discontinue the study at any time, will have a telephone interview at approximately the midpoint between the EOT Visit and the Follow-up Visit. For subjects who will not need to undergo Follow-up Visit (eg, when switching to commercially available Fycompa or enetering EAP after the last study drug administration), sites will conduct a telephone contact 28 (+6) days after the last dose of study drug to follow AEs and report any SAEs that occur within 28 days of the last study drug administration. (revised per Amendment 02)

EXTENSION PHASE STATISTICAL ANALYSES

All statistical analyses will be performed by the sponsor or designee. Statistical programming and analyses will be performed using SAS and/or other validated software.

DEMOGRAPHICS

Demographic and Baseline characteristics will be summarized. For continuous variables (eg, age, weight) the number of non-missing values, median, mean, standard deviation (SD), and minimum and maximum will be displayed. For categorical variables (eg, gender, ethnicity) the counts and proportions of each value will be tabulated.

ANALYSIS OF EFFICACY

Efficacy will be assessed in the Extension Phase with the following:

- Seizure Frequency: Percentage change in 28-day seizure frequency in the Extension Phase compared to baseline. The primary analysis will use data prospectively collected during the 2-week Pretreatment Phase to calculate baseline 28-day seizure frequency. A secondary analysis will use data prospectively collected during the 2-week Pretreatment Phase plus data retrospectively collected during the 4 week period before Visit 1 to calculate baseline 28-day seizure frequency. (revised per Amendment 02)
- Responder Rate: A responder is defined as a subject with a 50% decrease in 28-day seizure frequency during the Extension Phase when compared to baseline. The responder rate will be summarized. Analyses using the 2 different baseline definitions above will be performed.
- Seizure-free status: The proportion of subjects who are seizure-free will be summarized during the Extension Phase
- CGI-C

PHARMACOKINETIC ANALYSES

Not applicable.

PHARMACODYNAMIC ANALYSES

Not applicable.

PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

Not applicable.

PHARMACOGENOMIC ANALYSES

Not applicable.

ANALYSIS OF SAFETY

The safety of the study population exposed to perampanel will be examined based on nature, frequency, and severity of AEs, chemistry and hematology laboratory test results, vital signs, and 12-lead ECG abnormalities over the treatment period. Any potential safety signal will be explored by analysis of safety data by dose achieved in the study.

EXTENT OF EXPOSURE

Duration of Extension Phase exposure will be calculated as the number of days between the date the subject received the first dose of study drug and the date the subject received the last dose of study drug in the Extension Phase.

Overall Extension Phase compliance rate for each subject will be calculated as the mean compliance rate over all the visits.

ADVERSE EVENTS

Adverse events will be classified into standardized medical terminology from the verbatim description (investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be presented by preferred term nested within SOC. Verbatim description and MedDRA level terms, for all AEs will be contained in the data listings of the clinical study report for this protocol.

The TEAEs will be summarized by age group and by EIAED and non-EIAED groups. 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) and by relationship to study drug (Yes [related] and No [not related]).

Adverse events of special interest will also be summarized by SOC and PT using MedDRA SMQ terms.

A subject data listing will be produced for all deaths, SAEs, and discontinuation due to an AE.

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

Treatment-emergent adverse events are defined as:

- Adverse events that emerge during treatment, having been absent at pretreatment (Baseline)
- Reemerge during treatment, having been present at Baseline but stopped prior to treatment

- Worsen in severity during treatment relative to the pretreatment state, when the AE is continuous

LABORATORY VALUES

Clinical laboratory values will be evaluated for each laboratory parameter by subject. Descriptive summary statistics (eg, mean, standard deviation, median, minimum, maximum) for the laboratory parameters and changes from baseline (Visit 1) to the last visit in the Extension Phase (Follow-up Visit, Week 56) will be summarized by cohort and overall.

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. Shift tables will be used to compare the baseline (Visit 1) LNH classification to the LNH classification at end of study.

Clinical laboratory results post-baseline will be evaluated for markedly abnormal values. Appendix 1 presents the Sponsor's Grading for Laboratory Values that will be used to identify subjects with markedly abnormal laboratory values. For the incidence of markedly abnormal laboratory values, each subject may be counted once in the laboratory parameter value high and in the laboratory parameter low categories as applicable.

VITAL SIGNS

Vital sign values will be evaluated on an individual basis by subject. Abnormal vital sign values will be identified as those outside (above or below) the reference range, where appropriate. Reference ranges for vital sign parameters will be included in the clinical study report for this protocol. Descriptive summary statistics (eg, mean, standard deviation, median, minimum, maximum) for vital sign parameters and changes from baseline (Visit 2) to each visit and to the last visit in the Extension Phase (Follow- up Visit, Week 56) will be evaluated for each cohort and overall.

ECG RESULTS

For 12-lead ECG parameters, changes from baseline (Visit 1) to the last visit in the Extension Phase (Follow-up Visit, Week 56) will be summarized for each cohort and overall.

QTc (QTcF) and PR variables will also be analyzed to include a summary of the following:

- Number of subjects with QTc in the borderline or abnormal category (430-450 msec, >450 msec, and >500 msec) during treatment, and

- Number of subjects with an increment of 30-60 msec and > 60 msec from baseline (Visit 1).

OTHER ANALYSES

Growth

Descriptive summary statistics of changes from baseline in height and weight will be evaluated for each cohort and overall. This data will be compared with normative scores to assess clinical relevance.

Changes from baseline for thyroid function and IGF-1 testing will be summarized.

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	E2007-G000-238
Study Protocol Title:	An Open-Label Study With an Extension Phase to Evaluate the Pharmacokinetics of Perampanel (E2007) Oral Suspension When Given as an Adjunctive Therapy in Subjects From 1 Month to Less Than 4 Years of Age With Epilepsy (revised per Amendment 02)
Investigational Product Name:	E2007
IND Number:	112515
EudraCT Number:	2013-005391-17

SIGNATURES

Authors:

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Date

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INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2007-G000-238
Study Protocol Title:	An Open-Label Study With an Extension Phase to Evaluate the Pharmacokinetics of Perampanel (E2007) Oral Suspension When Given as an Adjunctive Therapy in Subjects From 1 Month to Less Than 4 Years of Age With Epilepsy (revised per Amendment 02)
Investigational Product Name:	E2007
IND Number:	112515
EudraCT Number:	2013-005391-17

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

<Name of institution>

Medical Institution

<Name, degree(s)>

Investigator	Signature	Date