Clinical trial results:
An Open-label Extension Phase of the Double-blind, Placebo-controlled, Dose-escalation, Parallel-group Study of E2007 (perampanel) as an Adjunctive Therapy in Patients With Refractory Partial Seizures

Summary

EudraCT number	2005-004293-24
Trial protocol	SE LT DE CZ GB ES LV BE FI EE FR NL
Global end of trial date	01 July 2014

Results information

Result version number	v1 (current)
This version publication date	26 March 2016
First version publication date	26 March 2016

Trial information

Trial identification

Sponsor protocol code	E2007-A001-207

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00368472
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Inc.
Sponsor organisation address	155 Tice Boulevard Woodcliff Lake, New Jersey, United States, 07677
Public contact	Medical Information, Eisai Europe limited, +44 845676 1400, LMedInfo@eisai.net
Scientific contact	Medical Information, Eisai Europe limited, +44 845676 1400, LMedInfo@eisai.net

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 August 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective for this study was to evaluate the safety and tolerability of E2007 given as adjunctive, long-term treatment in patients with refractory partial onset seizures with or without secondary generalization that completed the E2007-A001-206 or the E2007-G000-208 study.

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:
- Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008)
- International Conference on Harmonisation (ICH) E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	10 October 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Czech Republic: 24
Country: Number of subjects enrolled	Estonia: 4
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Latvia: 2
Country: Number of subjects enrolled	Lithuania: 29

Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	United States: 40
Country: Number of subjects enrolled	Netherlands: 2
Worldwide total number of subjects	138
EEA total number of subjects	89

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	136
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 138 subjects provided informed consent and were enrolled in this study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Perampanel

Arm description:

Participants previously receiving perampanel/placebo in the double-blind study, were titrated to receive perampanel 2 mg to 12 mg, once daily in the Open-Label Extension (OLE) study.

Arm type	Experimental
Investigational medicinal product name	Perampanel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Perampanel 2 mg to 12 mg, once daily.

Number of subjects in period 1	Perampanel
Started	138
Completed	33
Not completed	105
Request of investigator or sponsor	3
Consent withdrawn by subject	40
Adverse events	22
'Diary non-compliance '	1
Medication non-compliance	4
Not specified	32
Missing Final Disposition Date	1
Protocol deviation	2

Baseline characteristics

Reporting groups	
Reporting group title	Perampanel
Reporting group description:	
Participants previously receiving perampanel/placebo in the double-blind study, were titrated to receive perampanel 2 mg to 12 mg, once daily in the Open-Label Extension (OLE) study.	

Reporting group values	Perampanel	Total	
Number of subjects	138	138	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	40.7		
standard deviation	± 11.87	-	
Gender categorical			
Units: Subjects			
Female	80	80	
Male	58	58	

End points

End points reporting groups

Reporting group title	Perampanel

Reporting group description:

Participants previously receiving perampanel/placebo in the double-blind study, were titrated to receive perampanel 2 mg to 12 mg, once daily in the Open-Label Extension (OLE) study.

Primary: Number of Participants With Treatment-emergent Non-serious Adverse Events (AEs) and Treatment-emergent Serious (SAEs)

End point title	Number of Participants With Treatment-emergent Non-serious Adverse Events (AEs) and Treatment-emergent Serious (SAEs)[1]

End point description:

An AE was defined as any untoward medical occurrence in a clinical investigation participant administered an
investigational product. A SAE was defined as any untoward medical occurrence that at any dose resulted in death, was life-threatening (ie, the participant was at immediate risk of death from the AE as it occurred; this did not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death), required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or was as a congenital anomaly/birth defect (in the child of a participant who was exposed to the study drug). In this study, treatment emergent AEs (defined as an AE (serious or non-serious) that started/increased in severity on/after the first dose of study medication up to 30 days after the final dose of study medication) were assessed. The details are presented in the safety section of the result.

