REVISION HISTORY

Revisions to Version 10.0 **New version/Date: Final, v11.0, 19 Nov 2018 (per Amendment 05)**		
Change	**Rationale**	**Affected Protocol Sections**
Adjust timing of Visit 8 from Week 20 to Week 21, and Visit 9 from Week 22 to Week 23. Update Study Day numbering for these two visits accordingly.	To align study visit intervals with study product dispensing (every 2 weeks during Extension A Conversion period).	Table 7 Table 8
Editorial corrections.	To improve clarity.	Synopsis – Assessments Section 9.5.1.5 Table 5 Table 5Appendix 2 Table 8

Revisions to Version 9.0 **Amended version/Date: FINAL: v10.0, 19 Oct 2018 (per Amendment 04)**		
Change	**Rationale**	**Affected Protocol Sections**
Added an additional extension phase (Extension B) for subjects in Japan or subjects in countries where an extended access program (EAP) cannot be implemented or has not yet been implemented	To provide managed access to perampanel for subjects in Japan or subjects in countries where an EAP cannot be implemented or has not yet been implemented	Synopsis – Study Design Synopsis – Study Treatments Synopsis – Duration of Treatment Synopsis – Safety Assessments Synopsis – Statistical Methods Section 9.1 Section 9.1.2 Figure 1 Section 9.1.3 Section 9.1.4 Section 9.5.1.3 Section 9.5.1.5 Section 9.7.1 Section 9.7.1.6 Section 9.7.1.10 Section 9.7.1.11 Appendix 2 Appendix 4
Clarified Inclusion Criterion No. 4 that subjects must have an average of at least 2 drop seizures per week during the Baseline Period.	To clarify that the total number of drop seizures will be summed and then averaged over this 4-week period	Synopsis – Inclusion Criteria Section 9.1.1.2 Section 9.3.1
Revised Inclusion Criterion No. 5 that subjects must have been receiving 1 to 4 (changed from "1 to 3") concomitant anti-epileptic drugs (AEDs) at a stable dose for at least 30 days before Visit 1	To reflect current clinical reality (that most refractory subjects with Lennox-Gastaut Syndrome (LGS) are often receiving at least 4 concomitant AEDs).	Synopsis – Number of Subjects Synopsis – Inclusion Criteria Section 9.1.1.2 Section 9.3.1
Modification of Exclusion Criterion No. 28 and Inclusion Criterion No. 5 (concomitant use of cannabinoids) and current therapeutic options	To reflect approved AED medications	Synopsis – Inclusion Criteria Synopsis – Exclusion Criteria Synopsis – Concomitant Drug/Therapy Section 7.1.1 Section 9.3.2 Section 9.4.7.2 Table 5 Section 10
Added Exclusion Criterion No. 29 that subjects with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption will be excluded.	Per South Korea Ministry of Food and Drug Safety (MFDS) request	Synopsis – Exclusion Criteria Section 9.3.2

Added early pharmacokinetic (PK) sampling time points predose and 1 to 5 hours postdose; adjust dosing instructions around Visit 5 and Visit 6 accordingly	To support characterization of perampanel PK, especially during absorption and early distribution phase	Synopsis – Study Treatments Synopsis – Pharmacokinetic Analyses Table 1 Table 5 Table 6 Section 9.1.2.2 Section 9.4.1 Section 9.7.1.7
Added that subjects 12 or older may receive perampanel oral suspension, 0.5 mg/mL as medically necessary , at the discretion of the investigator	To ensure appropriate study drug formulation is to be administered based on individual subject conditions	Synopsis – Study Treatments Section 9.1.2.1 Section 9.4.1 Section 9.4.4
CCI		Synopsis – Assessments Section 9.5.1.5 Table 5 Appendix 2
Clarification of safety analysis set and analyses for Core and Extension A	Clarification	Synopsis – Statistical Methods Appendix 2
Clarification of language and dosing throughout study periods	Clarification	Synopsis – Study Design Synopsis – Study Treatments Figure 1 Section 9.1.2.1
Updated subject information and informed consent language	To align with sponsor updated protocol language	Section 5.3
Update and simplification of clinical experience section	To refer to Investigator's Brochure, which contains the most up-to-date clinical efficacy and safety information (updated on an annual basis)	Section 7.1.2.2 Section 7.1.2.3 (removed)
Clarified that Extension A conversion period is double-blind and Maintenance Period is open-label	Clarification	Table 7
Editorial corrections as needed	Document quality	throughout
Updated names of signatories	Administrative	Protocol (sponsor) signature page

Revisions to Version 8.0 **Amended version/Date: FINAL: v9.0, 24 Feb 2017 (per Amendment 03)**		
Change	**Rationale**	**Affected Protocol Sections**
Added that subjects with laboratory results that include elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than or equal to 3 × upper limit of normal (ULN) and elevated total bilirubin (TBIL) greater than or equal to 2 × ULN with an alkaline phosphatase (ALP) laboratory value that is less than 2 × ULN, ie, that meet criteria for Hy's law will be withdrawn from the study	Per VHP request	Section 9.3.3
Added that subjects who appear to have a high risk of suicidal behavior according to results of the Columbia Suicide Severity Rating Scale (C-SSRS) and/or clinical impression will be withdrawn from the study. Added that subjects who will reach the age of 8 years during the double-blind phase of the study will also be assessed using the C-SSRS starting at Baseline. The description in Section 9.5.4.3 and 9.5.4.4 was consolidated into a new Section 9.5.4.3.	Per VHP request	Synopsis - Safety Assessments – Core Study and Extension Phase Section 9.3.3 Section 9.5.1.5 Section 9.5.2, Table 5 Section 9.5.4.3
Editorial corrections as needed	document quality	throughout

Revisions to Version 7.0 **Amended version/Date: Final, v8.0, 04 Jan 2017 (per Amendment 02)**		
Change	**Rationale**	**Affected Protocol Sections**
Corrected misspelling of tiagabine	Editorial quality	Synopsis – Exclusion Criteria; Concomitant Drug Therapy Section 7.2 Section 9.3.2 Section 9.7.2
Added suicidal ideation to the list of exclusion criteria in the Synopsis	For consistency with body of protocol	Synopsis – Exclusion Criteria
Added instructions for laboratory abnormalities that might meet criteria for Hy's Law (elevated AST or ALT greater than or equal to 3 × ULN and elevated total bilirubin greater than or equal to 2 × ULN with an alkaline phosphatase laboratory value that is less than 2 × ULN). Stated that these laboratory results should always be reported as serious.	Per VHP request to clarify laboratory abnormalities that may meet criteria for Hy's Law.	Synopsis – Assessments Section 9.5.1.5 Section 9.5.4.3 Section 9.7.1.8 Appendix 2
Added language allowing for discontinuation if the C-SSRS and/or clinical impression indicates a high risk of suicidal behavior	Per VHP request	Synopsis – Assessments Section 9.5.1.5
Deleted text describing side effects associated with other antiepileptic drugs	This text repeats text in Section 7.1.1	Section 7.2
Deleted laboratory abnormalities and events of aggression and anger from events associated with special situations	Events of aggression and significant laboratory abnormalities are defined in the preceding paragraph	Section 9.5.1.5
Revised window for Maintenance Period visits from 7 days to 6.	For consistency	Table 5
Corrected numbering of study weeks during Conversion Period of Extension Phase	To allow sufficient time for titration	Table 7
Corrected numbering of study weeks during Conversion Period of Extension Phase	To correct an error	Appendix 2, Table 7 and Table 8
CCI [redacted]	Editorial style	Appendix 2, Table 8
Corrected table cross-referencing errors	For accuracy	Appendix 2 Appendix 3

Revisions to Version 6.0 **Amended version/Date: Final, v7.0, 06 Dec 2016 (per Amendment 01)**		
Change	**Rationale**	**Affected Protocol Sections**
Revised description of regions where the study will be conducted	Allow additional sites to be included in study	Synopsis – Investigators Section 6
Added text to define the end of the study	Per VHP request	Synopsis, Study Design Section 9.1.3
Revised exclusion criterion #17 to remove double-barrier contraception from set of acceptable methods, and to add recently updated safety language	Per VHP request and for compliance with Eisai standard language	Synopsis – Exclusion Criteria Section 9.3.2
Added assessment of criteria for Hy's Law	Per VHP request	Synopsis – Assessments Section 9.5.1.5 Section 9.5.3 Section 9.7.1.8 Appendix 2
Added C-SSRS and language pertaining to suicidal behavior	Per VHP request	Synopsis – Assessments Section 9.3.2 Section 9.5.1.5 Section 9.5.1.5 Appendix 2
CCI	Per VHP request	Synopsis -- Assessments Section 9.5.1.5 Table 5 Appendix 2
Stated that secondary endpoints (other than key secondary endpoints) and exploratory endpoints will not be analyzed statistically but will be summarized	Per VHP request	Synopsis --- Statistical Methods Section 9.7.1.1
CCI	Per VHP request	Synopsis – Statistical Methods Section 9.7.1.1
Added statement that treatment effect (efficacy) will be assessed using odds ratios.	Per VHP request	Synopsis – Statistical Methods Section 9.7.1.1
Revised introductory text and deleted references which were made redundant	Per VHP request	Section 7 Section 10
Corrected statement pertaining to number of Phase 2 and 3 studies completed	Update and for consistency with Investigators Brochure	Section 7.1.2.2
Added statement that any reaction with a fatal outcome will be considered unexpected	Per VHP request	Section 7.1.2.3 (removed)
CCI	Per VHP request	Section 7.2
Revised start and end dates of study	Updated information	Section 9.1
Corrected description of study phase	To correct an error	Section 9.4.1

Corrected description of dose packs	For accuracy	Section 9.4.2
Inserted "78" in table cell specifying the study day corresponding to Visit 6	To correct an error	Table 5
Updated visit window (6 days rather than 7)	For consistency	Table 5
Stated that height of adult subjects is to be obtained only at Screening	Per VHP request	Table 5 Appendix 2, Table 8
Added information and table stating volumes of blood to be drawn during the core study and the Extension Phase. Inserted new table and corrected numbering of tables occurring subsequently in text.	Per VHP request	Section 9.5.2 Table 6 Appendix 2, Table 8 Appendix 3
Added aggression and status epilepticus as study-specific events	As per clinical findings	Section 9.5.4.3
Revised numbering of study weeks during extension phase and corrected the numbering of the study day at the end of Week 74	For clarity and consistency	Appendix 2, Table 7

Revisions to Version 5.0 **New version/Date: Final, v6.0, 26 Aug 2016**		
Change	**Rationale**	**Affected Protocol Sections**
CCI [redacted]	CCI [redacted]	Synopsis -- Exploratory Objectives Synopsis -- Exploratory Endpoints Section 8.3 Section 9.7.1.1
Specified that in Japan, doses of perampanel may not exceed 8 mg/day	For subject safety as per PMDA request	Synopsis --Study Design Synopsis -- Treatments Figure 1 Table 1 Appendix 2
Editorial correction	Per Eisai style	Section 7.1.2.3 (removed) Section 9.4.4

Revisions to Version 4.0 **New version/Date: Final, v5.0, 06 May 2016**		
Change	**Rationale**	**Affected Protocol Sections**
Increased number of study sites from 50 to 70	To accelerate study completion	• Synopsis – Sites • Section 6 • Section 9.3
CCI [redacted]		• Synopsis –Secondary Objectives • Synopsis – Exploratory Objectives • Synopsis – Statistical Methods • Section 8.2 • Section 8.3 • Section 9.7.1.1
CCI [redacted]		• Synopsis – Exploratory Objectives • Synopsis – Assessments • Synopsis – Statistical Methods • Section 4 • Section 8.3 • Section 9.5.1.6 • Table 3and Table 5 • Section 9.7.1.1 • Section 9.7.1.9 • Section 10
CCI [redacted]		• Synopsis – Exploratory Objectives • Synopsis – Assessments • Synopsis – Statistical Methods • Section 4 • Section 8.3 • Section 9.5.1.6 • Table 4 and Table 5 • Section 9.7.1.1 • Section 9.7.1.9 • Section 10
Added inclusion criterion that weight must be at least 8 kg	To ensure subjects are of adequate weight to participate in a clinical study	• Synopsis – Inclusion Criteria • Section 9.3.1
Added exclusion criterion for cannabinoids	Cannabinoids may influence study results	• Synopsis – Exclusion Criteria • Section 7
Deleted country and added region and age group as independent variables	Likely that there will be too few subjects per country; therefore group by region instead. Age group is considered an important variable.	• Synopsis – Statistical Methods • Section 9.4.3 • Section 9.7.1.6

For subjects who do not roll over into the Extension Phase, added a visit at 7±2 days after the last dose of study drug and provided that a PK sample will be drawn at this visit.	The PK sample is to be drawn for correlation of potential withdrawal symptoms and signs with perampanel plasma levels. This sample will not be used for population PK analyses.	• Synopsis—Statistical Methods • Section 9.5.1.4 • Table 5 • Section 7 • Section 9.7.1.7
Modified literature reference style	To conform with changes in Eisai style	• Section 7.1.1 • Section 7.2 • Section 9.5.1.6 • Section 10
Added statement that sites should enroll subjects throughout the allowed age range	To allow for representation of younger as well as older children in the study	• Section 9.3
Provided that lifetime AED history be collected	To aid in interpretation of efficacy and safety findings	• Section 9.5.1.2 • Table 5
Added details of the handling and assay of PK samples	For clarity and completeness	• Section 9.5.1.4
CCI CCI	CCI CCI CCI	• Section 9.5.1.6 • Section 9.7.1.9
Clarified that Follow-up Visit intervals will have a window of ±2 days	To allow sufficient flexibility in scheduling visits	• Table 5
Clarified that the minimum interval of 10 days between visits does not apply to Visit 3	For accuracy, as Visit 3 is to occur less than 10 days after Visit 2.	• Table 5
Allowed a window of ±10 days for Follow-up Visits	To allow sufficient flexibility	• Table 5
Deleted reporting of study-specific events	Not applicable as there are no criteria for study-specific events	• Section 9.5.4.3
Editorial corrections	For quality and consistency	• Various locations
Changed visit window to ±6 instead of ±7 days in the Maintenance Period of the Extension Phase	Ensure that the shelf life of the investigational product is not exceeded.	• Table 8

Revisions to Version 3.0 **New version/Date: v4.0, 22 Nov 2015**		
Change	**Rationale**	**Affected Protocol Sections**
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 2, Table 5, and Table 8

Revisions to Version 2.0 **New version/Date: v3.0, 27 Oct 2014**		
Change	**Rationale**	**Affected Protocol Sections**
Revisions to grammar, spelling, etc.	Compliance with current company style guide and for general consistency	• Throughout protocol
Revisions made per new company protocol template	Alignment with current Eisai template	• Title page Synopsis - Safety Analyses • Synopsis - Inclusion/Exclusion Criteria • Section 9.3.1 • Section 7 • Section 9.5.1.5 • Section 9.5.4 • Section 9.5.4.1 • Section 9.5.4.2 • Section 9.5.4.3

Revised dosing to reduce frequency of titrations and overall titration period	Per recommendation by FDA	• Synopsis
		  ○ Study Design
		  ○ Study Treatments
		• Section 9.1
		• Figure 1
		• Section 9.1.2
		• Section 9.1.2.1
		• Section 9.4.1
		• Section 9.4.2
		• Section 9.4.4
		• Appendix 2
		• Table 5
		• Table 8

CCI	Per recommendation by FDA	• Synopsis
		  ○ Objectives
		  ○ Statistical Methods
		• Section 8.2
		• Section 8.3
		• Section 9.7.1.1
		• Section 9.7.1.6

Revised list of permitted AEDs	Per FDA feedback on inclusion of inducers	• Synopsis
		  ○ Inclusion Criteria
		  ○ Exclusion Criteria
		  ○ Concomitant Drugs/Therapies
		  ○ Statistical Methods
		• Section 7.1.2.3 (removed)
		Section 9.3.1
		• Section 7
		• Section 9.4.7.1
		• Section 9.4.7.2
		• Section 10

Revised language around dose adjustments	Clarification	• Section 9.1.2.1 • Appendix 2

Revisions to Version 2.0 **New version/Date: v3.0, 27 Oct 2014**		
Change	**Rationale**	**Affected Protocol Sections**
Removed all text regarding post Screening ECG	Correction as ECGs assessments are not performed after Screening	● Synopsis ○ Safety Assessments ○ Statistical Methods ● Section 9.5.1.5 ● Section 9.5.1.6 ● Section 9.7.1 ● Section 9.7.1.8
Added text to qualify that 30% of subjects will be recruited from the United States	Per SPA review request	● Synopsis – Number of Subjects ● Section 9.3
Revised text to indicate subjects who become pregnant will not be able to continue in the study	For consistency with perampanel clinical program	● Section 9.5.4.2
Revised sample size rationale text	Removed reference to the felbamate study because the endpoint was different (atonic seizures) not drop seizures. Clarified mean decreases in the clobazam study; the absolute decreases are not comparable between studies.	● Synopsis - Sample Size Rationale ● Section 9.7.2
Added vital signs assessments at Visit 14	Correction	● Table 5
Revised CGI assessments to include CGI-Severity and CGI-Improvement scales	Correction	● Synopsis ○ Efficacy Assessments ● Section 9.5.1.3
Removed language stipulating that laboratory assessments qualifying subjects for study entry will be performed by a local laboratory	Correction	● Section 9.5.1.5

Revisions to Version 1.0 **New version/Date: v2.0, 29 May 2014**		
Change	**Rationale**	**Affected Protocol Sections**
Allowed provision for subjects ≥12 years to be up-titrated to 12 mg/day perampanel	Although 8 mg/day is the selected dose in the Core study based on the expected efficacy and the low percentage of subjects expected to be on inducer AEDs, some subjects might still benefit from a higher dose for a better seizure control. The option to titrate to 12 mg/day, which is limited to subjects ≥12 years, will be based on the clinical judgment of the investigators and the subjects' agreement.	● Synopsis ○ Study Design ○ Extension Phase ● Section 9.1 ● Appendix 2 ○ Study Design and Plan ○ Table 4 ○ Study Drug Supplies/Perampanel Tablets
Revised text regarding the statistical and analytical plan	Clarification	● Section 9.7.1
Added sample size rationale for 71 subjects in each treatment arm for percent change from baseline in drop seizure frequency and 50% responder rate	Clarification	● Synopsis ● Section 9.7.2
Revised title to include age of subjects	Clarification	● Title page ● Synopsis, Study Protocol Title ● Protocol (sponsor) signature page ● Protocol (investigator) signature page
Revised "lactating" to "nursing"; populated full list of inclusion and exclusion criteria	Clarification	● Synopsis ○ Exclusion criteria ● Section 9.3.2, exclusion criterion #16
CCI [redacted]	Correction	● Table 3
Removed reference to the last visit of the Maintenance Period of the Core Study having a window of ±3 days	Correction	● Table 5, footnote b
Replaced IVRS with IxRS	Correction	● Section 9.4.2 ● Table 3 abbreviations ● Table 5 abbreviations
Qualified the collection of urine	Modified to take into account	● Table 3, footnote g

Revisions to Version 1.0 **New version/Date: v2.0, 29 May 2014**		
Change	**Rationale**	**Affected Protocol Sections**
samples	that urine collection in young children can be difficult.	● Table 5, footnote g
Removed respiratory rate and body temperature from assessments at all visits.	These assessments are no longer deemed necessary given the experience gathered from previous trials.	● Section 9.5.1.5 ● Section 9.7.1.8 ● Table 5
Removed Extension Phase eligibility requirement for subjects to be on a stable dose of 1 to 3 concomitant AEDs	Such requirement is not necessary in extension when efficacy endpoints are not collected.	● Appendix 2
Revised text for classification of causality of adverse events	To align with most current approved language for AE reporting	● Section 9.5.1.5
Revised text pertaining to quantity of study drug supplies; noted DEA scheduling of perampanel	To accommodate added weeks to the Titration Period; to adhere to requirements for DEA-scheduled drugs	● Section 9.4.2 ● Section 9.4.2.3 ● Section 9.4.2.4 ● Section 9.4.9 ● Appendix 2
Revised text for analysis of SAEs (removed seriousness)	Redundant text	● Synopsis ○ Safety analyses ● Section 9.7.1.8
Removed daily volumes for dosing of oral suspension	Not needed; details will be provided to the sites in a pharmacy manual.	● Table 1
Added age group to subgroup analyses and randomization	To take into consideration different titration schedules for subjects <12 years	● Synopsis ○ Efficacy analyses ● Section 9.4.3 ● Section 9.7.1.6
Added text to monitor anxiety and irritability	Per recommendation of CHMP	● Section 9.5.1.5
Qualified conduct of the Extension Phase	Clarification	● Synopsis ○ Study Design ● Section 9.1 ● Section 9.1.3 ● Appendix 2 ○ Study Design and Plan
Revised dosing regimens for subjects <12 years; extended the	Preliminary interim PK data of perampanel in subjects 2 to	● Table 1 ● Figure 1

Revisions to Version 1.0 **New version/Date: v2.0, 29 May 2014**		
Change	**Rationale**	**Affected Protocol Sections**
Titration and Conversion Periods of the study	<12 years of age with partial onset seizures indicated that a considerable number of plasma exposures when normalized to 0.18 mg/kg dose, were below the median of the 8 mg equivalent concentrations in adolescent subjects. The effect appeared to be more pronounced in 2 to 6 year-old subjects relative to 7 to 11 year-old subjects. The subsequent PK simulations indicated that maintenance doses up to 0.24 mg/kg in 7 to 11 year-old subjects and up to 0.36 mg/kg in 2 to 6 year-old subjects is necessary to achieve median exposures similar to adolescents at an 8-mg dose. In addition, the total daily dose is capped at 12 mg because of the limited experience of perampanel safety at doses above 12 mg in adults.	● Table 3 ● Table 4 ● Synopsis ○ Primary Objective ○ Secondary Objectives ○ Exploratory Objectives ○ Study Design ○ Study Treatments ○ Duration of Treatment ● Section 8.1 ● Section 8.2 ● Section 8.3 ● Section 9.1 ● Section 9.1.2 ● Section 9.1.2.1 ● Section 9.1.3 ● Section 9.4.1 ● Section 9.4.4 ● Appendix 2 ○ Eligibility Criteria ○ Study Design and Plan ○ Schedule of Procedures and Assessments
Extended Maintenance Period of the Extension Phase to allow 52 weeks of treatment for (Core study) placebo subjects	As specified per CHMP request	● Synopsis ○ Study Design ○ Duration of Treatment ● Figure 1 ● Section 9.1 ● Section 9.1.3 ● Appendix 2 ○ Study Design and Plan ○ Schedule of Procedures and Assessments ○ Table 5
Revised sample size rationale	Clarification	● Synopsis ○ Statistical Methods/Sample Size Rationale ● Section 9.7.2
Revised the definition of the FAS and added an ITT analysis set	To align the definition of FAS back to the company definition and added ITT	● Synopsis ○ Statistical Methods/Analysis Sets ● Section 9.7.1.2

Revisions to Version 1.0 **New version/Date: v2.0, 29 May 2014**		
Change	**Rationale**	**Affected Protocol Sections**
	analysis to address concerns of CHMP to include all randomized subjects in analysis	
CCI		• Synopsis ○ Statistical Methods/Study Endpoints ○ Statistical Methods/Efficacy Analyses Core Study • Section 9.7.1.1 • Section 9.7.1.6
CCI		• Synopsis ○ Secondary Objectives ○ Exploratory Objectives • Section 8.2 • Section 8.3
Removed specifying drop, non-drop, and total seizures from the PK and PK/PD secondary objective	Not needed; any seizures associated with LGS will be evaluated for this objective.	• Synopsis ○ Secondary Objectives • Section 8.2
CCI		• Synopsis ○ Secondary Objectives ○ Exploratory Objectives • Section 8.2 • Section 8.3
Specified reference to perampanel as 'test drug'	Consistency within the protocol	• Section 9.1.2.2 • Section 9.4.2 • Section 9.4.2.4
Revised text regarding up- and down- titration of study drug	Consistency within the protocol	• Section 9.1.2.1
Revised text regarding site audits	Clarification	• Section 9.6
Integrated like exclusion criteria	Clarification	• Section 9.3.2 (#16 and #18; #25 and 26)
Allowed provision for sub-investigators to review screening assessments and evaluations	The PI is not at every site.	• Section 9.1.2
Revised description of appropriate local country-specific mechanism	Clarification	• Synopsis ○ Study Design • Section 9.1 • Section 9.1.3 • Appendix 2 ○ Study Design and Plan

Revisions to Version 1.0 **New version/Date: v2.0, 29 May 2014**		
Change	**Rationale**	**Affected Protocol Sections**
		○ Schedule of Procedures/Assessments
Removed structural formula	Not needed	● Section 9.4.2.1
Revised study rationale, resulting in an additional cross reference (ILAE)	Clarification	● Section 7.2 ● Section 10
Revised protocol title to reflect open-label Extension Phase	Correction	● Title Page ● Synopsis- Study Protocol Title ● Sponsor Signature Page ● Investigator Signature Page
Revised start/end dates for the study and estimated duration	Correction	● Section 9.1
Changed the name of Clinical Pharmacology signatory	Administrative	● Protocol (sponsor) signature page
CCI [redacted]		● Appendix 3
Updated abbreviations	To align with current protocol	● List of Abbreviations and Definition of Terms
Removed ethyl alcohol as an example of drugs screened for in urine	Correction	● Section 9.5.1.2
Redistributed visits in the Titration Period of the Core Study and the Conversion Period of the Extension Phase	To make visit intervals more proportional to each other	● Table 1 ● Table 3
Removed reference to Table 4 (Extension Phase schedule) for serum pregnancy testing	Correction; serum pregnancy testing is not performed in the Extension Phase	● Section 9.5.1.5
Specified Screening Visit for collection of urine for drug screening	Clarification	● Section 9.5.1.2
Noted eslicarbazepine as a perampanel inducer	Correction	● Synopsis ○ Inclusion #5 ○ Concomitant Drug/Therapy ● Section 9.1.1.2 ● Section 9.3.1 ● Section 9.3.2

Revisions to Version 1.0 **New version/Date: v2.0, 29 May 2014**		
Change	**Rationale**	**Affected Protocol Sections**
		● Section 9.4.7.2
Qualified that ages are that at time of consent	Clarification	● Synopsis ○ Study Design ● Section 9.1
Removed analysis of secondary efficacy endpoints in the PP Analysis Set	Correction	● Synopsis ○ Efficacy Analyses ● Section 9.7.1.6
Specified number of subjects randomized	Clarification	● Section 9.3
Revised text for laboratory shift tables, out-of-range values, and vital signs	Correction	● Synopsis ○ Safety Analyses ● Section 9.7.1.8
Revised text regarding analysis of subjects who withdraw from treatment	Clarification	● Synopsis ○ Analysis Sets ● Section 9.7.1.2
Specified that all seizure types will be collected in the seizure diaries	Clarification	● Synopsis ○ Study Design ○ Efficacy Assessments ● Section 9.1 ● Section 9.1.2.2 ● Section 9.5.1.3 ● Appendix 2
Revised language in subsections on the effect of perampanel on oral contraceptives and concomitant AEDs	Clarifications	● Section 9.4.7.1
Qualified the use of concomitant AEDs by allowing carbamazepine, oxcarbazepine, and phenytoin	Clarification	● Synopsis ○ Concomitant Drug Therapy ● Section 9.3.2 ● Section 9.4.7.2 ●
Revised text regarding dose adjustment and down-titration	Clarification	● Section 9.1.2.1
Added daily volume for perampanel oral suspension	Clarification	● Table 1
Specified both tablet and suspension formulations of perampanel	The tablet formulation was added for subjects ≥12 years.	● Synopsis ○ Study Design ○ Study Treatments ● Section 9.1

Revisions to Version 1.0 **New version/Date: v2.0, 29 May 2014**		
Change	**Rationale**	**Affected Protocol Sections**
		• Section 9.1.2.1 • Section 9.1.2.2 • Section 9.4.1 • Table 1 • Section 9.4.2 • Section 9.4.4 • Appendix 2

Subjects <12 years of age will be treated with suspension formulation 0.5 mg/mL; subjects ≥12 will be treated with the tablet formulation; specified that subjects will remain on the same formulation throughout the study	A suspension formulation for those age 12 years and below has been introduced for ease of use in that age range.	• Synopsis
		  ○ Study Design
		  ○ Study Treatments
		• Section 9.1
		• Section 9.1.2.1
		• Section 9.1.2.2
		• Section 9.4.1
		• Table 1
		• Section 9.4.4
		• Appendix 2

Revised text to clearly state that subjects will be on a stable dose for at least 2 weeks during the Core Study Titration Period before entering the Maintenance Period	Clarification of existing text	• Synopsis ○ Study Design • Section 9.1 • Figure 1 – footnote b • Section 9.1.2.1 • Table 1

Revised primary objective and secondary objective #1 not to include reference to endpoints	Correction; endpoints are discussed in another section	• Synopsis
		  ○ Primary Objective
		  ○ Secondary Objectives
		• Section 8.1
		• Section 8.2

Added a secondary objective related to physicians evaluation of symptoms	To support secondary endpoint and related analysis	• Synopsis ○ Secondary Objectives • Section 8.2

Revised secondary objective related to total and non-drop seizure frequency	Clarification	• Synopsis
		  ○ Secondary Objectives
		  ○ Secondary Endpoints
		• Section 8.2
		• Section 9.7.1.1

CCI		• Synopsis- ○ Exploratory Objectives • Section 8.3
CCI		• Synopsis ○ Exploratory Objectives • Section 8.3

Revisions to Version 1.0 **New version/Date: v2.0, 29 May 2014**		
Change	**Rationale**	**Affected Protocol Sections**
CCI [redacted]	Clarification	• Synopsis ○ Exploratory Objectives • Section 8.3
Revised endpoints text by removing text related to analysis and moving to applicable analysis sections	Clarification	• Synopsis ○ Primary Endpoints ○ Secondary Endpoints ○ Exploratory Endpoints ○ Efficacy Analyses • Section 9.7.1.1 • Section 9.7.1.6
Combined secondary endpoint related to non-drop seizure frequency with the endpoint for total seizure frequency	Clarification	• Synopsis ○ Secondary Endpoints • Section 9.7.1.1
CCI [redacted]	Clarification	• Synopsis ○ Exploratory Endpoints • Section 9.7.1.1
CCI [redacted]	Clarification	• Synopsis ○ Exploratory Endpoints • Section 9.7.1.1
Added the secondary endpoint for PK	Clarification	• Synopsis ○ Secondary Endpoints • Section 9.7.1.1
Revised definition of the FAS	Correction	• Synopsis ○ Analysis Sets • Section 9.7.1.2
Revised definition of the PK Analysis Set	Clarification	• Synopsis ○ Analysis Sets • Section 9.7.1.2
CCI [redacted]	Clarification	• Synopsis ○ Exploratory Endpoint Analysis (Core Study) ○ Section 9.7.1.6
Removed description of the PK Analysis Set	Not needed; already in Section 9.7.1.2	• Section 9.7.1.7
Revised text around performing and reporting of pharmacogenomic analyses	Clarification	• Synopsis- ○ Pharmacogenomic Analysis (Core Study) • Section 9.7.1.7

Revisions to Version 1.0 **New version/Date: v2.0, 29 May 2014**		
Change	**Rationale**	**Affected Protocol Sections**
Added aggression and anger as other events of interest	For the safety of subject, given the rates of these events in other perampanel studies	● Section 9.5.1.5 ● Section 9.5.4.3 ● Section 9.7.1.8
Revised description of study periods	Clarification	● Section 9.1 ● Appendix 2
Added estimated study start/stop dates	Clarification	● Section 9.1
Removed "at least" in reference to the number of concomitant AEDs	Clarification	● Section 9.1.1.2
Specified viral tests	Correction	● Table 2 ● Table 3
Revised reporting window for SAEs, deaths, and life-threatening events	To comply with EC Directive 2011/C 172/01	● Section 9.5.4.1
Revised PK sampling method and information regarding PK analysis methodology	A low-volume plasma assay for measuring perampanel concentrations will be used instead of the dried blood spot method.	● Synopsis ○ PK and PD Assessments ○ Bioanalytical Methods ● Section 9.5.1.4 ● Table 3 – footnote l ● Section 9.7.1.7
Qualified that for inclusion, if the subject is under the legal age, a parent or legal guardian must provide informed consent	Clarification	● Section 9.3.1
Added use of prohibited medications to exclusion criteria	For consistency with text elsewhere	● Section 9.3.1
Qualified description of females who would have pregnancy testing	Clarification	● Section 9.5.1.5 ● Table 3 ● Table 4
Removed Photosensitivity Questionnaire as an assessment	No safety signal was seen in Phase 3 POS studies	● Synopsis ○ Safety Assessments ○ Safety Analyses ● Section 9.5.1.5 ● Table 3 ● Section 9.7.1.8
CCI [redacted]	Correction	● Synopsis CCI [redacted] ● Section 9.5.1.6

Revisions to Version 1.0 **New version/Date: v2.0, 29 May 2014**		
Change	**Rationale**	**Affected Protocol Sections**
Removed CBCL, thyroid hormone, and IGF-1 assessments	Correction	• Table 3
Revised text for PK/PD analyses	Clarification	• Synopsis ○ PK and PK/PD Analyses (Core Study) • Section 9.7.1.7
Moved location within protocol, of other safety analyses	Correction	• Section 9.7.1.8
Removed caregiver assessment of changes in symptoms (CGI-C)	Correction	• Synopsis ○ Efficacy Assessments ○ Secondary Endpoints ○ Efficacy Analyses • Section 9.5.1.3 • Section 9.7.1.1 • Section 9.7.1.6
Combined inclusion criteria formerly numbered #7 and #8 and re-numbered subsequent criteria	Related subject matter; combined for continuity	• Section 9.3.1
Deleted inclusion criterion #9 pertaining to male sterilization/contraceptive techniques (renumbered subsequent criteria)	Criterion is redundant to inclusion #8	• Section 9.3.1
CCI	Clarify plans for statistical analysis	• Section 9.7.1.6
Moved statement that by-subject listings would be presented for pregnancy tests	Correction	• Section 9.7.1.9
CCI		• Synopsis ○ Exploratory Objectives • Section 8.3
Revised pharmacogenomics-related instructions; removed reference to biomarker analysis	To conform with regulations pertaining to the use of subjects' DNA samples for pharmacogenomics	• Appendix 4
Revised version of the Declaration of Helsinki to the recently approved version	Update	• Section 5.2
Revised name of business unit and study Biostatistician	Update	• Protocol Signature page

Revisions to Version 1.0 **New version/Date: v2.0, 29 May 2014**		
Change	**Rationale**	**Affected Protocol Sections**
Editorial/template corrections	For interdocument consistency and compliance with current template and study guide	● Throughout protocol

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

Study Protocol Number:	E2007-G000-338
Study Protocol Title:	A Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial With an Open-Label Extension Phase of Perampanel as Adjunctive Treatment in Subjects at Least 2 Years of Age With Inadequately Controlled Seizures Associated With Lennox-Gastaut Syndrome
Sponsor:	Eisai Inc. 155 Tice Blvd Woodcliff Lake, New Jersey 07677 US Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 Japan
Investigational Product Name:	Perampanel
Indication:	Seizures associated with Lennox-Gastaut Syndrome (LGS)
Phase:	3
Approval Date:	v1.0, 11 Feb 2013 (original protocol) v2.0, 29 May 2014 (revised protocol) v3.0, 27 Oct 2014 (revised protocol) v4.0, 22 Nov 2015 (revised protocol) v5.0, 06 May 2016 (revised protocol) v6.0, 26 Aug 2016 (revised protocol) v7.0, 06 Dec 2016 (amended protocol per Amendment 01) v8.0, 04 Jan 2017 (amended protocol per Amendment 02) v9.0, 24 Feb 2017 (amended protocol per Amendment 03) v10.0, 19 Oct 2018 (amended protocol per Amendment 04) v11.0, 19 Nov 2018 (amended protocol per Amendment 05)
IND Number:	112515
EudraCT Number:	2014-002321-35
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.

E2007

Name of Active Ingredient

CCI [redacted]

Study Protocol Title

A Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial With an Open-Label Extension Phase of Perampanel as Adjunctive Treatment in Subjects at Least 2 years of Age With Inadequately Controlled Seizures Associated With Lennox-Gastaut Syndrome

Investigators

Investigators in North America, Europe, and Asia (revised per Amendment 01)

Sites

Approximately 70 sites

Study Period and Phase of Development

Approximately 36 months

Phase 3

Objectives

Primary Objective

To demonstrate that perampanel given as adjunctive anti-epileptic treatment is superior to placebo in reducing the incidence of drop seizures during 18 weeks of treatment in subjects with inadequately controlled seizures associated with Lennox-Gastaut Syndrome (LGS)

Secondary Objectives

1. To demonstrate that perampanel given as adjunctive anti-epileptic treatment is superior to placebo in reducing the incidence of all seizures during 18 weeks of treatment in subjects with inadequately controlled seizures associated with LGS
2. To demonstrate that perampanel given as adjunctive anti-epileptic treatment is superior to placebo in the 50%, 75%, and 100% responder rates for drop seizures during 12 weeks of the Maintenance Period in subjects with inadequately controlled seizures associated with LGS
3. To demonstrate that perampanel given as adjunctive anti-epileptic treatment is superior to placebo in the 50%, 75%, and 100% responder rates for total seizures during 12 weeks of the Maintenance Period in subjects with inadequately controlled seizures associated with LGS
4. To demonstrate that perampanel given as adjunctive anti-epileptic treatment is superior to placebo in reducing the incidence of non-drop seizures during 18 weeks of treatment in subjects with inadequately controlled seizures associated with LGS
5. To evaluate the 50%, 75%, and 100% responder rates in non-drop seizure frequency during 12 weeks of the of the Maintenance Period in subjects with inadequately controlled seizures associated with LGS
6. To evaluate physicians' global evaluation of subjects' overall changes in symptoms
7. To evaluate the safety of perampanel relative to placebo as adjunctive therapy in subjects with inadequately controlled seizures associated with LGS during both the Core Study and the Extension Phase
8. To evaluate the pharmacokinetics (PK) and the pharmacokinetic/pharmacodynamic (PK/PD) relationships of perampanel as adjunctive therapy in subjects with inadequately controlled seizures associated with LGS

Exploratory Objectives

CCI

[redacted]

Study Design

This will be a multicenter, double-blind, randomized, placebo-controlled, parallel-group study of perampanel as adjunctive therapy in subjects with inadequately controlled seizures associated with LGS. The study will consist of 3 phases: Prerandomization, Randomization, and Extension.

The Core Study will consist of the Prerandomization and Randomization Phases. The Prerandomization Phase will consist of a 4- to 8- week Screening/Baseline Period during which subjects will be assessed for overall eligibility to participate in the study, including seizure activity. Baseline seizure count will be assessed using all diary data before randomization (at least 4 weeks prospectively). Following successful completion of this period, subjects will be randomized to receive perampanel or placebo in a 1:1 ratio.