End point type	Primary

End point timeframe:

From date of first dose of perampanel up to 30 days after the last dose of perampanel or up to approximately 8 years

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study group and the study drug administered for this outcome.

End point values	Perampanel			
Subject group type	Reporting group			
Number of subjects analysed	138[2]			
Units: Participants				
Treatment-emergent non serious AEs	112			
Treatment-emergent SAEs	33			

Notes:

[2] - All participants who received at least 1 dose of study drug and were evaluable for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in Seizure Frequency Per 28 Days Relative to Pre-Perampanel Baseline

End point title	Percent Change in Seizure Frequency Per 28 Days Relative to Pre-Perampanel Baseline

End point description:

Seizure frequency was derived from information (seizure count and type) recorded in participant diary. The seizure frequency per 28 days was calculated as the number of seizures divided by the number of days in the interval and multiplied by 28. The percent change in 28-day seizure frequency from baseline was assessed for all partial-onset seizures types. For participants who had been assigned to treatment with perampanel (previous treatment), preperampanel Baseline referred to the Prerandomization Phase of the Core Double Blind study. For participants who had been assigned to treatment with placebo (previous treatment), pre-perampanel Baseline was computed from all data during the Core Double Blind study (including Prerandomization Phase) prior to treatment with perampanel.

End point type	Secondary

End point timeframe:

Baseline up to Week 221

End point values	Perampanel			
Subject group type	Reporting group			
Number of subjects analysed	138[3]			
Units: Percent change				
median (full range (min-max))	-31.5 (-99.2 to 576.1)			

Notes:

[3] - All participants who received ≥ 1 dose of study drug and had valid seizure data during OLE study.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Experienced a 50% or Greater Reduction in Seizure Frequency Per 28 Days Relative to the Pre-perampanel Baseline

End point title	Percentage of Participants Who Experienced a 50% or Greater Reduction in Seizure Frequency Per 28 Days Relative to the Pre-perampanel Baseline

End point description:

Seizure frequency was derived from information (seizure count and type) recorded in participant diary. The percentage
of participants who experienced a 50% or greater reduction in seizure frequency per 28 days relative to the preperampanel
Baseline (responders) was assessed. For participants who had been assigned to treatment with perampanel (previous treatment), pre-perampanel Baseline referred to the Prerandomization Phase of the Core Double Blind study. For participants who had been assigned to treatment with placebo (previous treatment), pre-perampanel Baseline was computed from all data during the Core Double Blind study (including Prerandomization Phase) prior to treatment with perampanel. The data is presented as percent responders.

End point type	Secondary

End point timeframe:

Baseline up to week 221

End point values	Perampanel			
Subject group type	Reporting group			
Number of subjects analysed	138[4]			
Units: Percent responders				
number (not applicable)	36.2			

Notes:

[4] - All participants who received ≥ 1 dose of study drug and had valid seizure data during OLE study.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of first dose of perampanel up to 30 days after the last dose of perampanel or up to approximately 8 years.

Adverse event reporting additional description:

Treatment emergent adverse events (TEAEs) (defined as an adverse event that started/increased in severity
on/after the first dose of study medication up to 30 days after the final dose of study medication) were assessed.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Perampanel

Reporting group description:

Subjects previously receiving perampanel/placebo in the double blind study, were titrated to receive perampanel 2 mg to 12 mg, once daily in the OLE study

Serious adverse events	Perampanel		
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 138 (23.91%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer in situ			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer recurrent			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			

subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Contusion			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fibula fracture			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Overdose			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Scapula fracture			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Therapeutic agent toxicity			

subjects affected / exposed	1 / 138 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	1 / 138 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac arrest				
subjects affected / exposed	1 / 138 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Nervous system disorders				
Cerebrovascular accident				
subjects affected / exposed	1 / 138 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Convulsion				
subjects affected / exposed	5 / 138 (3.62%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	1 / 138 (0.72%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	5 / 138 (3.62%)			
occurrences causally related to treatment / all	2 / 6			
deaths causally related to treatment / all	0 / 0			
Grand mal convulsion				
subjects affected / exposed	1 / 138 (0.72%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Guillain-Barre syndrome				