The Randomization Phase will consist of 3 periods: Titration (6 weeks), Maintenance (12 weeks), and Follow-up. (4 weeks, only for subjects not entering into Extension A). Subjects will start perampanel at a dose of 2 mg/day (or matching placebo). Thereafter, the dose will be increased up to a maximum target dose of 8 mg/day (or matching placebo) according to individual subject tolerability and efficacy. Once titrated, all subjects will be kept at a stable dose for at least 2 weeks (to reach steady-state) before the start of the Maintenance Period. The dose of study drug during the Maintenance Period will be the last dose achieved at the end of the Titration Period. Upon completion of the Titration Period, subjects will begin the Maintenance Period of the study. Subjects will enter this period on the study drug dose (or matching placebo) they achieved during the Titration Period. In general, dose adjustment during the Maintenance Period is not recommended; however, the investigator may reduce a subject's dose if, in his/her clinical judgment, the subject experiencing intolerable adverse event(s) [AE(s)] that warrant(s) such an action. Subjects whose dosage has been down-titrated can have their dose increased again, as soon as tolerability improves. Changes of baseline anti-epileptic drugs (AEDs, addition, deletion, or adjustment in dose) are not allowed during the Randomization Phase. Parents or caregivers will complete seizure diaries throughout the Core Study; seizures will be collected as drop seizures or non-drop seizures. Subjects will remain on the same formulation of perampanel (or matching placebo) throughout the course of the study. (revised per Amendment 04)

Subjects who complete the Maintenance Period of the Core Study will have the option to roll over into Extension A and will immediately begin the blinded Conversion Period. During the Conversion Period (6 weeks), subjects who received perampanel during the Core Study will continue receiving perampanel in a blinded manner at the same dose received during the Core Maintenance Period. Subjects who received placebo during the Core Study will begin treatment with perampanel in a blinded manner, following the same dosing regimen and titration schedule as that in the Core Study, starting at 2 mg/day and will then be up-titrated as described above for the Core Study, to the optimal dose per the investigator's discretion, not to exceed a maximum dose of 8 mg/day. After the double-blind Conversion Period, subjects can be titrated up to 12 mg/day (except in Japan, where the maximum

allowed dose remains at 8 mg/day), in 2-week intervals during the Extension A Maintenance Period (46 weeks) as per the investigator's discretion. The total treatment duration in Extension A is 52 weeks for evaluation of long term safety and efficacy. Addition, deletion, and dose changes to the concomitant AEDs are allowed during Extension Maintenance Period. (revised per Amendment 04)

After completion of Extension A, an additional Extension Phase (Extension B) with open-label treatment will be available for optional participation to subjects who reside in Japan or subjects in countries where an extended access program (EAP) cannot be implemented, and who in the opinion of the investigator continue to benefit from treatment with perampanel. Participation in Extension B will continue as long as clinically appropriate according to the judgment of the investigator until perampanel is commercially available. (revised per Amendment 04)

For subjects residing in countries where commercial perampanel is not yet available and EAP can be implemented (provided that a positive risk/benefit is demonstrated based on analysis of the Core Study data), subjects who have completed Extension A and who in the opinion of the investigator continue to benefit from treatment with perampanel may opt to enroll into EAP (if activated), or temporarily into Extension B until EAP is activated or until perampanel is commercially available, whichever occurs first. At that point, the subject will complete his/her participation in Extension B. (revised per Amendment 04)

In the event that a risk-benefit assessment of perampanel for the treatment of LGS is found to be negative, this study will be terminated and no EAP will be set up. (revised per Amendment 04)

Subjects who do not continue in Extension A or those who prematurely discontinue from the study will return to the study site for Follow-up visits 1 week and 4 weeks after the last study drug administration. Subjects who do not enter into Extension B will enter a 4-week Follow-up Period. At the end of the 4-week Follow-up Period, subjects will return to study site to complete the End-of-Study assessments (Follow-Up visit). (revised per Amendment 04)

The end of the study will be the date of the last visit of the last subject. (revised per Amendment 01)

Number of Subjects

Approximately 142 male and female subjects with inadequately controlled seizures associated with LGS, receiving 1 to 4 concomitant anti-epileptic drugs (AEDs). Approximately 30% of subjects will be recruited from the US. (revised per Amendment 04)

Inclusion Criteria

1. Subjects must have diagnosis of LGS as evidenced by:
   - More than one type of generalized seizures, including drop seizures (atonic, tonic, or myoclonic) for at least 6 months before Visit 1
   - An electroencephalogram (EEG) reporting diagnostic criteria for LGS at some point in their history (abnormal background activity accompanied by slow, spike and wave pattern <2.5 Hz)
2. Subjects must be at least 2 years old at the time of consent/assent
3. Subjects must have been <11 years old at the onset of LGS
4. Subjects must have experienced an average of at least 2 drop seizures per week in the 4-week Baseline Period preceding randomization; the Baseline Period within the Prerandomization Phase is (minimum) 4 weeks (revised per Amendment 04)
5. Subjects must have been receiving 1 to 4 concomitant AEDs at a stable dose for at least 30 days before Visit 1 (vagal nerve stimulation [VNS] and ketogenic diet do not count as an AED). Use of cannabidiol (CBD) products is allowed and is counted as one of the 4 maximum allowed concomitant AEDs. CBD dose and product must have remained stable for at least 30 days before Visit 1 and is to remain the same throughout the course of the Core Study. (revised per Amendment 04)
6. In the investigator's opinion, parents or caregivers must be able to keep accurate seizure diaries
7. Body weight at least 8 kg

Exclusion Criteria

1. Presence of progressive neurological disease
2. Presence of drop seizure clusters where individual seizures cannot be reliably counted (seizure clusters are defined as ≥2 drop seizures with <5 minutes between any two consecutive seizures)
3. Prior treatment with perampanel with discontinuation due to safety issues (related to perampanel)
4. Prior treatment with perampanel within 30 days before Visit 1
5. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal disease, hepatic disease) that in the opinion of the investigator(s) could affect the subject's safety or study conduct
6. Scheduled for epilepsy-related surgery or any other form of surgery during the projected course of the study
7. Ketogenic diet and VNS, unless stable and ongoing for at least 30 days before Visit 1
8. Treatment with an investigational drug or device within 30 days before Visit 1
9. Status epilepticus within 12 weeks of Visit 1
10. If felbamate is used as a concomitant AED, subjects must be on felbamate for at least 1 year, with a stable dose for 60 days before Visit 1. They must not have a history of white blood cell (WBC) count below ≤2500/µL (2.50 1E+09/L), platelets <100,000/µL, liver function tests (LFTs) >3 times the upper limit of normal (ULN), or other indication of hepatic or bone marrow dysfunction while receiving felbamate.
11. Concomitant use of vigabatrin: Subjects who took vigabatrin in the past must be discontinued for at least 5 months before Visit 1, and must have documentation showing no evidence of a vigabatrin-associated clinically significant abnormality in an automated visual perimetry test
12. 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
13. Evidence of significant active hepatic disease. Stable elevations of liver enzymes, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) due to concomitant medication(s) will be allowed if they are < 3 times the ULN
14. Adrenocorticotropic hormone within the 6 months before Visit 1
15. Had history of anoxic episodes requiring resuscitation within 6 months before Visit 1
16. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG] with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG or hCG). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
17. Females of childbearing potential who:
    - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
    - total abstinence (if it is their preferred and usual lifestyle)
    - an intrauterine device or intrauterine hormone-releasing system (IUS)
    - an oral contraceptive (with additional barrier method if using contraceptive containing levogesterol) (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
    - have a vasectomized partner with confirmed azoospermia.
    - Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

For sites outside of the EU, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide (revised per Amendment 01)

(NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal

[amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

18. Had intermittent use of benzodiazepine of more than 4 single administrations in the month before Visit 1
19. A prolonged QT/QTc interval (QTc >450 ms) as demonstrated by a repeated electrocardiogram (ECG)
20. Hypersensitivity to the study drug or any of the excipients
21. Any history of a medical condition or a concomitant medical condition that in the opinion of the investigator(s) would compromise the subject's ability to safely complete the study
22. Known to be human immunodeficiency virus (HIV) positive
23. Active viral hepatitis (B or C) as demonstrated by positive serology at Screening
24. Psychotic disorder(s) or unstable recurrent affective disorder(s) evident by use of antipsychotics or prior suicide attempt(s) within approximately the last 2 years
25. History of drug or alcohol dependency or abuse within approximately the last 2 years; use of illegal recreational drugs
26. Concomitant use of medications known to be inducers of cytochrome P450 (CYP3A) including, but not limited to: rifampin, troglitazone, St John's Wort, efavirenz, nevirapine, glucocorticoids (other than topical usage), modafinil, pioglitazone, and rifabutin
27. Use of AEDs not recommended by Epilepsy Treatment Guidelines for use in LGS including, but not limited to carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, and vigabatrin (revised per Amendment 02)
28. Any suicidal ideation with intent with or without a plan within 6 months before Visit 2 (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the Columbia Suicide Severity Rating Scale [C-SSRS]) in subjects aged 8 and above. (revised per Amendment 02)
29. Subjects with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. (revised per Amendment 04)

Study Treatments

Test drug: Perampanel

Dosing should occur orally once a day before bedtime.

Note: For Visit 5 and Visit 6, predose and early postdose (within 1 to 5 hours after dosing) PK samples are to be collected. For these visits, if due to infeasibility of PK sample collection before and after evening/bedtime dose administration, then the following steps are to be followed:

- Study drug administration **in the evening immediately before Visit 5 and Visit 6 should be withheld** (all other AEDs should be administered per the subject's usual AED regimen).
- During Visit 5 and Visit 6, 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 in the evening on the day of Visit 5 and Visit 6.
- In these cases, dosing date and time of the previous 3 doses before each PK sampling visit will continued to be recorded.

(revised per Amendment 04)

Perampanel will be supplied as 2-mg oral tablets and 0.5 mg/mL oral suspension. It is recommended that oral tablet be used for dosing subjects ≥12 years of age, and oral suspension for subjects <12 years of age. However, the most appropriate formulation may be selected based on the subject's condition and at the discretion of the investigator. The same formulation should be used for a given subject throughout the course of the study.

Comparator Drug: Matching-placebo

Core Study: Subjects will start perampanel at a dose of 2 mg/day (or matching placebo). Thereafter, the dose will

be increased up to a maximum target dose of 8 mg/day (or matching placebo) according to individual subject tolerability and efficacy. Once titrated, all subjects will be kept at a stable dose for at least 2 weeks (to reach steady-state) before the start of the Maintenance Period. The dose of study drug during the Maintenance Period will be the last dose achieved at the end of the Titration Period. See the dosing table for the dosing schedule in the Titration Period. (revised per Amendment 04)

Dosage Schedule in E2007-G000-338 (Randomization Phase –Core Study)

Randomization Phase/ Titration Period	**Visit**	**All Subjects**
Week 1 (starting dose)	Visit 2	2 mg/day
Week 2	Visit 3	4 mg/day
Week 3	-	6 mg/day
Week 4	Visit 4	6 mg/day
Week 5[a]	-	8 mg/day
Week 6[a]	-	8 mg/day
Randomization Phase/ Maintenance Period (Week 7/Visit 5)[b]	Starts the Maintenance Period at the last dose achieved in the Titration Period	

a: Subjects will remain on dose for at least 2 weeks before entering the Maintenance Period.
b: Dosing should occur orally once a day before bedtime, except on the evenings immediately before (and the evening on the day of) Visits 5 and 6. Study drug administration in the evening immediately before (and the evening on the day of) Visit 5 and Visit 6 **should be withheld** (all other AEDs should be administered per the subject's usual AED regimen). **Study drug will be given during Visit 5 and Visit 6 at the study site, after collection of predose PK sample** (within 1 to 5 hours after dose administration). Bedtime dosing will resume in the evening on the day of Visit 5 and Visit 6. (revised per Amendment 04).

Extension A: During the Conversion Period, subjects who received perampanel during the Core Study will continue receiving perampanel in a blinded manner at the same dose last received during the Core Maintenance Period. Subjects who received placebo during the Core Study will begin treatment with perampanel in a blinded manner, following the same dosing regimen and titration schedule as that in the Core Study, starting at 2 mg/day and will then be up-titrated to the optimal dose, not to exceed 8 mg/day, per the investigator's discretion. After the double-blind Conversion Period, subjects can be titrated up to 12 mg/day (except in Japan, where the maximum allowed dose remains at 8 mg/day), at 2-week intervals per the investigator's discretion. During the Conversion and Maintenance Periods, all dose adjustments will be done via 1 dose level up or down. Those who cannot tolerate a minimum of 2 mg dose must discontinue from the study. (revised per Amendment 04)

Extension B: Perampanel dosing in Extension B will be the last dose the subject received at the end of Extension A. During the Treatment Period, all dose adjustments will be done via 1 dose level up or down. Those who cannot tolerate a minimum of 2 mg dose must discontinue from the study. (revised per Amendment 04):

Duration of Treatment (revised per Amendment 04)

Core Study:

- **Prerandomization Phase (Screening/Baseline):** 4 (minimum) to 8 weeks
- **Randomization Phase (Titration, Maintenance, Follow-up):** 18 weeks (6+12 weeks, respectively, for subjects continuing into Extension A) or 22 weeks (6+12+4 weeks, respectively, for subjects not entering into Extension A)

Extension A (Conversion, Maintenance, Follow-up): 52 weeks (6+46 weeks, respectively, for subjects continuing into Extension B) or 56 weeks (6+46+4 weeks, respectively, for subjects not entering into Extension B)

Extension B: Until perampanel is available commercially for the treatment of LGS, or accessible via EAP (if activated in the country in which a subject resides), unless the sponsor terminates the study or terminates the study in a particular country

Concomitant Drug/Therapy

Concomitant use of medications known to be inducers of cytochrome P450 (CYP3A) including, but not limited to rifampin, troglitazone, St John's Wort, efavirenz, nevirapine, glucocorticoids (other than topical usage), modafinil, pioglitazone, and rifabutin, will not be permitted and are to be discontinued 30 days before Visit 1. Use of AEDs not recommended by Epilepsy Treatment Guidelines for use in LGS (including, but not limited to carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, and vigabatrin) is prohibited throughout the study. (revised per Amendment 02) Use of CBD products is allowed and is counted as one of the 4 maximum allowed concomitant AEDs). CBD dose and product must have remained stable for at least 30 days before Visit 1 and is to remain the same throughout the course of the Core Study. (revised per Amendment 04)

Assessments

Efficacy Assessments – Core Study and Extension A

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

The Clinical Global Impression of Severity (CGI-S) and CGI-Improvement (CGI-I) scales will be used to evaluate overall changes in symptoms by the physician during the Core Study only.

Pharmacokinetic and Pharmacodynamic Assessments – Core Study

Plasma concentrations of perampanel will be determined using sparse sampling collected at prespecified timepoints**.** Efficacy and selected safety endpoints may be correlated against exposure and/or dose.

Pharmacogenomic Assessments – Core Study

Genomic DNA samples may be used to examine the role of genetic variability in subject's absorption, distribution, metabolism, and excretion, or the development of adverse events.

Variations in perampanel exposure or adverse events (AEs) may be evaluated by correlation of single-nucleotide polymorphisms with PK, safety, or PD data.

Safety Assessments – Core Study and Extension A

Safety assessments will consist of monitoring and recording all AEs and serious adverse events (SAEs); regular laboratory evaluation for hematology, blood chemistry, including assessment of criteria for Hy's Law, and urinalysis values; periodic measurement of vital signs and physical examination. (revised per Amendment 01)

The investigator is required to evaluate laboratory results related to liver function (AST, ALT, total bilirubin [TBIL], and alkaline phosphatase [ALP]) that could potentially meet criteria for Hy's Law. If these laboratory results include an elevated AST or ALT greater than or equal to 3 × ULN and elevated TBIL greater than or equal to 2 × ULN with an ALP laboratory value that is less than 2 × ULN, the subject will be discontinued from the study and an SAE will be reported. (revised per Amendment 02)

In addition, an assessment of suicidal ideation and behavior using the C-SSRS will be performed throughout the study for subjects aged 8 years and older at the time of consent/assent; subjects who will reach the age of 8 years during the double-blind phase of the study will also be assessed using the C-SSRS starting at Baseline. (revised per Amendment 03) Suicidal ideation and behavior will be monitored throughout the study for subjects less than 8 years at the time of consent/assent and during the study, based upon clinical impression. (revised per Amendments 01 and 03). Subjects who appear to have a high risk of suicidal behavior according to results from the C-SSRS and/or clinical impression will be withdrawn from the study. (revised per Amendment 02)

CCI [redacted]

Safety Assessments – Extension B (revised per Amendment 04)

Safety assessments will consist of monitoring of AEs, withdrawal from treatment, clinical laboratory tests, vital signs, and weight. Concomitant medication usage will be monitored.

CCI [redacted]

CCI [redacted]

Bioanalytical Method

Plasma concentrations of perampanel will be analyzed using a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) assay method.

Statistical Methods

Study Endpoints

Primary Endpoints

The primary efficacy endpoint will be the median percent change in drop seizure frequency per 28 days during double-blind treatment (Titration Period and Maintenance Period) relative to the Prerandomization Phase in the Full Analysis Set (FAS)

Secondary Endpoints

The following key secondary endpoints will be evaluated sequentially using the FAS:

1. Median percent change in total seizure frequency per 28 days during double-blind treatment (Titration Period and Maintenance Period) relative to the Prerandomization Phase
2. The 50% responder rate in the Maintenance Period of the double-blind treatment relative to the Prerandomization Phase for drop seizures
3. The 50% responder rate in the Maintenance Period of the double-blind treatment relative to the Prerandomization Phase for total seizures.

Other secondary endpoints are as follows. These will not be analyzed statistically but will be summarized: (revised per Amendment 01)

4. Median percent change in non-drop seizure frequency per 28 days during double-blind treatment (Titration Period and Maintenance Period) relative to the Prerandomization Phase
5. Proportion of subjects with 75%, and 100% responder rates for drop, non-drop, and total seizures in the Maintenance Period relative to the Prerandomization Phase
6. Proportion of subjects with 50% responder rate in the Maintenance Period of the double-blind treatment relative to the Prerandomization Phase for non-drop seizures
7. Physicians' global evaluation of the subject's overall changes in symptoms (using a 7-point Likert scale with 1=very much improved and 7=very much worse) at the end of the double-blind treatment.
8. Incidence of AEs and SAEs, changes in clinical laboratory values, and vital signs
9. Model-derived average perampanel concentrations at steady state (Cav,ss) during the Maintenance Period of the Core Study

Exploratory Endpoints

CCI [redacted]

CCI

[redacted]

Analysis Sets (revised per Amendment 04)

Safety Analysis Set (Core Study): The group of subjects who received at least one dose of study drug and had at least one post-dose safety assessment.

Full Analysis Set (FAS, Core Study): The group of randomized subjects who received at least one dose of study drug and had at least one postdose seizure measurement

Per Protocol (PP) Analysis Set: The group of subjects who sufficiently complied with the protocol. Details of the evaluability criteria will be determined before database lock and treatment unblinding and will be specified in the Statistical Analysis Plan (SAP).

Pharmacokinetic Analysis Set: The group of subjects receiving perampanel and with at least one quantifiable perampanel concentration during the Maintenance Period of the Core Study and adequately documented dosing history

Pharmacokinetic-Pharmacodynamic Analysis Set: The group of subjects receiving either perampanel or placebo who have seizure frequency data with documented dosing history. Subjects receiving perampanel should have at least one quantifiable perampanel concentration as per the PK Analysis Set.

Intention to Treat Set (ITT): The group of randomized subjects who received at least one dose of study drug

Safety Analysis Set (Extension A): The group of subjects who received at least one dose of perampanel and had at least one post-perampanel safety assessment.

FAS (Extension A): The group of subjects who received at least one dose of perampanel and had at least one post-perampanel seizure measurement.

Safety Analysis Set (Extension B): The group of subjects who received at least one dose of study drug and had at least one postdose safety assessment in Extension B.

All subjects who withdraw from treatment will be summarized and their withdrawal reasons will be tabulated. Prior and concomitant medication usage and demographics will also be summarized.

Efficacy Analyses:

Core Study

The analysis of the primary endpoint, percentage change in drop seizure per 28 days in the FAS, will be conducted

using rank analysis of covariance (ANCOVA) with ranked percentage change from Baseline in drop seizures per 28 days as the dependent variable; and treatment, region, age group, and ranked baseline drop seizure rate per 28 days as the independent variables. Seizure frequency will be based on the number of drop seizures per 28 days, calculated as the number of drop seizures over the entire time interval divided by the number of days in the interval and multiplied by 28.