subjects affected / exposed	1 / 138 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Paraplegia				
subjects affected / exposed	1 / 138 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Postictal state				
subjects affected / exposed	1 / 138 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sciatica				
subjects affected / exposed	1 / 138 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Status epilepticus				
subjects affected / exposed	4 / 138 (2.90%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Sudden unexplained death in epilepsy				
subjects affected / exposed	1 / 138 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Gastrointestinal disorders				
Ileitis				
subjects affected / exposed	1 / 138 (0.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure				

subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Schizophrenia			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rotator cuff syndrome			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral discitis			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pneumonia			
subjects affected / exposed	3 / 138 (2.17%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 138 (0.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Perampanel		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	112 / 138 (81.16%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 138 (8.70%)		
occurrences (all)	8		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	19 / 138 (13.77%)		
occurrences (all)	27		
Irritability			
subjects affected / exposed	8 / 138 (5.80%)		
occurrences (all)	9		
Oedema peripheral			
subjects affected / exposed	7 / 138 (5.07%)		
occurrences (all)	7		
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	7 / 138 (5.07%)		
occurrences (all)	8		
Oropharyngeal pain			
subjects affected / exposed	6 / 138 (4.35%)		
occurrences (all)	12		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	11 / 138 (7.97%)		
occurrences (all)	13		
Depression			
subjects affected / exposed	6 / 138 (4.35%)		
occurrences (all)	6		
Insomnia			
subjects affected / exposed	8 / 138 (5.80%)		
occurrences (all)	10		
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	5 / 138 (3.62%)		
occurrences (all)	8		
Weight decreased			
subjects affected / exposed	2 / 138 (1.45%)		
occurrences (all)	2		
Weight increased			
subjects affected / exposed	6 / 138 (4.35%)		
occurrences (all)	6		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	15 / 138 (10.87%)		
occurrences (all)	20		
Fall			
subjects affected / exposed	13 / 138 (9.42%)		
occurrences (all)	22		
Foot fracture			
subjects affected / exposed	4 / 138 (2.90%)		
occurrences (all)	4		

Head injury			
subjects affected / exposed	5 / 138 (3.62%)		
occurrences (all)	5		
Procedural pain			
subjects affected / exposed	4 / 138 (2.90%)		
occurrences (all)	5		
Skin laceration			
subjects affected / exposed	12 / 138 (8.70%)		
occurrences (all)	23		
Nervous system disorders			
Ataxia			
subjects affected / exposed	7 / 138 (5.07%)		
occurrences (all)	10		
Balance disorder			
subjects affected / exposed	6 / 138 (4.35%)		
occurrences (all)	6		
Convulsion			
subjects affected / exposed	15 / 138 (10.87%)		
occurrences (all)	18		
Dizziness			
subjects affected / exposed	60 / 138 (43.48%)		
occurrences (all)	124		
Headache			
subjects affected / exposed	31 / 138 (22.46%)		
occurrences (all)	52		
Paraesthesia			
subjects affected / exposed	4 / 138 (2.90%)		
occurrences (all)	9		
Somnolence			
subjects affected / exposed	29 / 138 (21.01%)		
occurrences (all)	51		
Tremor			
subjects affected / exposed	8 / 138 (5.80%)		
occurrences (all)	8		
Ear and labyrinth disorders			