The primary endpoint of median percent change will be tested at 0.05 level and if it is significant then the 3 key secondary efficacy endpoints will proceed in a sequential manner.

Median percent change in total seizure frequency per 28 days during double-blind treatment will be tested first. If this test is significant at 0.05 level, then the 50% responder rate in the Maintenance Period for drop seizures will be tested. If this is significant then the 50% responder rate in the Maintenance Period for total seizures will be tested. All tests will be at a 2-sided 5% significance level.

50% responder rates will be analyzed using the Cochran-Mantel-Haenszel (CMH) test, adjusting for region and age group. 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 double-blind treatment duration if < 8 weeks of data are available) will be used in lieu of Maintenance Period. The treatment effect will be assessed using odds ratios. The common odds ratio and 95% CI as well as response rate from each treatment group will be presented. (revised per Amendment 01)

The same ANCOVA model employed for the primary efficacy endpoint will be employed to analyze percentage change from baseline in total seizures.

In addition, a sensitivity analysis for the primary efficacy endpoint and the 3 key secondary endpoints will performed in the PP and ITT analysis sets.

Physicians' global evaluations over time will be analyzed using the CMH test.

CCI [redacted]

Extension A

Summary statistics will be provided for the efficacy endpoints in the Extension A.

Pharmacokinetic Analyses (Core Study): (revised per Amendment 04)

Perampanel concentrations will be listed by subject, dose, and visit.

A population PK approach will be used to characterize the PK of perampanel, utilizing PK sample data collected during the Maintenance Phase of the study. The effect of intrinsic (ie, demographics) and extrinsic factors (ie, most common concomitant AEDs) on perampanel PK will be evaluated. Derived exposure parameters such as area under the concentration-time curve at steady-state (AUC_{ss}) or the average steady-state drug concentration ($C_{av,ss}$) will be calculated from the model using the individual posterior estimates of CL/F and dosing history.

Pharmacodynamic Analyses (Core Study):

Efficacy and selected safety endpoints may be correlated against exposure and/or dose.

Pharmacokinetic Pharmacodynamic Analyses (Core Study):

The relationship between exposure to perampanel and response will be explored graphically and any emergent relationship will be further subjected to population PK/PD modeling.

Pharmacogenomic Analysis (Core Study):

Pharmacogenomics analyses may be performed and reported separately. Details of these analyses may be described in a separate analysis plan.

Other Endpoint Analyses (Core Study):

CCI [redacted]

CCI

Safety Analyses:

Core Study

Safety analyses will be conducted on the Safety Analysis Set (Core). (revised per Amendment 04)

The incidence of treatment-emergent adverse events (TEAEs, defined as AEs occurring from the time of first dose through 28 days after the last dose of study medication), SAEs, AEs associated with fatal outcomes or leading to discontinuations, and AEs leading to dose adjustment will be summarized by treatment group. Incidence of TEAEs also will be summarized by severity (mild, moderate, or severe), as well as by relationship to treatment (not related, possibly related, or probably related).

Changes from Baseline in laboratory values will be summarized by treatment groups for continuous variables. Lab shift tables showing incidence of new or worsening clinically significant findings from Baseline to the last visit will be displayed by treatment groups. Shift from Baseline to the highest lab value and from Baseline to the lowest lab value will also be displayed.

Incidence of out-of-normal-range values and markedly abnormal change from Baseline in laboratory safety test variables will be tabulated by treatment group. These out-of-normal-range values and markedly abnormal changes from Baseline will be obtained from laboratory-defined normal ranges and using modified National Cancer Institute (NCI) criteria, respectively.

Laboratory analyses will also include analysis of outliers. For ALT and AST analysis, the number of subjects with > 3 times but < 5 times the ULN and the number of subjects with >5 times the ULN will be summarized. For bilirubin, a summary of the number of subjects with serum concentrations >2 times the ULN will be created.

Changes in vital signs from Baseline to each visit and to the last visit of double-blind treatment will be summarized by treatment groups.

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

Extension A

Safety analyses will be performed similarly to the Core Study analyses and all analyses will be on the perampanel treatment duration (Randomization Phase + Extension A for subjects randomized to perampanel and Extension A for subjects randomized to placebo). TEAEs are defined as AEs occurring from the time of first perampanel through 28 days after the last perampanel dose. Baseline for laboratory and vital sign parameters is the last non-missing value before first perampanel dose.

Extension B

Safety analyses will be performed similarly to the Core Study analyses and all analyses will be on the perampanel treatment duration (Randomization Phase + Extension A + Extension B for subjects randomized to perampanel and Extension A + Extension B for subjects randomized to placebo). TEAEs are defined as AEs occurring from the time of first perampanel through 28 days after the last perampanel dose. Baseline for laboratory and vital sign parameters is the last non-missing value before first perampanel dose.

Interim Analyses

Not applicable

Sample Size Rationale

Seventy-one (71) subjects will be randomized to each treatment arm and this sample size will provide adequate power for the primary endpoint and the key secondary endpoints.

Primary endpoint percent change from baseline in drop seizures:

Placebo rates in drop seizures in the rufinamide and clobazam clinical trials were +1.4%, and -12.1%, respectively. In the active treatment arm, rufinamide had a median decrease of 42.5% in drop seizures and clobazam had mean decreases of 41.2%, 49.4%, and 68.3% for the low, medium, and high doses, respectively. A standard deviation of ~63% was observed for both rufinamide and for the medium dose of clobazam for drop seizures. It is assumed that comparable results will be seen in this trial for the placebo and perampanel treatment arms for drop seizures.

A sample size of 71 subjects in each treatment arm in the FAS will have 94% power to detect a treatment difference in median percentage seizure frequency change in drop seizures per 28 days of 40% (common SD of 63%) between placebo and perampanel based on a Wilcoxon rank-sum test at the 0.05 two-sided significance level.

50% responder rate for drop seizures:

A sample size of 71 subjects per treatment arm will have 97% power to detect a 30% difference in responder rate proportions between placebo (assuming a placebo response rate of 20%) and perampanel treatment groups at the 0.05 two-sided significance level in drop seizures per 28 days using a two-group chi-square test.

Percent change in seizure frequency for total seizures:

Decreases in total seizures for placebo, and low, medium, and high doses in the clobazam trial were approximately 9%, 35%, 45%, and 65% respectively; common standard deviations ranged from 63% to 83%. It is assumed that comparable results will be seen in this trial for the placebo and perampanel treatment arms for total seizures.

A sample size of 71 subjects in each treatment arm in the FAS will have 80% power to detect a treatment difference in median percentage seizure frequency change in total-seizures per 28 days of 36% (SD=73%) between placebo and perampanel based on a Wilcoxon rank-sum test at the 0.05 two-sided significance level.

50% responder rate in total seizures:

A sample size of 71 subjects per treatment arm (142 total) will have more than 80% power to detect a 22% difference in responder rate proportions between placebo (assuming a placebo response rate of 20%) and perampanel treatment groups at the 0.05 two-sided significance level in total-seizures per 28 days using a two-group chi-square test.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
AED	anti-epileptic drugs
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMPA	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ß-hCG	beta-human chorionic gonadotropin
BP	blood pressure
CA	Competent Authority
CFR	Code of Federal Regulations
CL/F	apparent clearance
CMH	Cochran-Mantel-Haenszel
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CV	curriculum vitae
EAP	extended access program
ECG	electrocardiogram
CCI [redacted]	
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
CCI [redacted]	
ICF	informed consent form
ICH	International Conference on Harmonisation
CCI [redacted]	
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IxRS	interactive voice and web response system

Abbreviation	Term
LGS	Lennox-Gastaut Syndrome
LNH	low/normal/high
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamics
PET	polyethylene terephthalate
PG	pharmacogenomic
PI	principal investigator
PK	pharmacokinetics
POS	partial-onset seizure
PP	per protocol
PT	preferred term
CCI	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SOP	standard operating procedure
TBIL	total bilirubin
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
ULN	upper limit of normal
VNS	vagal nerve stimulation
WBC	white blood cell
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 International Conference on Harmonisation (ICH) E6 (Good Clinical Practice [GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRAs], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

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

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

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority (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 (Committee for Proprietary Medicinal Products [CPMP]/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH 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

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, in accordance with applicable professional standards and local laws/regulations, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician. (revised per Amendment 04)

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable representative should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. In countries where specific laws for children are established for informed consent, those local laws will be applied. After the ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the screening visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained. (revised per Amendment 04)

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

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

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 70 investigational site(s) in North America, Europe, and Asia. (revised per Amendment 01).

The name and telephone and fax numbers of the medical monitor and other contact personnel will be provided to each site.

7 INTRODUCTION

7.1 INDICATION

Lennox-Gastaut Syndrome (LGS) is one of the most rare and severe forms of childhood epilepsy. The syndrome usually affects children between the ages of 1 and 8 years (typically between 3 and 5 years), but occasionally has its onset in children who are older than 8 years. Lennox-Gastaut Syndrome begins in childhood, but continues to manifest into adulthood and has a significant morbidity and mortality. It accounts for approximately 1% of all new cases of epilepsy, although LGS may account for as many as 10% of the severe epilepsy cases.

7.1.1 Current Therapeutic Options

Treatment options for subjects with LGS are limited because of the resistance of seizures to pharmacological treatment. In addition, as there is no animal model for LGS, progress in our understanding and treatment of this disorder is impeded because novel targets for intervention cannot be rigorously studied. The choice of the most appropriate anti-epileptic drugs (AEDs) is complex and there is little guidance available for practicing physicians.

Owing to the many seizure types, many drugs are used in combinations that are mostly guided by anecdotal evidence or personal experience. Opinions towards treatment are further complicated because an AED might be of some benefit for the control of one seizure type while aggravating another type. Concomitantly, polytherapy increases the potential for AEs (Arzimanoglou et al., 2009).

Currently, 6 AEDs are approved for the indication of LGS: clobazam, rufinamide, lamotrigine, felbamate, topiramate, and epidiolex. Randomized clinical trials with these drugs aimed for a reduction of seizures associated with LGS (Devinsky et al., 2018; Thiele et al., 2018; Ng et al., 2011; Glauser et al., 2008; Motte et al., 1998; Sachdeo et al., 1999; Anonymous, 1993). Some of these drugs are associated with potentially severe adverse reactions, such as severe skin rashes (lamotrigine), aphasia in this cognitively impaired population (topiramate), and serious hematologic and hepatic toxicity (felbamate). (revised per Amendments 01 and 04)

Also, treatment options for subjects with LGS are limited because of the resistance of seizures to pharmacological treatment. The choice of the most appropriate AEDs is complex and there is little guidance available for practicing physician. Owing to the many seizure types, many drugs are used in combinations and some AEDs might be of some benefit for the control of one seizure type while aggravating another type. Concomitantly, polytherapy increases the potential for AEs. Perampanel is a novel AED with a unique mechanism of action, which has been demonstrated to be effective in the treatment of both partial and primary generalized types of seizures, making it a viable opportunity for the treatment of LGS. The benefit of improving the seizures associated with LGS, especially the severe drop attacks, outweigh the potential risks associated with the use of the drug. (revised per Amendment 01)

7.1.2 **Perampanel**

7.1.2.1 Mechanism of Action

In an alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) induced seizure model, oral perampanel significantly prolonged seizure latency, suggesting that perampanel is an orally active, selective noncompetitive AMPA receptor antagonist.

7.1.2.2 Clinical Experience with Perampanel

Clinical efficacy and safety of perampanel has been established in other epilepsy indications, including partial-onset seizures (POS) and PGTC seizures. Detailed information regarding the clinical efficacy and safety of perampanel is provided in the E2007 Global Investigator's Brochure. (revised per Amendment 04)

7.2 STUDY RATIONALE

(revised per Amendment 02)

The proposed study follows a similar design utilized for the studies of previously approved AEDs in this indication. The primary endpoint of the study is the change in count of seizures resulting in drop attacks (tonic, atonic or myoclonic). Drop seizure is defined as a drop attack or spell involving the entire body, trunk, or head that led to a fall, injury, slumping in a chair, or the patient's head hitting a surface or that could have led to a fall or injury, depending on the patient's position at the time of the attack or spell. This endpoint was chosen over the alternative endpoint of total seizures count based on review of the relevant publications and input from key opinion leaders. Non-drop seizures are defined according to the International League Against Epilepsy guidelines (1981).

Subjects on carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, and vigabatrin will not be permitted to participate in Study 338. (revised per Amendment 02) This is based on the lack of approval of these drugs in any region for this indication, and on the recommendation in guidelines against using these AEDs for the treatment of LGS, which are based on literature reports of worsening of some types of seizures associated with LGS when these AEDs are used (Thomas et al., 2006; Snead and Hosey, 1985; Eldridge et al., 1983; Osorio et al., 1989).

CCI [redacted]

8 STUDY OBJECTIVES

8.1 PRIMARY OBJECTIVE

The primary objective of the study is to demonstrate that perampanel given as adjunctive anti-epileptic treatment is superior compared to placebo in reducing the incidence of drop seizures during 18 weeks of treatment in subjects with inadequately controlled seizures associated with LGS.

8.2 SECONDARY OBJECTIVES

The secondary objectives of the study are:

1. To demonstrate that perampanel given as adjunctive anti-epileptic treatment is superior to placebo in reducing the incidence of all seizures during 18 weeks of treatment in subjects with inadequately controlled seizures associated with LGS
2. To demonstrate that perampanel given as adjunctive anti-epileptic treatment is superior to placebo in the 50%, 75%, and 100% responder rates for drop seizures during 12 weeks of the Maintenance Period in subjects with inadequately controlled seizures associated with LGS
3. To demonstrate that perampanel given as adjunctive anti-epileptic treatment is superior to placebo in the 50%, 75%, and 100% responder rates for total seizures during 12 weeks of the Maintenance Period in subjects with inadequately controlled seizures associated with LGS
4. To demonstrate that perampanel given as adjunctive anti-epileptic treatment is superior to placebo in reducing the incidence of non-drop seizures during 18 weeks of treatment in subjects with inadequately controlled seizures associated with LGS
5. To evaluate the 50%, 75%, and 100% responder rates in non-drop seizure frequency in the Maintenance Period
6. To evaluate physicians' global evaluation of subjects' overall changes in symptoms
7. To evaluate the safety of perampanel relative to placebo as adjunctive therapy in subjects with inadequately controlled seizures associated with LGS during both the Core Study and the Extension Phase
8. To evaluate the pharmacokinetics and the pharmacokinetic/pharmacodynamic (PK/PD) relationships of perampanel as adjunctive therapy in subjects with inadequately controlled seizures associated with LGS

8.3 EXPLORATORY OBJECTIVES

CCI


CCI

9 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN

This will be a multicenter, double-blind, randomized, placebo-controlled, parallel-group study of perampanel as adjunctive therapy in subjects with inadequately controlled seizures associated with LGS. The study will consist of 3 phases: Prerandomization, Randomization, and Extension. The Core Study will consist of the Prerandomization and Randomization Phases.

The Prerandomization Phase will consist of a 4- to 8-week Screening/Baseline Period during which subjects will be assessed for overall eligibility to participate in the study, including seizure activity. Baseline seizure count will be assessed using all diary data before randomization (at least 4 weeks prospectively). Following successful completion of this period, subjects will be randomized to receive perampanel or placebo in a 1:1 ratio.

The Randomization Phase will consist of 3 periods: Titration (6 weeks), Maintenance (12 weeks), and Follow-up (4 weeks, only for subjects not entering into Extension A). As required by some regulatory agencies, the following estimates are provided:

- The study will begin approximately Jan 2017 and will end approximately Jan 2020. (revised per Amendment 01)
- The maximum estimated period for each subject (except subjects continuing in Extension B) on the study is anticipated to be approximately 82 weeks. (revised per Amendment 04)

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

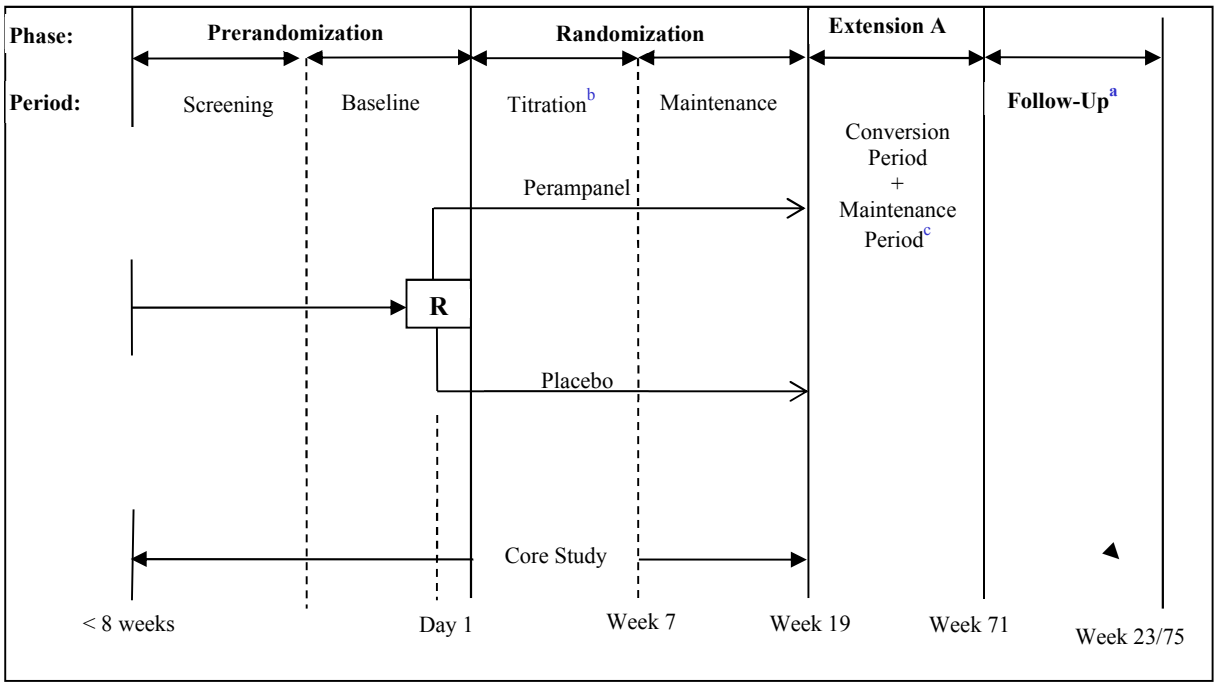

Figure 1 Study Diagram for Study E2007-G000-338 (revised per Amendment 04)

R = randomization.
a: Subjects who do not continue in Extension A or those who prematurely discontinue from the study will return to the study site for Follow-up visits 1 week and 4 weeks after the last study drug administration.
b: Subjects will be up-titrated to optimize efficacy while maintaining good tolerability, up to a maximum dose of 8 mg/day. Once titrated, all subjects will be kept at a stable dose for at least 2 weeks (to reach steady-state) before the start of the Maintenance Period. The dose of study drug during the Maintenance Period will be the last dose achieved at the end of the Titration Period.
c: After the double-blind Conversion Period of Extension A, subjects can be titrated (except in Japan, where the maximum allowed dose remains at 8 mg/day) up to 12 mg/day in 2-week intervals, as per the investigator's discretion.

9.1.1 **Prerandomization Phase**

The Prerandomization Phase will last 4 (minimum) to 8 weeks and will include a Screening and a Baseline period. (revised per Amendment 04)

9.1.1.1 Screening Period

During this period, subjects will be assessed for overall eligibility to participate in the study, including seizure activity. A minimum of 4 consecutive weeks of diary data before randomization will be required for study participation. Baseline seizure count will be assessed using all diary data before randomization. Following successful completion of this period, subjects will be randomized to receive perampanel or placebo in a 1:1 ratio.