Vertigo subjects affected / exposed occurrences (all)	12 / 138 (8.70%) 17		
Eye disorders Diplopia subjects affected / exposed occurrences (all)	7 / 138 (5.07%) 8		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	10 / 138 (7.25%) 15 13 / 138 (9.42%) 16 7 / 138 (5.07%) 8		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	12 / 138 (8.70%) 16		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Neck pain subjects affected / exposed occurrences (all) Pain in extremity	8 / 138 (5.80%) 10 16 / 138 (11.59%) 23 8 / 138 (5.80%) 13 10 / 138 (7.25%) 15		

subjects affected / exposed	9 / 138 (6.52%)		
occurrences (all)	11		
Infections and infestations			
Bronchitis			
subjects affected / exposed	6 / 138 (4.35%)		
occurrences (all)	6		
Influenza			
subjects affected / exposed	7 / 138 (5.07%)		
occurrences (all)	11		
Nasopharyngitis			
subjects affected / exposed	15 / 138 (10.87%)		
occurrences (all)	23		
Rhinitis			
subjects affected / exposed	5 / 138 (3.62%)		
occurrences (all)	6		
Upper respiratory tract infection			
subjects affected / exposed	16 / 138 (11.59%)		
occurrences (all)	28		
Urinary tract infection			
subjects affected / exposed	14 / 138 (10.14%)		
occurrences (all)	15		
Viral infection			
subjects affected / exposed	5 / 138 (3.62%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 October 2005	Protocol amendment #1 dated 13 Oct 2005: • Site number was increased from 30 to 50 sites to meet planned enrollment numbers. • Language was added to address the addition of European and North American sites and the deletion of US sites to this study in "Contact Details. • Language was added to clarify that Week 52 assessments should be performed at Week 52 or if patient prematurely terminates from the study. • Miscellaneous changes such as added European contact information for shipment of laboratory samples; ESL personnel contact information; EudraCT number; IND number; and clarification that patients with clinically significant laboratory abnormalities may be discontinued from the study at the investigator's discretion. • The International System of Units (SI) equivalent was added to the WBC and absolute neutrophil values • The controlled room temperature was revised to meet European standards. • Laboratory assessments were revised. • Revised current version of Declaration of Helsinki with the 1996 version. • Administrative changes, correction of minor spelling and typographical errors.
07 June 2006	Protocol amendment #2 dated 07-JUN-2006 • The title was changed to reflect the extended study timeframe. • Administrative changes that do not impact the scientific meaning of the trial. • Twice a day (BID) dosing may not be necessary and was removed as an option in protocol. • Once a day (QD) vs BID efficacy comparison was removed as a secondary objective. • Determination of E2007 levels was removed as a secondary objective in protocol since ample PK data was collected from core Phase II and III studies. • The duration of the Titration Phase was reduced to 6 weeks. The Maintenance Phase was increased to allow patients to receive E2007 at the highest tolerated dose for 52 weeks. • Additional sites were added to increase enrollment. • Revisions to protocol for clarification purpose. • Revisions to inclusion and exclusion criteria. • Revisions in the test assessments to maintain consistency across all sites globally and to clarify the procedures. • Anti-epileptic drugs (AED) sampling was removed as it was not necessary to the main purpose of this study. • Clinical and Patient Global Impressions of change scales were removed.