Screening will occur from up to Day -56 to Day -1. The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3.

Subjects must have at least a 6 month diagnosis of LGS as evidenced by more than one type of generalized seizures, including drop seizures (atonic, tonic, or myoclonic). This must be confirmed by an electroencephalography (EEG) reporting diagnostic criteria (abnormal background activity accompanied by slow, spike and wave pattern < 2.5 Hz) at some point in the subject's history.

9.1.1.2 Baseline Period

During the 4-week Baseline Period, subjects must have an average of at least 2 drop seizures per week as computed from a seizure diary. To satisfy inclusion criterion #4, the total number of drop seizures will be summed and then averaged over this 4-week period. Subjects must also demonstrate at least a 30-day stable dosing regimen of 1 to 4 concomitant AEDs before Visit 1. (revised per Amendment 04).

Subjects who complete the Baseline Period and meet the criteria for inclusion/exclusion (Sections 9.3.1and 9.3.2) will begin the Randomization Phase.

9.1.2 **Randomization Phase**

The duration of the Randomization Phase will be either 18 (for subjects continuing into Extension A) or 22 weeks (for subjects not continuing into Extension A) and will include 3 periods: Titration, Maintenance, and Follow-up (for subjects not rolling over into Extension A and those who terminate early from the study). Subjects whose screening assessments and evaluations are completed and reviewed by the PI or designee and who continue to meet all of the inclusion/exclusion criteria will enter the Core Titration Period. (revised per Amendment 04)

Subjects will be randomized in 1:1 ratio to receive either perampanel or placebo. Changes of baseline AEDs (addition, deletion, or adjustment in dose) are not allowed during the Randomization Phase). (revised per Amendment 04)

9.1.2.1 Core Titration Period

During the 6-week Titration Period, subjects will be started on 2 mg/day of perampanel tablets (recommended for ≥12 years at time of consent/assent), oral suspension (recommended for <12 years at time of consent/assent), or matching placebo. However, the most appropriate formulation may be selected based on the subject's condition and at the discretion of the investigator. The same formulation should be used for a given subject throughout the course of the study. Thereafter, the dose will be increased up to a maximum target dose of 8 mg/day (or matching placebo) according to individual tolerability and efficacy. Once titrated, all subjects will be kept at a stable dose for at least 2 weeks (to reach steady-state) before the start of the Maintenance Period. The dose of study drug during the Maintenance Period will be the last dose

achieved at the end of the Titration Period. According to the investigators' clinical judgment, subjects experiencing intolerable AEs may remain on the same dose or have their dose reduced to the previously tolerated dose during the Titration Period. Subjects whose dosage has been down-titrated can have their dose increased again, as soon as tolerability improves. This can be done at the next clinic visit or at an unscheduled clinic visit after the investigator has deemed it adequate in view of the resolution of AE(s). The decision to down-titrate a subject's dose can be made via telephone. (revised per Amendment 04)

In general, more than one down-titration will be discouraged; however, if the subject continues to present significant intolerable AE(s) and the investigator deems it is necessary, the dose may be reduced further.

At the end of the Titration Period, all subjects should be at their optimum dose level. Subjects who do not tolerate a daily dose of 2 mg/day will be discontinued from the study.

9.1.2.2 Core Maintenance Period

During the 12-week Maintenance Period, subjects will continue treatment with the dose and formulation of test drug (perampanel) or placebo achieved during the Titration Period, taking the study drug once daily in blinded fashion. The Maintenance Period will begin with Visit 5, and subjects will continue treatment at the last dose (or matching placebo) achieved in the Titration Period. Study drug administration in the evening immediately before (and the evening on the day of) Visit 5 and Visit 6 should be withheld (all other AEDs should be administered per the subject's usual AED regimen). Study drug will be given during Visit 5 and Visit 6 at the study site (within 1 to 5 hours after dose administration). Bedtime dosing will resume in the evening on the day of Visit 5 and Visit 6. In these cases, dosing date and time of the previous 3 doses before each PK sampling visit will continued to be recorded. Parents or caregivers will complete seizure diaries throughout the Core Study; all seizure types will be collected. Subjects will continue to take their baseline anti-epileptic medications throughout the study. (revised per Amendment 04)

Dose adjustment during the Maintenance Period is not recommended; however, the investigator may down-titrate a subject's dose if, in his/her clinical judgment, the subject experiencing intolerable AE(s) that warrant(s) such an action. In general, more than one down-titration of a subject's dose will be discouraged; however, if the subject continues to present significant intolerable AE(s) and the investigator deems it is necessary, the dose may be reduced further. During the Maintenance Period, subjects whose dose has been down-titrated can have their dose increased again, as soon as tolerability improves. This can be done at an unscheduled clinic visit or at the next clinic visit after the investigator has deemed it appropriate based on the resolution of AE(s).

Subjects who complete the Maintenance Period will have the option to roll over into Extension A and will immediately begin the blinded Conversion Period.

Subjects who do not continue in Extension A or those who prematurely discontinue from the study will return to the study site for Follow-up visits 1 week and 4 weeks after the last study drug administration. (revised per Amendment 04)

9.1.2.3 Follow-up Period

Subjects who do not continue in Extension A or those who prematurely discontinue from the study will return to the study site for Follow-up visits 1 week and 4 weeks after the last study drug administration. At the end of the 4-week Follow-up Period, subjects will return to study site to complete the End-of-Study assessments (Follow-Up visit). These assessments will also be performed if a subject prematurely discontinues from the study, after the Early Discontinuation Visit. (revised per Amendment 04)

9.1.3 **Extension A**

A subject who completes the Maintenance Period of the Core Study will be eligible to enter Extension A, which consists of 3 periods: Conversion Period (6 weeks), Maintenance Period (46 weeks), and Follow-up (4 weeks; only for those subjects not entering into Extension B). The total treatment duration in Extension A is 52 weeks for evaluation of long term safety and efficacy. (revised per Amendment 04)

Subjects will immediately begin the blinded Conversion Period starting at Week 19. During the Conversion Period, subjects who received perampanel during the Core Study will continue receiving perampanel in a blinded manner at the same dose received during the Core Maintenance Period. Subjects who received placebo during the Core Study will begin treatment with perampanel in a blinded manner, following the same dosing regimen and titration schedule as that in the Core Study, starting at 2 mg/day and will then be up-titrated as described above for the Core Study, to the optimal dose per the investigator's discretion, not to exceed a maximum dose of 8 mg/day. After the double-blind Conversion Period, subjects can be titrated up to 12 mg/day (except in Japan, where the maximum allowed dose remains at 8 mg/day), in 2-week intervals during the Extension A Maintenance Period as per the investigator's discretion. The total treatment duration in Extension A is 52 weeks for evaluation of long term safety and efficacy. Addition, deletion, and dose changes to the concomitant AEDs are allowed during Extension Maintenance Period. (revised per Amendment 04)

After completion of Extension A, an additional Extension Phase (Extension B) with open-label treatment will be available for optional participation to subjects who reside in Japan or subjects in countries where an extended access program (EAP) cannot be implemented or has not yet been implemented, and who in the opinion of the investigator continue to benefit from treatment with perampanel. All subjects, except for those entering Extension B, will enter a 4-week Follow-up Period, which will have 1 visit during which End-of-Study assessments will be performed. (revised per Amendment 04)
Further information regarding Extension A is provided in Appendix 2 .

9.1.4 Additional Extension Phase (Extension B)

Extension B will be open for subjects who reside in Japan or subjects residing in countries where an EAP cannot be implemented, and who in the opinion of the investigator continue to benefit from treatment with perampanel. Participation in Extension B will continue as long as clinically appropriate according to the judgment of the investigator until perampanel is commercially available. (revised per Amendment 04)

For subjects residing in countries where commercial perampanel is not yet available and EAP can be implemented (provided that a positive risk/benefit is demonstrated based on analysis of the Core Study data), subjects who have completed Extension A and who in the opinion of the investigator continue to benefit from treatment with perampanel may opt to enroll into EAP (if activated), or temporarily into Extension B until EAP is activated or until perampanel is commercially available, whichever occurs first. At that point, the subject will complete his/her participation in Extension B. (revised per Amendment 04)

In the event that a risk-benefit assessment of perampanel for the treatment of LGS is found to be negative, this study will be terminated and no EAP will be set up. (revised per Amendment 04)

See Appendix 4 for a full description of Extension B. (revised per Amendment 04)

The end of the study will be the date of the last visit of the last subject. (revised per Amendment 01)

9.2 Discussion of Study Design, Including Choice of Control Groups

Randomization will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

9.3 Selection of Study Population

Approximately 142 subjects will be randomized at approximately 70 sites in regions that include North America, Europe, and Asia. Approximately 30% of subjects will be recruited from the US. Sites will be encouraged to enroll subjects throughout the allowed age range (2 years and older). Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

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

1. Subjects must have diagnosis of LGS as evidenced by:
    a. More than one type of generalized seizures, including drop seizures (atonic, tonic, or myoclonic) for at least 6 months before Visit 1

b. An EEG reporting diagnostic criteria for LGS at some point in their history (abnormal background activity accompanied by slow, spike and wave pattern < 2.5 Hz)

2. Subjects must be at least 2 years old at the time of consent/assent
3. Subjects must have been <11 years old at the onset of LGS
4. Subjects must have experienced an average of at least 2 drop seizures per week in the 4-week Baseline Period preceding randomization; the Baseline Period within the Prerandomization Phase is (minimum) 4 weeks. (revised per Amendment 04)
5. Subjects must have been receiving 1 to 4 concomitant AEDs at a stable dose for at least 30 days before Visit 1 (vagal nerve stimulation [VNS] and ketogenic diet do not count as an AED). Use of cannabidiol (CBD) products is allowed and is counted as one of the 4 maximum allowed concomitant AEDs. CBD dose and product must have remained stable for at least 30 days before Visit 1 and is to remain the same throughout the course of the Core Study. (revised per Amendment 04)
6. In the investigator's opinion, parents or caregivers must be able to keep accurate seizure diaries
7. Body weight at least 8 kg

9.3.2 **Exclusion Criteria**

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

1. Presence of progressive neurological disease
2. Presence of drop seizure clusters where individual seizures cannot be reliably counted (seizure clusters are defined as ≥2 drop seizures with <5 minutes between any 2 consecutive seizures)
3. Prior treatment with perampanel with discontinuation due to safety issues (related to perampanel)
4. Prior treatment with perampanel within 30 days before Visit 1
5. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal disease, hepatic disease) that in the opinion of the investigator(s) could affect the subject's safety or study conduct
6. Scheduled for epilepsy-related surgery or any other form of surgery during the projected course of the study
7. Ketogenic diet and VNS, unless stable and ongoing for at least 30 days before Visit 1
8. Treatment with an investigational drug or device within 30 days before Visit 1
9. Status epilepticus within 12 weeks of Visit 1
10. If felbamate is used as a concomitant AED, subjects must be on felbamate for at least one year, with a stable dose for 60 days before Visit 1. They must not have a history of white blood cell (WBC) count below ≤2500/µL (2.50 1E+09/L), platelets < 100,000/µL,

liver function tests >3 times the upper limit of normal (ULN), or other indication of hepatic or bone marrow dysfunction while receiving felbamate.

11. Concomitant use of vigabatrin: Subjects who took vigabatrin in the past must be discontinued for at least 5 months before Visit 1, and must have documentation showing no evidence of a vigabatrin-associated clinically significant abnormality in an automated visual perimetry test
12. 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
13. Evidence of significant active hepatic disease. Stable elevations of liver enzymes, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) due to concomitant medication(s) will be allowed if they are < 3 times the ULN
14. Adrenocorticotropic hormone within the 6 months before Visit 1
15. Had history of anoxic episodes requiring resuscitation within 6 months before Visit 1
16. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG] with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG or hCG). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
17. Females of childbearing potential who:

    (revised per Amendment 01)

    - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
        - Total abstinence (if it is their preferred and usual lifestyle)
        - An intrauterine device or intrauterine hormone-releasing system (IUS)
        - An oral contraceptive (with additional barrier method if using contraceptive containing levogesterol) (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
        - Have a vasectomized partner with confirmed azoospermia.
    - Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

For sites outside of the EU, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide. (revised per Amendment 01)

(NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie,

bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).

18. Had intermittent use of benzodiazepine of more than 4 single administrations in the month before Visit 1
19. A prolonged QT/QTc interval (QTc >450 ms) as demonstrated by a repeated electrocardiogram (ECG)
20. Hypersensitivity to the study drug or any of the excipients
21. Any history of a medical condition or a concomitant medical condition that in the opinion of the investigator(s) would compromise the subject's ability to safely complete the study
22. Known to be human immunodeficiency virus (HIV) positive
23. Active viral hepatitis (B or C) as demonstrated by positive serology at Screening
24. Psychotic disorder(s) or unstable recurrent affective disorder(s) evident by use of antipsychotics or prior suicide attempt(s) within approximately the last 2 years
25. History of drug or alcohol dependency or abuse within approximately the last 2 years; use of illegal recreational drugs
26. Concomitant use of medications known to be inducers of cytochrome P450 (CYP3A) including, but not limited to: rifampin, troglitazone, St John's Wort, efavirenz, nevirapine, glucocorticoids (other than topical usage), modafinil, pioglitazone, and rifabutin.
27. Use of AEDs not recommended by Epilepsy Treatment Guidelines for use in LGS including, but not limited to carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, and vigabatrin (revised per Amendment 02)
28. Any suicidal ideation with intent with or without a plan within 6 months before Visit 2 (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the C-SSRS) in subjects aged 8 and above. (revised per Amendment 01)
29. Subjects with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. (revised per Amendment 04)

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.

Subjects with laboratory results that include elevated AST or ALT greater than or equal to 3 × ULN and elevated total bilirubin (TBIL) greater than or equal to 2 × ULN with an alkaline phosphatase (ALP) laboratory value that is less than 2 × ULN, ie that meet criteria for Hy's law, will be withdrawn from the study. (revised per Amendment 03) Subjects who appear to have a high risk of suicidal behavior according to results of the C-SSRS and/or clinical impression will be withdrawn from the study. (revised per Amendment 03)

A subject who discontinues study treatment should be followed for subsequent protocol-specified visits and procedures. If a subject discontinues study drug(s) but remains in the study (Core Study), the set of end-of-treatment procedures will be administered, and protocol-specified information will be collected. The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the Subject Disposition case report form (CRF) page (or the Early Discontinuation from Study Drug CRF page). In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing CRF page. If a subject discontinues study treatment and the study at the same time, the End-of-Study procedures (Final Visit) will be followed.

9.4 TREATMENTS

9.4.1 Treatments Administered

The following treatments will be administered during the Randomization Phase:

- Perampanel: single daily dose of perampanel oral 2-mg tablets with multiple tablets dispensed to give a dose of 2 mg/day to 8 mg/day. (revised per Amendment 04)
- Perampanel: single daily dose of perampanel oral suspension 0.5 mg/mL, with the volume dispensed adjusted to give a dose of 2 mg/day to 8 mg/day. (revised per Amendment 04)
- Placebo matched to perampanel 2-mg tablets
- Placebo matched to perampanel oral suspension

It is recommended that oral tablet be used for dosing subjects ≥12 years of age and oral suspension be used for subjects <12 years of age (at the time of signing informed consent); however, the most appropriate formulation may be selected based on the subject's condition and at the discretion of the investigator. The same formulation should be used for a given subject throughout the course of the study. Dosing should occur orally once a day before bedtime. Before the PK sampling visits, the dosing date and time of the previous 3 doses before each PK sampling visit will be recorded. Study drug administration in the evening immediately before (and the evening on the day of) Visit 5 and Visit 6 should be withheld (all other AEDs should be administered per the subject's usual AED regimen). Study drug will be given during Visit 5 and Visit 6 at the study site (within 1 to 5 hours after dose administration). Bedtime will resume in the evening on the day of Visit 5 and Visit 6. (revised per Amendment 04)

The subject will continue to take their baseline anti-epileptic medication regimen throughout the Randomization Phase. Changes of baseline AEDs (addition, deletion, or adjustment in dose) are not allowed during the Randomization Phase. (revised per Amendment 01)

The following treatments will be administered to subjects in this study (Table 1). The dosage form administered at the start of the Titration Period (tablets or suspension [ie, the most appropriate formulation selected based on the subject's condition and at the discretion of the investigator]) will be continued throughout the study (Core and Extension) even if a subject reaches 12 years of age during this time. (revised per amendment 04)

Table 1 Dosage Schedule in E2007-G000-338 (Randomization Phase Core Study)

Randomization Phase/ Titration Period	Visit	All Subjects
Week 1 (starting dose)	Visit 2	2 mg/day
Week 2	Visit 3	4 mg/day
Week 3	-	6 mg/day
Week 4	Visit 4	6 mg/day
Week 5[a]	-	8 mg/day
Week 6[a]	-	8 mg/day
Randomization Phase/ Maintenance Period (Week 7/Visit 5)[b]	Starts the Maintenance Period at the last dose achieved in the Titration Period	

a: Subjects will remain on dose for at least 2 weeks before entering the Maintenance Period.
b: Dosing should occur orally once a day before bedtime, except on the evenings immediately before (and the evening on the day of) Visit 5 and Visit 6. Study drug administration in the evening immediately before (and the evening on the day of) Visit 5 and Visit 6 should be withheld (all other AEDs should be administered per the subject's usual AED regimen). Study drug will be given during Visit 5 and Visit 6 at the study site, after collection of predose PK sample (within 1 to 5 hours after dose administration). Bedtime dosing will resume in the evening on the day of Visit 5 and Visit 6. (revised per Amendment 04)

9.4.2 Identity of Investigational Products

E2007 (perampanel) is a US Drug Enforcement Administration (DEA) Scheduled III Drug Product (C-III).

PERAMPANEL TABLETS

Perampanel 2-mg tablets will be provided as orange, 6.6 mm diameter, biconvex film-coated tablets for oral administration. The front and reverse sides of the tablets will be debossed with "E274." Each tablet will contain 2 mg of perampanel. The certificate(s) of analysis (CoA) will provide manufacturer information.

Perampanel-matched placebo tablets will be provided as orange, 6.6 mm diameter, biconvex film-coated tablets for oral administration. The front and reverse sides of the tablets will be debossed with "E274." The CoA will provide manufacturer information.

The Eisai-approved vendor will package the study drugs in a double-blind configuration. Each subject's study drug will consist of either perampanel and/or perampanel-matched placebo and will be supplied in a subject medication kit bearing a multilanguage booklet label.

During the Titration Period, subjects will be given blinded 2-week dose packs containing 2 × 28 tablets plus 3 days of additional medication. During the Maintenance Period, subjects will be given blinded 2-week dose packs, each containing 2 x 28 tablets plus 3 days of additional medication. (revised per Amendment 01)

PERAMPANEL SUSPENSION

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 CoA will provide manufacturer information. Placebo solution (for dilution purposes) will consist of

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 CoA will provide manufacturer information.

Both the perampanel and placebo oral suspensions will be provided by Eisai Co. Ltd. to an Eisai-approved vendor in 400-mL polyethylene terephthalate (PET) bottles containing 340 mL of oral suspension. The approved vendor will label the bottles and ship them to the study sites

The PET bottles will be, if necessary, fitted with appropriately sized press-in bottle adaptors (PiBA) to aid in accurate aliquoting. Dosing devices (eg, oral syringes) will also be provided for subject use.

During the Titration and Maintenance Periods subjects will be given bottles containing oral suspension. The same bottle can be returned to the subject/caregiver. Instructions regarding routine dosage changes during the Titration Period will also be conveyed to the investigator via IxRS as described in Section 9.4.3.

Detailed instructions on weekly/biweekly increments in dosage during the Titration Period will be provided to the subject's caregiver by the site investigator or the designated pharmacy.

Details for the identity of the investigational product for Extension A can be found in Appendix 2.

9.4.2.1 Chemical Name, Structural Formula of E2007

- Test drug code: E2007

CCI

9.4.2.2 Comparator Drug

Not applicable

9.4.2.3 Labeling for Study Drug

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

9.4.2.4 Storage Conditions

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

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

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

After the Baseline Period, subjects will be randomized to 1 of 2 treatment groups. One treatment group will receive perampanel and the other treatment group will receive placebo once daily.

Randomization will be performed centrally by IxRS. The IxRS or clinical supply vendor will generate randomized identification numbers. At enrollment (and after successful completion of Visit 1), the investigator or designee will access the IxRS to register the subject information. At randomization (Visit 2), the IxRS will assign each subject a unique 6-digit randomization number. At every subsequent dose change, the investigator or a designee will access the IxRS to obtain dispensing instructions and register the subject's visit.

Randomization will be stratified by age group and region.

9.4.4 Selection of Doses in the Study

All subjects will start perampanel at a dose of 2 mg/day (or matching placebo). Thereafter their dose will be increased up to a maximum dose of 8 mg/day (or matching placebo) according to individual tolerability and efficacy. See Table 1 for the dosing schedule and titration steps.

It is recommended that oral tablet be used for dosing subjects ≥12 years of age (at the time of signing informed consent). It is recommended oral suspension be used for subjects <12 years of age (at the time of signing informed consent). However, the most appropriate formulation may be selected based on the subject's condition and at the discretion of the investigator. The same formulation should be used for a given subject throughout the course of the study. (revised per Amendment 04)

The choice of a maintenance dose up to 8 mg/day was based on the population PK analysis of the data from the clinical study in subjects 2 to 12 years of age with epilepsy (E2007-G000-232). The analysis included data from a total of 42 subjects with age range between 2 to 11 years and wide range of body weights (ie, 12.2 to 90.9 kg). The dataset included 14 females out of 42 subjects. The results of the analysis demonstrated that perampanel PK was linear as there was no dose or time-dependency to oral clearance (CL/F). The CL/F was not significantly affected by age, body weight, gender, race, hepatic function markers (ALT or AST), renal function marker

(creatinine clearance) or the use of 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. These results suggest that a similar dosing approach as in adolescents or adults without presence of enzyme inducing AEDs (ie, flat dosing with a target dose of 8 mg would be appropriate for the pediatric subjects between 2 to <12 years of age).

9.4.5 Selection and Timing of Dose for Each Subject

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

9.4.6 Blinding

Study drugs will be administered on a double-blind basis. During the Randomization Phase, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or contract research organization (CRO) and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per standard operating procedure (SOP).

A master list of all treatments and the subject numbers associated with them will be maintained in a sealed envelope by the clinical supply vendor, the IxRS vendor, and the sponsor. In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication CRF or Non-Pharmacological Procedures CRF. The investigator will record on the Adverse Event CRF any AE for which the concomitant medication/therapy was administered.

If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition CRF.

9.4.7.1 Drug-Drug Interactions

Oral Contraceptives

At a dose of 12 mg/day, perampanel reduces levonorgestrel maximum concentration (C_{max}) and area under the concentration-time curve (AUC) by approximately 40%. The possibility of decreased efficacy of contraceptives containing levonorgestrel should be considered for women taking perampanel. Females using hormonal contraceptives containing levonorgestrel must be on another form of contraception as well, as specified in Section 7.

Cytochrome P450

Perampanel is considered to be neither a potent inhibitor, nor a potent inducer of cytochrome P450 (CYP) enzymes. A drug-drug interaction study in healthy subjects showed a 3-fold increased clearance of perampanel when administered with carbamazepine. A similar result was seen in a population pharmacokinetic analysis of subjects with partial-onset seizures (POS) receiving perampanel up to 12 mg/day in placebo-controlled clinical trials. The total clearance of perampanel was increased 3-fold when administered with carbamazepine, 2-fold with phenytoin, and 2-fold with oxcarbazepine; all of which are known inducers of cytochrome P450 3A4 (CYP3A4).

Effect of Perampanel on Concomitant AEDs

In a population pharmacokinetic analysis of subjects with POS receiving perampanel up to 12 mg/day in placebo-controlled clinical trials, perampanel did not significantly affect the clearance of clonazepam, levetiracetam, phenobarbital, phenytoin, topiramate, or zonisamide. Perampanel had a marginally statistically significant effect on the clearance of carbamazepine, clobazam, lamotrigine, and valproic acid, but the effect was of no clinical relevance.

Alcohol

A pharmacodynamic interaction study in healthy subjects found that the effects of perampanel on complex tasks such as driving ability were additive or supra-additive to the impairment effects of alcohol. Multiple dosing of perampanel 12 mg/day also enhanced the effects of alcohol on vigilance and alertness and increased levels of anger, confusion, and depression. These effects may also be seen when perampanel is used in combination with other central nervous system (CNS) depressants.

9.4.7.2 Prohibited Concomitant Therapies and Drugs

Use of prior or concomitant therapies and drugs as dictated by the exclusion criteria (Section 7) will preclude a subject's participation on the study.

Concomitant use of non-AED medications known to be inducers of cytochrome P450 (CYP3A) including, but not limited to: rifampin, troglitazone, St John's Wort, efavirenz, nevirapine, glucocorticoids (other than topical usage), modafinil, pioglitazone, and rifabutin will not be permitted during the study.

Use of AEDs not recommended by Epilepsy Treatment Guidelines for use in LGS (including, but not limited to carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, and vigabatrin) is prohibited throughout the study. (revised per Amendment 02) Use of CBD products is allowed and is counted as one of the 4 maximum allowed concomitant AEDs. CBD dose and product must have remained stable for at least 30 days before Visit 1 and is to remain the same throughout the course of the Core Study. (revised per Amendment 04)

9.4.8 **Treatment Compliance**

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

9.4.9 **Drug Supplies and Accountability**

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

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- 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 trials agreement
- A copy of the regulatory authority approval for the country in which the study is being conducted and the Import License

- For US Sites only: A copy of the Controlled Substance Registration Certificate (DEA-form 223), which must be current (ie not expired) and have the appropriate controlled substance schedule listed for the study drug. Study drug will only be shipped to the exact address found on the DEA form 223 registration.

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

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

Under no circumstances will the investigator allow the study drugs/study supplies to be used other than as directed by this protocol. Study drugs/study supplies will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs/study supplies, dispensing of study drugs/study supplies to the subject, collection and reconciliation of unused study drugs/study supplies that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs/study supplies to the sponsor or (where applicable) destruction of reconciled study drugs/study supplies at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs/study supplies, (b) study drugs/study supplies dispensing/return reconciliation log, (c) study drugs/study supplies accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs/study supplies that occurs at the site. 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/study supplies 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/study supplies and empty and partially empty containers from used study drugs/study supplies are to be returned to the investigator by the subject and together with unused study drugs/study supplies 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/study supplies 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/study supplies 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/study supplies that are to be returned to the sponsor's designated central or local depot(s)

must be boxed and sealed and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs/study supplies may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs/study supplies are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

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

9.5 STUDY ASSESSMENTS

9.5.1 Assessments

9.5.1.1 Demography

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

9.5.1.2 Baseline Assessments

MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history and current medical conditions will be recorded at the Screening/Baseline Visit. All pertinent medical and surgical history must be noted in the Medical History and Current Medical Conditions CRF. The subject's lifetime AED history will also be collected.

Physical examinations (comprehensive or symptom directed) will be performed as designated on the Schedule of Procedures/Assessments (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. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF.

ELECTROCARDIOGRAMS

Electrocardiograms will be obtained at Screening / Baseline as designated on the Schedule of Procedures/Assessments (Table 5).

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

VIRAL TESTS

A 6-mL sample of blood will be taken for hepatitis B surface antigen and hepatitis C antibodies, antibodies at Screening.

URINE DRUG TEST

A 30-mL urine sample will be collected at Screening. This sample will be tested for common drugs of use/abuse (eg, cocaine, phencyclidine [PCP], opioids [as a group], benzodiazepines, barbiturates, and amphetamines). (revised per Amendment 04)

9.5.1.3 Efficacy Assessments

SEIZURE DIARIES

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

CLINICAL GLOBAL IMPRESSION SCALES

The Clinical Global Impression of Severity (CGI-S) and CGI-Improvement (CGI-I) scales will be used by the physician to evaluate overall changes in symptoms from baseline during the Core Study only.

Information regarding efficacy assessments in Extension A is provided in Appendix 2.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic/Pharmacogenetic Assessments

PHARMACOKINETIC ASSESSMENTS

Blood samples (1 mL) for determination of plasma perampanel concentrations will be collected during the Core Study at prespecified timepoints as shown in Table 5. Samples from subjects receiving active treatment will be analyzed. Plasma concentrations of analytes will be quantified by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) methodology using a previously validated assay. A detailed description of collection, handling, and shipping procedures of PK samples will be provided in a manual to be supplied to the study sites, or the details will be included in the central laboratory manual. (revised per Amendment 04)

PHARMACODYNAMIC ASSESSMENTS

Efficacy and selected safety endpoints may be correlated against exposure and/or dose.

PHARMACOGENOMIC ASSESSMENTS

Genomic DNA samples may be used to examine the role of genetic variability in subject's absorption, distribution, metabolism, and excretion, or the development of adverse events. Variation in perampanel exposure or AEs may be evaluated by correlation of single-nucleotide polymorphisms with PK, safety or PD data.

Further information regarding pharmacogenomic assessments is provided in Appendix 3.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular laboratory evaluation for hematology, blood chemistry, including assessment of criteria for Hy's Law and urine values; and periodic measurement of vital signs as detailed in Table 5. Reports of

anxiety and irritability will be closely monitored during the study by both the investigators and the Medical Monitor. (revised per Amendment 01)

The investigator at each site is required to evaluate laboratory results related to liver function (AST, ALT, TBIL, andALP), as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing. If these laboratory results include elevated AST or ALT greater than or equal to 3 × ULN and elevated TBIL greater than or equal to 2 × ULN with an ALPlaboratory value that is less than 2 × ULN, the subject will be discontinued from the study. Any laboratory results that are more than 3 times greater than the ULN for ALT or AST will be flagged by the central laboratory for investigator review. These laboratory abnormalities should be reported as an SAE. (revised per Amendment 02)

Please note that besides the laboratory abnormalities noted above, the criteria for Hy's Law include the stipulation that no other reason can be found to explain the combination of increased ALT, AST and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury. The investigator should document causality. (revised per Amendment 02)In addition, assessments of suicidal ideation and behavior using the C-SSRS will be performed during the study for subjects aged 8 years and older at the time of consent/assent; subjects who will reach the age of 8 years during the double-blind phase of the study will also be assessed using the C-SSRS starting at Baseline. (revised per Amendment 03) Suicidal ideation and behavior will be monitored in subjects less than 8 years at the time of consent/assent and during the study, on the basis of clinical impression. (revised per Amendments 01 and 03) Subjects who appear to have a high risk of suicidal behavior according to results from the C-SSRS and/or clinical impression will be withdrawn from the study. (revised per Amendment 03)

Information regarding safety assessments in Extension A is provided in Appendix 2.
Information regarding safety assessments in Extension B is provided in Appendix 4. (revised per Amendment 04)

ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

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

The criteria for identifying AEs 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 in the Treatment Phase after the subject's last dose. Serious AEs 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.

Seizures, all of which will be captured in the Patient Seizure Diary as part of the efficacy outcome measure, should not generally also be captured on the AE page of the CRF. A seizure should only be recorded as an AE if it is a new type of seizure experienced by subject or if the seizure is greater in intensity or frequency than was experienced by the subject before signing the ICF.

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, Serious Adverse Events and Events Associated with Special Situations 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 SAE is any untoward medical occurrence that at any dose:

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

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above

should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event if they do not meet other serious criteria: status epilepticus, laboratory results of elevated AST or ALT greater than or equal to 3 × ULN and elevated TBIL greater than or equal to 2 × ULN with an ALP laboratory value that is less than 2 × ULN, and reports of aggression when the aggressive act resulted in another person requiring medical treatment or the aggressive act or threat involved a weapon. (revised per Amendment 02)

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. (revised per Amendment 02) 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.

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

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for administration of 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 blood concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 2. Subjects should be in a seated or supine position during blood collection.

The Schedule of Procedures/Assessments (Table 5) shows the visits and timepoints at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study (Core Study).

Table 2 Clinical Laboratory Tests

Category	Parameters
Hematology	hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	bicarbonate, chloride, potassium, sodium
Liver function tests	alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, direct bilirubin, total bilirubin
Renal function parameters	blood urea/blood urea nitrogen, creatinine
Other	albumin, calcium, cholesterol, globulin, glucose[a], lactate dehydrogenase, phosphorus, total protein, lipid panel[a], uric acid
Urinalysis	bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs
Viral tests	HbsAg, HepC

HbsAg = Hepatitis B surface antigen; HepC = Hepatitis C; RBC = red blood cell, WBC = white blood cell.
a: Fasting samples to be taken at Baseline and at Visit 7 (end of Maintenance Period) or Early Discontinuation

Clinical laboratory tests during the study will be performed by a designated laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or two samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available may be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5, Adverse Events and Events Associated with Special Situations) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], pulse [beats per minute], height, and weight (kg) will be obtained at the visits designated on the Schedule of Procedures/Assessments (Table 5) by a validated method. (revised per Amendment 01) Blood pressure and pulse will be measured after the subject has been sitting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

OTHER SAFETY ASSESSMENTS

Pregnancy Test

A serum β-hCG test will be performed for postpuberty, premenopausal females and postmenopausal females who have been amenorrheic for less than 12 months. A 6-mL sample of

blood will be taken at designated timepoints as specified in the Schedule of Procedures/Assessments (Table 5).

Urine pregnancy testing will be conducted at timepoints specified in Table 5. (revised per Amendment 01)

CCI

9.5.1.6 Other Assessments

CCI

CCI

CCI

[redacted]

CCI

[redacted]

9.5.2 **Schedule of Procedures/Assessments Core Study**

Table 5 presents the Schedule of Procedures/Assessments for the Core Study.

Table 5 Schedule of Procedures/Assessments in Study E2007-G000-338 (Core Study)

(revised per Amendments 01, 04, and 05)

Phase	**Prerandomiz-ation**	**Randomization**									
Period	**Screening/Base line**	**Titration[a]**			**Maintenance[b]**			**Early DC**	**Follow-up**		**Unsched-uled**
Visit	**1[a]**	**2[c]**	**3**	**4**	**5**	**6**	**7[d]**		**Follow-up, 1 week[e]**	**Follow-up, 4 weeks[e]**	
Week	**(up to -8)**	**1**	**2**	**4**	**7**	**13**	**19**		**20**	**23**	
Day	**(up to -56)**	**1**	**8**	**22**	**43**	**85**	**127**		**134**	**155**	
Procedures/ Assessments											
Informed consent/assent	X										
Inclusion/exclusion	X	X[f]									
Randomization		X[f]									
Physical and neurological examination	X										
Medical history[g]	X										
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Vital signs, height and weight[h]	X	X	X	X	X	X	X	X		X	(X)[i]
ECG	X										(X)[i]
CCI											
C-SSRS[k]	X					X		X		X	(X)[i]

Table 5 Schedule of Procedures/Assessments in Study E2007-G000-338 (Core Study)

(revised per Amendments 01, 04, and 05)

Phase	**Prerandomiz-ation**	**Randomization**									
Period	**Screening/Base line**	**Titration[a]**			**Maintenance[b]**			**Early DC**	**Follow-up**		**Unsched-uled**
Visit	**1[a]**	**2[c]**	**3**	**4**	**5**	**6**	**7[d]**		**Follow-up, 1 week[e]**	**Follow-up, 4 weeks[e]**	
Week	**(up to -8)**	**1**	**2**	**4**	**7**	**13**	**19**		**20**	**23**	
Day	**(up to -56)**	**1**	**8**	**22**	**43**	**85**	**127**		**134**	**155**	
Procedures/ Assessments											
Urine pregnancy test[l]		X	X	X	X	X	X	X		X	(X)[i]
Serum pregnancy test[l]	X										
Clinical laboratory tests[m]	X	X[n]		X			X[n]	X[n]		X	(X)[i]
Viral tests (HBsAg, HepC)	X										
Urine drug testing[o]	X										
Dispense/collect seizure diary	X	X	X	X	X	X	X[p]	X	X	X	(X)[i]
IxRS	X	X	X	X	X	X	X	X		X	(X)[i]
Dispense study drug		X	X	X	X	X	X				(X)[i]
Administer study					X[r]	X[r]					

Table 5 Schedule of Procedures/Assessments in Study E2007-G000-338 (Core Study)

(revised per Amendments 01, 04, and 05)

Phase	**Prerandomiz-ation**	**Randomization**									
Period	**Screening/Base line**	**Titration[a]**			**Maintenance[b]**			**Early DC**	**Follow-up**		**Unsched-uled**
Visit	**1[a]**	**2[c]**	**3**	**4**	**5**	**6**	**7[d]**		**Follow-up, 1 week[e]**	**Follow-up, 4 weeks[e]**	
Week	**(up to -8)**	**1**	**2**	**4**	**7**	**13**	**19**		**20**	**23**	
Day	**(up to -56)**	**1**	**8**	**22**	**43**	**85**	**127**		**134**	**155**	
Procedures/ Assessments											
drug at site											
Retrieve unused study drug			X	X	X	X	X	X			(X)[i]
Adverse events	X	X	X	X	X	X	X	X	X	X	X
CCI											
Perampanel blood concentration samples					X[r]	X[r]	X[s]	X[s]	X[s]		(X)[i]
CGI-S		X									
CGI-I							X	X			(X)[i]
Pharmacogenomic blood samples[t]		X									

Footnotes for Table 5:

AED = antiepileptic drug; CGI-I = Clinical Global Impression of Improvement; CGI-S = Clinical Global Impression of Severity; C-SSRS = Columbia Suicide Severity Rating Scale; DC = discontinuation; ECG = electrocardiogram; EEG = electroencephalogram; CCI HBsAg = Hepatitis B surface antigen; HepC = Hepatitis C; CCI PK = pharmacokinetic

a: Visits will have a window of ±3 days with at least 10 days between visits (with the exception of Visit 3).
b: Visits will have a window of ±6 days.
c: There must be at least 4 weeks between Visits 1 and 2.
d: For those subjects who have completed Visit 7 study assessments and who are rolling over into Extension A, Visit 7 will serve as the End-of-Core Study visit and the beginning of the blinded Conversion Period of Extension A. (revised per Amendments 04 and 05)
e: Only for those subjects not rolling over into Extension A, and for those subjects who prematurely discontinued from the study, the Follow-up visits will take place at 1 week and 4 weeks after the last study drug administration (ie, Visit 7 or Early Discontinuation Visit, respectively). These visits will not be conducted if the subject continues into Extension A, in which case, a Follow-up visit will be performed 4 weeks after the last Extension visit. Visits will have a window of ±6 days. (revised per Amendments 01 and 04)
f: Final determination of eligibility and, if eligible, randomization to occur before any study drug administration. (revised per Amendment 04)
g: Lifetime AED history will be collected as part of medical history.
h: Height of adult subjects is to be recorded only at the Screening Visit (Visit 1). (revised per Amendment 01)
i: CCI
j:
k: Subjects ≥8 years of age at time of informed consent/assent and subjects who will reach the age of 8 years during the double-blind phase of the study will also be assessed using the C-SSRS starting at Baseline. (revised per Amendment 03)
l: Urine and serum pregnancy testing is for postpuberty, premenopausal females and postmenopausal females who have been amenorrheic for less than 12 months.
m: Clinical laboratory tests include chemistry, hematology, and urinalysis. If a urine sample cannot be obtained; the subject will still be eligible for enrollment. However, every effort should be made to collect a sample.
n: Fasting samples to be taken at indicated time points for glucose and lipid panel.
o: Drug screen includes cocaine, phencyclidine [(PCP)], opioids ([as a group)], benzodiazepines, barbiturates, and amphetamines. Positive CBD results in subjects taking CBD products will not be exclusionary. (revised per Amendment 04)
p: Collect diaries at Visit 7 from subjects not rolling over into Extension A. Dispense diaries at Visit 7 to subjects rolling over into Extension A.
q: CCI
r: Two blood samples (1.0 mL each) will be collected at Visit 5 and Visit 6 for the determination of perampanel plasma concentrations. One blood sample will be collected before dose administration and the second sample will be collected anytime between 1 to 5 hours postdose. Study drug administration in the evening immediately before (and the evening on the day of) Visit 5 and Visit 6 should be withheld (all other AEDs should be administered per the subject's usual AED regimen). Study drug will be given during Visit 5 and Visit 6 at the study site, after collection of predose PK sample (within 1 to 5 hours after dose administration). Bedtime dosing will resume in the evening on the day of Visit 5 and Visit 6. Each PK sample is to be split into 2 aliquots before storage per instructions provided in the laboratory manual. (revised per Amendment 04)
s: One blood sample (1.0 mL) will be collected for the determination of perampanel plasma concentrations. The blood sample may be collected at any time during the specified visits
t: A sample will be collected predose on Day 1, or at another visit if it cannot be collected at this time.

The volume of blood to be taken at each visit in the core study is shown in Table 6. The total volume of blood taken during the core study for subjects who complete all core study visits and enter Extension A will be 36 mL. For subjects who do not enter Extension A after completing all core study visits, the total volume of blood taken during the core study will be 43 mL (not including unscheduled visits). (revised per Amendments 01 and 04)

Table 6 Blood Volumes Taken During Core Study
(revised per Amendments 01 and 04)

Visit No.	V1	V2	V4	V 5	V 6	V7	EDC	Follow-up, Wk19	Follow-up, Wk 22	Unsched-uled Visit
Chemistry	X	X	X			X	X		X	X
Serology	X									X
PK sample				X	X	X	X	X		
Haematology	X	X	X			X	X		X	X
PGx		X								
Total Vol. (mL)	10	9	6	2	2	7	-	1	6	-

EDC = early discontinuation, V = visit, Wk = week

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of LGS.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, assessment of AEs, and assessment of criteria for Hy's Law are standard evaluations to ensure subject safety. (revised per Amendment 01)

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 and for 28 days after the last dose of study medication. 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 should be reported to the sponsor regardless of the length of time that has passed since study completion.

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

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

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

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

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

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

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

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

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

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

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

The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

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

9.5.4.3 Reporting of Events Associated with Special Situations

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

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

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

All AEs associated with an overdose should be captured on the Adverse Event CRF. Adverse events associated with overdose, misuse, abuse, or medication error should be 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

For this study, the following events should always be considered serious and reported as an important medical event even if it does not meet other serious criteria: status epilepticus, laboratory results of elevated AST or ALT greater than or equal to 3 × ULN and elevated TBIL greater than or equal to 2 × ULN with an ALP laboratory value that is less than 2 × ULN, and reports of aggression when the aggressive act resulted in another person requiring medical treatment or if the aggressive act or threat involved a weapon. (revised per Amendments 01 and 02)

9.5.4.4 Expedited Reporting

The sponsor must inform investigator 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

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for

an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

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 GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 **Completion/Discontinuation of Subjects**

A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 5). (revised per Amendment 01)

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

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

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

9.5.6 **Abuse or Diversion of Study Drug**

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

Adverse events associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.4.3. Abuse is always to be captured as an AE.

9.5.7 **Confirmation of Medical Care by Another Physician**

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether

he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, should 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, where applicable, 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 a snapshot of the database is obtained and released for unblinding. 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 the Core Study data for the purposes of registration are described in this section. Further details of the analytical plan will be provided in the Core Study SAP, which will be finalized before database lock for the Core Study and treatment unblinding. Separate

SAPs will be produced for Extension A and Extension B of the study. (revised per Amendment 04)

9.7.1.1 Study Endpoints

PRIMARY ENDPOINTS

The primary efficacy endpoint will be the median percent change in drop seizure frequency per 28 days during double-blind treatment (Titration Period and Maintenance Period) relative to the Prerandomization Phase in the Full Analysis Set (FAS).

SECONDARY ENDPOINTS

The following key secondary endpoints will be evaluated sequentially using the FAS:

1. Median percent change in total seizure frequency per 28 days during double-blind treatment (Titration Period and Maintenance Period) relative to the Prerandomization Phase.
2. The 50% responder rate in the Maintenance Period of the double-blind treatment relative to the Prerandomization Phase for drop seizures
3. The 50% responder rate in the Maintenance Period of the double-blind treatment relative to the Prerandomization Phase for total seizures.

Other secondary endpoints are as follows. They will not be analyzed statistically but will be summarized. (revised per Amendment 01):

4. Median percent change in non-drop seizure frequency per 28 days during double-blind treatment (Titration Period and Maintenance Period) relative to the Prerandomization Phase
5. Proportion of subjects with 75%, and 100% responder rates for drop, non-drop, and total seizures in the Maintenance Period relative to the Prerandomization Phase
6. Proportion of subjects with 50% responder rate in the Maintenance Period of the double-blind treatment relative to the Prerandomization Phase for non-drop seizures
7. Physicians' global evaluation of the subject's overall changes in symptoms (using a 7-point Likert scale with 1=very much improved and 7=very much worse) at the end of the double-blind treatment.
8. Incidence of AEs and SAEs, changes in clinical laboratory values, and vital signs
9. Model-derived average perampanel concentrations at steady state ($C_{av,ss}$) during the Maintenance Period of the Core Study

EXPLORATORY ENDPOINTS

CCI [redacted]

9.7.1.2 Definitions of Analysis Sets

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

The FAS is the group of randomized subjects who received at least one dose of study drug and had at least one postdose seizure measurement.

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

The Pharmacokinetic Analysis Set is the group of subjects who received perampanel and had at least one quantifiable perampanel concentration during the Maintenance Period of the Core Study and adequately documented dosing history.

The PK/PD analysis set is the group of subjects who received perampanel or placebo who had seizure frequency data with documented dosing history. Subjects who received perampanel should have at least one quantifiable perampanel concentration as per the PK analysis set.

Intention to Treat (ITT) analysis set is the group of randomized subjects who received at least one dose of study drug.

All subjects who withdraw from treatment will be summarized and their withdrawal reasons will be tabulated. Prior and concomitant medication usage and demographics will also be summarized.

9.7.1.3 Subject Disposition

Subject disposition summary tables will include the number (percent) of subjects who were:

- Randomized into each treatment group
- Discontinued early from the study by primary and secondary reasons for discontinuation

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the safety and FAS will be summarized for each treatment group and for all study drug groups combined using descriptive statistics.

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

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the safety and full analysis set by treatment group, Anatomical Therapeutic Chemical (ATC) class and WHO DD PT. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 28 days after the subject's last dose. All medications will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

PRIMARY EFFICACY ANALYSIS

The analysis of the primary endpoint, percentage change in drop seizure per 28 days in the FAS, will be conducted using rank analysis of covariance (ANCOVA), with ranked percentage change from baseline in drop seizures per 28 days as the dependent variable and treatment, age group, region, and ranked baseline drop seizure rate per 28 days as the independent variables. Seizure frequency will be based on the number of drop seizures per 28 days, calculated as the number of

drop seizures over the entire time interval divided by the number of days in the interval and multiplied by 28.

Treatment effect in different age groups will be investigated.

A 5% (2-sided) level of significance will be used for all analyses.

SECONDARY EFFICACY ANALYSIS

The 3 key secondary efficacy endpoints will proceed in a sequential manner.

Median percent change in total seizure frequency per 28 days during double-blind treatment will be tested first. If this test is significant at 0.05 level, then the 50% responder rate in the Maintenance Period for drop seizures will be tested. If this is significant then the 50% responder rate in the Maintenance Period for total seizures will be tested. All tests will be at a 2-sided 5% significance level.

50% responder rates will be analyzed using the Cochran-Mantel-Haenszel (CMH) test, adjusting for region and age group. 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 double-blind treatment duration if <8 weeks of data are available) will be used in lieu of Maintenance Period. The treatment effect will be assessed using odds ratio. The common odds ratio and 95% CI as well as response rate from each treatment group will be presented. (revised per Amendment 01)

The same ANCOVA model employed for the primary efficacy variable will be employed to analyze percentage change from baseline in total seizures.

Physicians' global evaluations over time will be analyzed using the CMH test.

EXPLORATORY EFFICACY ANALYSIS

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[redacted]

9.7.1.7 Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic/Pharmacogenetic Analyses

PHARMACOKINETIC ANALYSES

Perampanel concentrations will be listed by subject, dose, and visit.

Analysis variable(s): Plasma concentrations of perampanel

Analysis methods: A population PK approach will utilize PK sample data collected during the Maintenance Phase of this study, and will be used to characterize the PK of perampanel. The effect of intrinsic (ie, demographics) and extrinsic factors (ie, most common concomitant AEDs) on perampanel PK will be evaluated. Derived exposure parameters such as area under the concentration-time curve at steady-state (AUC_{ss}) or the average steady-state drug concentration ($C_{av,ss,}$) will be calculated from the model using the individual posterior estimates of CL/F and dosing history. (revised per Amendment 04)

PHARMACODYNAMIC ANALYSES

Efficacy and selected safety endpoints may be correlated against exposure and/or dose.

PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

The relationship between exposure to perampanel and response will be modeled using population PK/PD analysis.

PHARMACOGENOMIC ANALYSES

Pharmacogenomics analyses may be performed and reported separately. Details of these analyses may be described in a separate analysis plan.

9.7.1.8 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data, presented by treatment group, will be summarized on an "as treated" basis using descriptive statistics (eg, n, mean, SD, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include TEAEs, clinical laboratory parameters, and vital signs. Study Day 1 for all safety analyses will be defined as the date of the first dose of study drug.

EXTENT OF EXPOSURE

The extent of exposure will be characterized according to the number of subjects exposed, the duration of exposure, and the dose to which they were exposed using descriptive statistics.

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 15 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as an AE that occurs from the time of first dose through 28 days after the last dose of study medication, or:

- Re-emerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or

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

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

TEAEs will be summarized by treatment group. 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 a SOC and PT, even if the subject experienced more than one 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 (possibly related, probably related, and not related).

The number (percentage) of subjects with TEAEs leading to death, treatment-emergent SAEs, and TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group.

Adverse events of special interest (ie, aggression and anger) will also be summarized by treatment groups.

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

LABORATORY VALUES

Laboratory results will be summarized using Système International units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5, Safety Assessments (Laboratory Measurements), the actual value and the change from baseline to each postbaseline visit and to the end of treatment will be summarized by visit and treatment group using descriptive statistics.

Incidence of out-of-normal-range values and markedly abnormal change from Baseline in laboratory safety test variables will be tabulated by treatment group. These out-of-normal-range values and markedly abnormal changes from Baseline will be obtained from laboratory-defined normal ranges and using modified National Cancer Institute (NCI) criteria, respectively.

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 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 (TEMAV). 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.

Laboratory analyses will also include analysis of outliers. For ALT and AST analysis, the number of subjects with >3 times but <5 times the ULN and the number of subjects with >5 times the ULN will be summarized. For bilirubin, a summary of the number of subjects with serum concentrations >2 times the ULN will be created. The number of subjects who meet the criteria for Hy's Law (Section 9.5.1.5) will be summarized by visit and during the treatment duration. (revised per Amendment 02) The number of subjects who meet each of the criteria for Hy's Law during treatment (but not all necessarily at the same visit) will also be summarized. (revised per Amendment 01)

VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, diastolic and systolic BP, pulse) and changes from baseline to each visit and to the last visit of the double-blind treatment will be presented by treatment group.

OTHER SAFETY ANALYSES

Pregnancy Test

By-subject listings will be presented for pregnancy tests.

9.7.1.9 Other Analyses

Only subjects with a baseline and at least 1 post-baseline score for a given assessment will be included in the analyses of data from that assessment. Thus, the subject population may vary depending on the score that is calculated.

9.7.1.10 Extension A Analyses

See Appendix 2 for further information.

9.7.1.11 Extension B Analyses

See Appendix 4 for further information. (revised per Amendment 04)

9.7.2 **Determination of Sample Size**

Randomization of 71 subjects to each treatment arm will provide a sample with adequate power for the primary endpoint and the key secondary endpoints.

Primary endpoint percent change from baseline in drop seizures:

Placebo rates in drop seizures in the rufinamide and clobazam clinical trials were +1.4%, and -12.1%, respectively. In the active treatment arm, rufinamide had a median decrease of 42.5% in drop seizures and clobazam had mean decreases of 41.2%, 49.4%, and 68.3% for the low, medium, and high doses, respectively. A standard deviation of ~63% was observed for both rufinamide and for the medium dose of clobazam for drop seizures. It is assumed that comparable results will be seen in this trial for the placebo and perampanel treatment arms for drop seizures.

A sample size of 71 subjects in each treatment arm in the FAS will have 94% power to detect a treatment difference in median percentage seizure frequency change in drop seizures per 28 days of 40% (common SD of 63%) between placebo and perampanel based on a Wilcoxon rank-sum test at the 0.05 two-sided significance level.

50% responder rate in drop seizures:

A sample size of 71 subjects per treatment arm will have 97% power to detect a 30% difference in responder rate proportions between placebo (assuming a placebo response rate of 20%) and perampanel treatment groups at the 0.05 two-sided significance level in drop seizures per 28 days using a two-group chi-square test.

Percent change in seizure frequency for total seizures:

Decreases in total seizures for placebo, and low, medium, and high doses in the clobazam trial were approximately 9%, 35%, 45%, and 65% respectively; common standard deviations ranged

from 63% to 83%. It is assumed that comparable results will be seen in this trial for the placebo and perampanel treatment arms for total seizures.

A sample size of 71 subjects in each treatment arm in the FAS will have 80% power to detect a treatment difference in median percentage seizure frequency change in total-seizures per 28 days of 36% (SD=73%) between placebo and perampanel based on a Wilcoxon rank-sum test at the 0.05 two-sided significance level.

50% responder rate in total seizures:

A sample size of 71 subjects per treatment arm (142 total) will have more than 80% power to detect a 22% difference in responder rate proportions between placebo (assuming a placebo response rate of 20%) and perampanel treatment groups at the 0.05 two-sided significance level in total-seizures per 28 days using a two-group chi-square test.

9.7.3 **Interim Analysis**

No interim analysis is planned for this study.

9.7.4 **Other Statistical/Analytical Issues**

Not applicable

9.7.5 **Procedure for Revising the Statistical Analysis Plan**

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

10 REFERENCE LIST

Anonymous. Efficacy of felbamate in childhood epileptic encephalopathy (Lennox-Gastaut syndrome). The Felbamate Study Group in Lennox-Gastaut Syndrome. N Engl J Med. 1993 Jan 7;328(1):29-33.

Arzimanoglou A, French J, Blume WT, Cross JH, Ernst JP, Feucht M, et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. Lancet Neurol. 2009 Jan;8(1):82-93. Review.

CCI [redacted]

Devinsky O, Patel AD, Cross JH, Villanueva V, Wirrell EC, Privitera M, et al. Effect of cannabidiol on drop seizures in the Lennox–Gastaut Syndrome. N Engl J Med. 2018;378:1888-97.

Eldridge R, Stern R, Koerber T, Iivanainen M, Wilder BJ. "Baltic" myclonus epilepsy: hereditary disorder of childhood made worse by phenytoin. Lancet. 1983;838-42

CCI [redacted]

Glauser T, Kluger G, Sachdeo R, Krauss G, Perdomo C, Arroyo S. Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome. Neurology. 2008 May 20;70(21):1950-8. Epub 2008 Apr 9.

Motte J, Trevathan E, Arvidsson JF, Barrera MN, Mullens EL, Manasco P. Lamotrigine for generalized seizures associated with the Lennox-Gastaut syndrome. Lamictal Lennox-Gastaut Study Group. N Engl J Med. 1997 Dec 18;337(25):1807-12. Erratum in: N Engl J Med 1998 Sep 17;339(12):851-2.

Ng YT, Conry JA, Drummond R, Stolle J, Weinberg MA. OV-1012 Study Investigators. Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. Neurology. 2011 Oct 11;77(15):1473-81. Epub 2011 Sep 28.

Osorio I, Burnstine TH, Remler B, Manon-Espillat R, Reed RC. Phenytoin-induced seizures: A paradoxical effect at toxic concentrations in epileptic patients. Epilepsia. 1989;30(2):230-4.

Proposal for revised clinical and electrographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia. 1981;22(4):489-501.

Sachdeo RC, Glauser TA, Ritter F, Reife R, Lim P, Pledger G. A double-blind, randomized trial of topiramate in Lennox-Gastaut syndrome. Topiramate YL Study Group. Neurology. 1999 Jun 10;52(9):1882-7.

Snead OC, Hosey LC. Exacerbation of seizures in children with carbamazepine. New Engl J Med. 1985;13(15):916-21.

Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. The Lancet. 2018 Mar391;10125:1085-96.

Thomas P, Valton L, Genton P. Absence and myoclonic status epilepticus precipitated by antiepileptic drugs in idiopathic generalized epilepsy. Brain. 2006; 129:1281-92.

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 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 (or, if regionally required, the head of the medical institution) detailing such changes.

11.2 ADHERENCE TO THE PROTOCOL

The investigator will conduct the study in strict accordance with the protocol (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 IRB/IEC review.

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

1. Clinic, office, or hospital charts
2. Copies or transcribed health care provider notes which have been certified for accuracy after production

3. Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports, (eg, sonograms, computed tomography (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
4. Pain, CCI or medical history questionnaires completed by subjects
5. Records of telephone contacts
6. Diaries or evaluation checklists
7. Drug distribution and accountability logs maintained in pharmacies or by research personnel
8. Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
9. Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
10. 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). In addition, the sponsor will send a list of treatment codes by study subject to the investigator after the clinical database for this study has been locked. 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 the routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 HANDLING OF STUDY DRUG

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

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

11.9 PUBLICATION OF RESULTS

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

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

11.10 DISCLOSURE AND CONFIDENTIALITY

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

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

11.11 DISCONTINUATION OF STUDY

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

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

11.12 SUBJECT INSURANCE AND INDEMNITY

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

12 APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	< LLN – 10.0 g/dL < LLN – 100 g/L < LLN – 6.2 mmol/L	< 10.0 – 8.0 g/dL < 100 – 80 g/L < 6.2 – 4.9 mmol/L	< 8.0 g/dL < 80 g/L < 4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	< LLN – 3.0 x 10^9/L < LLN – 3000/mm^3	< 3.0 – 2.0 x 10^9/L < 3000 – 2000/mm^3	< 2.0 – 1.0 x 10^9/L < 2000 – 1000/mm^3	< 1.0 x 10^9/L < 1000/mm^3
Lymphocytes				
≥2 to ≤6 years				
≥7 to <12 years				
≥12 years	< LLN – 800/mm^3 < LLN – 0.8 x 10^9/L	< 800 – 500/mm^3 < 0.8 – 0.5 x 10^9/L	< 500 – 200/mm^3 < 0.5 – 0.2 x 10^9/L	< 200/mm^3 < 0.2 x 10^9/L
Neutrophils	< LLN – 1.5 x 10^9/L < LLN – 1500/mm^3	< 1.5 – 1.0 x 10^9/L < 1500 – 1000/mm^3	< 1.0 – 0.5 x 10^9/L < 1000 – 500/mm^3	< 0.5 x 10^9/L < 500/mm^3
Platelets	< LLN – 75.0 x 10^9/L < LLN – 75,000/mm^3	< 75.0 – 50.0 x 10^9/L < 75,000 – 50,000/mm^3	< 50.0 – 25.0 x 10^9/L < 50,000 – 25,000/mm^3	< 25.0 x 10^9/L < 25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	< LLN – 3 g/dL < LLN – 30 g/L	< 3 – 2 g/dL < 30 – 20 g/L	< 2 g/dL < 20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
ALT	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
AST	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
Bicarbonate, serum-low	< LLN – 16 mmol/L	< 16 – 11 mmol/L	<11 – 8 mmol/L	< 8 mmol/L
Bilirubin (hyperbilirubinemia)	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 10.0 x ULN	> 10.0 x 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 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 6.0 x ULN	> 6.0 x ULN
GGT (γ-Glutamyl transpeptidase)	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: > ULN – 160 mg/dL > ULN – 8.9 mmol/L	Fasting glucose value: > 160 – 250 mg/dL > 8.9 – 13.9 mmol/L	> 250 – 500 mg/dL; > 13.9 – 27.8 mmol/L; hospitalization indicated	> 500 mg/dL; > 27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	< LLN – 55 mg/dL < LLN – 3.0 mmol/L	< 55 – 40 mg/dL < 3.0 – 2.2 mmol/L	< 40 – 30 mg/dL < 2.2 – 1.7 mmol/L	< 30 mg/dL < 1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low (hypophosphatemia)	< 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

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
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 Extension A

ELIGIBILITY CRITERIA (revised per Amendment 04)

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

1. Have completed Visit 7 of the Core Study E2007-G000-338
2. Be considered reliable, willing to be available for the study duration, willing to comply with study procedures, and are able to record seizures in subject diaries and report AEs themselves or have a caregiver who can record and report the events for them
3. Continue to abide by concomitant drug/therapy restrictions (Section 9.4.7.2).

Subjects who meet the following will not be eligible to participate in Extension A of this study:

1. Those who, for any reason, discontinued early from the preceding double-blind Core Study.

STUDY DESIGN AND PLAN

Extension A will comprise 3 periods: 6-week Conversion, 46-week Maintenance, and 4-week Follow-up (except for subjects who are entering into Extension B). Extension A will last approximately 52 weeks overall, or until such time that perampanel is made commercially available or accessible to subjects via an EAP if activated in the country in which they reside, whichever happens sooner. (revised per Amendment 04)

During the Conversion Period, subjects who received perampanel during the Core Study will continue receiving perampanel in a blinded manner at the same dose last received during the Core Maintenance Period. Subjects who received placebo during the Core Study will begin treatment with perampanel in a blinded manner, following the same dosing regimen and titration schedule as that in the Core Study, starting at 2 mg/day and will then be up-titrated to the optimal dose per the investigator's discretion, not to exceed a maximum dose of 8 mg/day (Table 7). After the double-blind Conversion Period, subjects can be titrated up to 12 mg/day (except in Japan, where the maximum allowed dose remains at 8 mg/day), at 2-week intervals per the investigator's discretion. Addition, deletion, and dose changes to the concomitant AEDs are allowed during Extension Maintenance Period. (revised per Amendment 04)

The dosing schedule for Extension A is summarized in Table 7 (revised per Amendment 01)

Table 7 Dosage Schedule in E2007-G000-338 (Extension A)
(revised per Amendments 01, 02, 04, and 05)

Extension A/ Double-blind Conversion Period	**Visit**	**All Subjects Converting from Placebo**
Week 19 (starting dose)	Visit 7	2 mg/day
Week 20	--	4 mg/day
Week 21	Visit 8	6 mg/day
Week 22	--	6 mg/day
Week 23[a]	Visit 9	8 mg/day
Week 24	--	8 mg/day
Extension A/ Open-label Maintenance Period (beginning Week 25)	Visit 10	Starts Extension A Maintenance Period at the last dose achieved in the Conversion Period[b]

a. Subjects will remain on the same dose for at least 2 weeks before entering the Open-label Maintenance Period.
b. After the double-blind Conversion Period, subjects can be titrated up to 12 mg/day (except in Japan, where the maximum allowed dose remains at 8 mg/day), in 2-week intervals as per the investigator's discretion.

Per the investigators' judgment, all subjects will be allowed to have their dose decreased only if they experience intolerance, or their dose increased only if needed for better seizure control until the optimal dose is found. Subjects whose dose has been decreased can have their dose increased again, as soon as tolerability improves. Dose decreases can be done at an unscheduled clinic visit or via telephone.

After the double-blind Conversion Period, subjects can be titrated up to 12 mg/day (except in Japan where the maximum allowed dose remains at 8 mg/day), in 2-week intervals as per the investigator's discretion.

All dose adjustments during this phase will be done by going one dose level up or down. Subjects who do not tolerate a daily dose of 2 mg will be discontinued from the study.

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 to 105 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 (or at the end of Extension A) with the Medical Monitor.

During Extension A, changes of concomitant AEDs (addition, deletion or adjustment in dose) will be allowed. However, if changes do occur subjects should be carefully monitored.

EXTENSION A ASSESSMENTS

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

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular laboratory evaluation for hematology, blood chemistry, including assessment of criteria for Hy's Law, urine values; and periodic measurement of vital signs, as detailed in Table 5. Reports of

anxiety and irritability will be closely monitored during the study by both the investigators and the Medical Monitor. (revised per Amendment 01)

SAEs and events of special interest will be reported in the same manner as described for the Core Study (see Section 9.5.4.1 and Section 9.5.4.3). (revised per Amendment 01)

CCI

The Follow-up Period of Extension A will have 1 visit during which End-of-Study assessments will be performed, except for subjects who are entering into Extension B. These assessments will also be performed if a subject prematurely discontinues from Extension A, after the Early Discontinuation Visit. (revised per Amendment 04)

STUDY DRUG SUPPLIES

Where applicable, test drug (perampanel) will be stored and labeled in accordance with the US FDA Drug DEA Regulations for Scheduled III - V Drugs. See Section 9.4.2 and Section 9.4.9 for other information regarding requirements for DEA-scheduled perampanel.

PERAMPANEL TABLETS

Perampanel 2-mg tablets will be provided as orange, 6.6 mm diameter, biconvex film-coated tablets for oral administration. The front and reverse sides of the tablets will be debossed with "E274." Each tablet will contain 2 mg of perampanel.

Perampanel-matched placebo tablets will be provided as orange, 6.6 mm diameter, biconvex film-coated tablets for oral administration. The front and reverse sides of the tablets will be debossed with "E274."

The Eisai-approved vendor will package the study drugs in a double-blind configuration. Each subject's study drug will consist of either perampanel and/or perampanel-matched placebo and will be supplied in a subject medication kit bearing a multilanguage booklet label.

During the Conversion Period, subjects will be given blinded 2-week dose pack containing 2 x 28 tablets plus 3 days of additional medication. (revised per Amendment 01)

During the Maintenance Period, subjects will be given the required quantity of open-label 4-week dose packs, each containing 4 x 42 tablets plus 7 days of additional medication.

PERAMPANEL ORAL SUSPENSION

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.

Perampanel oral suspension will be provided by Eisai Co. Ltd. to an Eisai-approved vendor in 400-mL PET bottles containing 340 mL of oral suspension. The approved vendor will label the bottles and ship them to the study sites.

The PET bottles will be, if necessary, fitted with appropriately sized PiBA to aid in accurate aliquoting. Dosing devices (eg, oral syringes) will also be provided for subject use.

During the Conversion and Maintenance Periods subjects will be given bottles containing oral suspension. The same bottle can be returned to the subject/caregiver. Instructions regarding routine dosage changes during the Conversion Period will also be conveyed to the investigator via IxRS as described in Section 9.4.3.

Detailed instructions on weekly/biweekly increments in dosage during the Conversion Period will be provided to the subject's caregiver by the site investigator or the designated pharmacy.

SCHEDULE OF PROCEDURES/ASSESSMENTS

Table 8 presents the Schedule of Procedures/Assessments for Extension A of the study. (revised per Amendment 01) Extension A will last approximately 52 weeks overall, or until such time that perampanel is made commercially available or accessible to subjects via an EAP if activated in the country in which they reside, whichever happens sooner. The assessments to be administered are described in Section 9 (Core Study).

Table 8 Schedule of Procedures/Assessments in Study E2007-G000-338 (Extension A)
(revised per Amendment 01, 02, 04, and 05)

Phase	Extension A[a]									
Period	Conversion[b]		Maintenance[c]						Follow-up[c]	
Visit	8	9	10	11	12	13	14	Early DC	F/U	Unscheduled
Week	21	23	25	34	46	58	71		75	
Day	141	155	169	232	316	400	491		519	
Procedures/Assessments										
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X	(X)[e]
Urine pregnancy test[f]	X	X	X	X	X	X	X	X	X	(X)[e]
Clinical laboratory tests[g]	X[g]		X		X		X[h]	X[h]	X	(X)[e]
CCI										
C-SSRS			X	X	X	X	X	X	X	(X)[e]
Dispense/collect seizure diary	X	X	X	X	X	X	X	X		(X)[e]
IxRS	X	X	X	X	X	X				(X)[e]
Dispense study drug	X	X	X	X	X	X				(X)[e]
Retrieve unused study drug	X	X	X	X	X	X	X	X		(X)[e]
Adverse events	X	X	X	X	X	X	X	X	X	X[e]

bpm = beats per minute; C-SSRS = Columbia Suicide Severity Rating Scale; DC = discontinuation; EEG = electroencephalogram, F/U = Follow-up; IxRS = interactive voice and web response system.

a: Extension A begins with Week 19 after the completion of end of Core Study Visit (Visit 7) assessments. That is, for those subjects rolling over into Extension A, Visit 7 (Week 19) will mark the end of the Core Study and the beginning of the blinded Conversion Period of Extension A. (revised per Amendment 04)

b: Conversion Period visits (Visits 8 and 9 of Extension A) will have a window of ±3 days with at least 10 days between visits

c: Visit will have a window of ±6 days

d: Systolic blood pressure, diastolic blood pressure, heart rate (bpm), height, and weight (kg). Height of adult subjects is to be recorded only at the Screening Visit (Visit 1). (revised per Amendment 01).

e: Unscheduled procedures to be conducted as needed. (revised per Amendment 04)

f: Urine pregnancy testing is for postpuberty, premenopausal females and postmenopausal females who have been amenorrheic for less than 12 months. (revised per Amendment 04)

g: Clinical laboratory tests include chemistry, hematology, and urinalysis.

h: Fasting samples to be taken at indicated time points for glucose and lipid panel Fasting samples to be taken at indicated time points for glucose and lipid panel

i: CCI

Table 9 presents the blood volumes to be collected during Extension A. The total volume of blood taken in Extension A for subjects who complete all visits will be 30 mL. For subjects who complete both the core study and Extension A, the blood volume will be 66 mL (not including unscheduled visits). (revised per Amendment 04)

Table 9 Blood Volumes Taken During Extension A (revised per Amendment 04)

Visit No.	Visit 8	Visit 10	Visit 12	Visit 14	Early Discon-tinuation	Follow-up Visit	Unscheduled Visit
Chemistry	X	X	X	X	X	X	X
Serology							
Haematology	X	X	X	X	X	X	X
Total Volume (mL)	6	6	6	6	-	6	-

PGx = pharmacogenomic (sample)

EXTENSION A STATISTICAL ANALYSES (revised per Amendment 04)

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.

Definitions of Study Populations:
The Safety Analysis Set (Extension A) is the group of subjects who received at least one dose of perampanel and had at least one post-perampanel safety assessment.

The FAS (Extension A) is the group of subjects who received at least one dose of perampanel and had at least one post-perampanel seizure measurement.

Demographics

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

Safety Analyses

Safety analyses will be performed similarly to the Core Study analyses (Section 9.7.1.8) and all analyses will be on perampanel treatment duration (Randomization Phase + Extension A for subjects randomized to perampanel and Extension A for subjects randomized to placebo). The Safety Analysis Set is defined for Extension A as the group of subjects who received at least one dose of perampanel and had at least one post-perampanel safety assessment. TEAEs are defined as AEs occurring from the time of first perampanel through 28 days after the last perampanel dose. Baseline for laboratory and vital sign parameters will be the last non-missing value before first perampanel dose.

Extent of Exposure

Duration of exposure will be calculated as the number of days between the date the subject received the first dose of perampanel (Core Study for subjects randomized to perampanel and Extension A for subjects randomized to placebo) and the date the subject received the last dose of perampanel.

Overall Extension A 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 MedDRA. Adverse events will be coded to the MedDRA (Version 15 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary SOC are also captured in the database.

Laboratory Values

Clinical laboratory values will be evaluated for each laboratory parameter by subject. Descriptive summary statistics (eg, mean, SD, median, minimum, maximum) for the laboratory parameters and changes from Baseline to the last on-treatment visit will be summarized.

Laboratory test results will be assigned a LNH classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Shift tables will be used to compare the baseline 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 modified National Cancer Institute-common toxicity criteria (NCI-CTC)criteria 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. Descriptive summary statistics (eg, mean, SD, median, minimum, maximum) for vital sign parameters and changes from baseline and to the last on-treatment visit will be evaluated.

Appendix 3 Pharmacogenomic Information

Subjects enrolled in this clinical study will have biological samples collected for pharmacogenomic (PG) analysis. Those samples may be used for discovery and validation to identify biomarkers that, for evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

The PG samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential adverse events related to study treatment and to explore the role of genetic variability in response/resistance. Samples may be analyzed to determine subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug pharmacokinetics or therapeutic response.

Collection of the samples for pharmacogenomic analysis will be bound by the same principles and processes outlined in the main study protocol. Sample collection for PG analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample collection and handling

The pharmacogenomic samples will be collected according to the schedule of assessments. If for operational or medical reasons the blood samples for pharmacogenomic analysis cannot be obtained at the prespecified visit, the sample can be taken at any study visit at the discretion of the investigator and site staff. For anticipated volume of blood samples to be collected during this study, please refer to Table 6. (revised per Amendments 01 and 02)

Security of the samples, use of the samples, retention of the samples

Sample processing, including DNA extraction and genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the Sponsor. Processing, analysis and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain patient privacy.

Samples will only be used for the purposes described in this protocol by the Sponsor. Laboratories contracted to perform the analysis on behalf of the Sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis, and will not transfer or sell those samples. The Sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report [CSR] to appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored for longer if a Health Authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double-coded (according to the ICH15 guidelines) in order to maintain patient privacy.

Right to withdraw

If during the time the pharmacogenomic samples are stored a participant would like to withdraw his or her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Patient privacy and return of data

No patient-identifying information (eg, initials, date of birth, government identifying number) will be associated with the samples. Samples that are processed for analysis (DNA/RNA extracted) may be double-coded. Double coding involves removing the initial code and replacing with another code such that the subject can be re-identified by use of two code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded (the first code being the subject number) as long as the initial tube does not carry any personal identifiers or the random code assigned by the central laboratory or biorepository. Laboratory personnel performing genetic analysis will not have access to the "key". Clinical data collected as part of the clinical trial will be cleaned of patient identifying information, and linked by use of the sample ID "key".

The Sponsor will take steps to ensure that data are protected accordingly and that confidentiality is maintained as far as possible. Data from patients enrolled in this study may be analyzed worldwide, regardless of location of collection.

The Sponsor, its representatives and agents, may share anonymized data with persons and organizations involved in the conduct or oversight of this research. These include:

- Clinical research organizations retained by the Sponsor
- Independent ethics committees or institutional review boards that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the anonymized data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the planned analysis, it will not be possible to return individual data to subjects participating in the pharmacogenomic analysis.

Appendix 4 Additional Extension Phase (Extension B) (revised per Amendment 04)

Extension B is planned to be implemented in Japan and in countries where an EAP cannot be implemented or has not yet been implemented.

Study Design and Plan

Extension B will consist of a Treatment Period and a Follow-up Period (up to 4 weeks). Treatment will continue as long as clinically appropriate according to the judgment of the investigator. However, treatment of a subject in the Extension B will be completed when perampanel is commercially available or when EAP is activated in the subject's country of residence.

Subjects eligible for Extension B shall be subjects in Japan or subjects in countries where an EAP cannot be implemented or has not yet been implemented, who have completed Extension A of this study and who, in the opinion of the investigator, continue to benefit from treatment with perampanel.

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

A minimum perampanel dose of 2 mg/day is required to continue in the program. The maximum dose of perampanel is 8 mg/day (Japan) or 12 mg/day (other countries). Subjects who do not tolerate the minimum perampanel dose of 2 mg/day during the study will be discontinued from the study.

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

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

Once perampanel is commercially available in the subject's country of residence:

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

- Subjects who switch to the commercial product will require an End-of-Study Visit. A Follow-up visit will not be required for subjects who switched to the commercial product and attended an End-of-Study Visit.

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

Study Drug Supplies

Perampanel will be supplied as 2-mg oral tablets and 0.5 mg/mL oral suspension. It is recommended that oral tablet be used for dosing subjects ≥12 years of age, and oral suspension for subjects <12 years of age. However, the most appropriate formulation may be selected based on the subject's condition and at the discretion of the investigator. The same formulation used in the Core Study and Extension A for a given subject should be used throughout the course of the study, including Extension B, unless a change in formulation is medically indicated.

Schedule of Procedures/Assessments

Table 10 presents the Schedule of Procedures/Assessments for the Extension B. During Extension B, laboratory tests will be performed by the local laboratory.

Assessments

Safety Assessments

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

Other Assessments

Concomitant medication usage will be monitored.

Statistical Analyses

Analysis Sets

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

Safety Analyses

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

Safety analyses will be performed similarly to the Core Study analyses and all analyses will be on the perampanel treatment duration (Randomization Phase + Extension A + Extension B for subjects randomized to perampanel and Extension A + Extension B for subjects randomized to placebo). TEAEs are defined as AEs occurring from the time of first perampanel through 28 days after the last perampanel dose. Baseline for laboratory and vital sign parameters will be the last non-missing value before first perampanel dose.

Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using MedDRA. Adverse events will be coded to the

MedDRA (version 18.1 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary SOC are also captured in the database.

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

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

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

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

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

Laboratory Values

Laboratory results will be summarized using SI units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on treatment value) will be summarized by visit using descriptive statistics. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Vital Signs

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

Table 10 Schedule of Procedures/Assessments in Study E2007-G000-338: Extension B (revised per Amendment 04)

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

AED = antiepileptic drug, LGS=Lennox-Gastaut Syndrome

a: Perform on the final visit of Extension A Maintenance Period (ie, Visit 14).
b: Visit window ±6 days.
c: At the unscheduled visit, selected assessments will be performed based on investigator's judgment of subject's condition.
d: Once perampanel is commercially available in the subject's country of residence, the subject will have to switch to the commercial perampanel product promptly. If a subject does not switch to the commercial product promptly, study drug treatment will be discontinued. A Discontinuation Visit and a Follow-up Visit 4 weeks (±7 days) later should be conducted for the subject.
e: Follow-up visit is not required for subjects who will be switching to the commercial product or rolling over to EAP.
f: Data collected during the final visit of Extension A Maintenance Period (ie, Visit 14) will serve to fulfill initial assessments on Study Day 1 in Extension B.
g: Unscheduled procedures to be conducted as needed.
h: Female subjects age 8 years old and above, or of childbearing potential, only.

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E2007-G000-338

Study Protocol Title: A Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial With an Open-Label Extension Phase of Perampanel as Adjunctive Treatment in Subjects at Least 2 Years of Age With Inadequately Controlled Seizures Associated With Lennox-Gastaut Syndrome

Investigational Product Name: Perampanel

IND Number: 112515

EudraCT Number: 2014-002321-35

SIGNATURES
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INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2007-G000-338
Study Protocol Title:	A Multicenter, Double-Blind, Randomized, Placebo-controlled Trial With an Open-Label Extension Phase of Perampanel as Adjunctive Treatment in Subjects at Least 2 Years of Age With Inadequately Controlled Seizures Associated With Lennox-Gastaut Syndrome
Investigational Product Name:	Perampanel
IND Number:	112515
EudraCT Number:	2014-002321-35

I have read this protocol and agree to conduct this trial 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 GCP guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date