19 November 2006	Protocol amendment #3 dated 19-NOV-2006 • Incorporate recent preclinical findings of in vitro phototoxicity into the safety information. • Clarified that the study drug would be taken at bedtime based on current tolerability data. • Clarified timing for enrollment from the double-blind study into the open-label study. • Revised criterion for excluding patients with ECG abnormalities to be uniform for males and females. • Updated SAE Reporting section with contract research organization (CRO) information (previously unavailable), and with updated SAE text concerning follow-up. • Revised Visit 5 window to adjust for drug packaging. • Inhibitors of CYP3A4/5 not excluded. • Editorial, formatting, and typo corrections.
15 February 2007	Protocol amendment #4 dated 15-FEB-2007 • Incorporation of patients from E2007-G000-208 (Phase IIb, double blind, placebo controlled, maximum tolerated dose (MTD) trial, 48 patients, up to 12mg/day E2007) into E2007-G000-207 (open label extension) so that there is one extension study for both E2007-A001-206 (double blind, placebo-controlled, Phase II, proof-of-concept (PoC) epilepsy trial, 153 randomized, up to 4mg/day E2007) and E2007-G000-208 patients. • Allow the former E2007-A001-206 patients a chance to access higher doses (up to 12mg/dayE2007) if up to 4mg/day E2007 (original OLE) is insufficient in controlling seizures (at least 3 partial seizures per month on average) during the maintenance phase of the open label extension study (E2007-A001-207). • Harmonize remaining aspects of E2007-A001-206 and E2007-G000-208 • Miscellaneous changes such as clarifications to protocol sections; revise formulation and packaging; revise contact information; revise the AED and non AED dosing plan to allow flexibility; updated SAE reporting information to clarify hospitalization; and editorial and formatting changes. • Revise rationale for dose selection based on data PK data for concomitant use of CYP3A-inducing AEDs and/or non-CYP3A-inducing AEDs.
04 June 2007	Protocol amendment #5 dated 04-JUN-2007 • Updated phototoxicity / photoallergy results from in vivo studies. • Extended the open label extension phase to an additional 3 years to monitor long-term safety of E2007 given as adjunctive, long-term treatment in patients with refractory partial onset seizures. • Administrative changes, miscellaneous editorial/format changes.

08 June 2009	Protocol amendment #6 dated 08 June 2009, v2.0 • Study title was revised to remove the study duration from the title to avoid the need for additional amendments should the study duration be extended in the future • Change in sponsor name and address from Eisai Medical Research, Inc. to Eisai Inc., • Clarify that tolerability is also a component of the primary objective • Study design, treatment, synopsis, rational, duration, Physical and Neurological Examination, vital signs, etc. was revised to consolidate the text for consistency and clarity (ie, subjects from the preceding double-blind studies are treated similarly except where noted) and to remove redundancy throughout the protocol • Revised protocol deviation/violation text for consistency with other ongoing perampanel studies. • To clarify that 1 mg tablets are no longer permitted for dispensing in the study and that all subjects on an odd dose (eg, 1, 3, 5 mg) should be titrated to an even dose (eg, 2, 4, 6 mg). • To update the number of concomitant AEDs allowed (as subject may now discontinue all concomitant AEDs). • To revise the list of prohibited medications. • Miscellaneous changes such as change assessment times specified from Weeks to Visits, provide the abbreviation for lactate dehydrogenase, corrected for consistency of terminology throughout protocol, clarify durations (all text references to months have been converted to weeks eg, 1 month = 4 weeks), update SAE reporting fax and phone numbers according to the reassignment of CRO responsibilities, etc. • To clarify the instructions in regard to early terminations and the Sponsor’s position on the need for down titrations upon early termination. • To update the protocol with Eisai’s current standard Pregnancy reporting text. • To generalize text to ensure consistency in instructions with study drug labeling and Investigator’s Brochure.
08 July 2010	Protocol amendment 7 v1.0 dated 08-Jul-2010 • Secondary objective, study procedures, efficacy assessments, statistics was revised to evaluate the long term maintenance of E2007 efficacy to the last efficacy collecting visit of the E2007-A001-207 study as dispensing, collection, and review of seizure diaries will no longer be required, as sufficient and more standardized data for efficacy has been collected in the Phase 3 program for perampanel. • Extension of study duration for an additional 216 weeks for a total duration of approximately 8 years. Revised relevant protocol sections to implement this change. • Orthostatic vitals will no longer be required (only standard sitting vitals), as the current information on the • Revise safety profile of perampanel to indicate that only standard sitting vitals need be collected. • Miscellaneous changes such as update status of studies E2007-A001-206 and E2007-A001-208. • Added information on the instructions regarding study drug compliance when phone visits. • To allow flexibility in the timing of electrocardiograms (ECGs) in relation to blood draws.
26 June 2012	Protocol amendment 8 dated 26 June 2012 • Corrected Eisai US Address. • The perampanel Phase 3 program in partial onset seizures (POS) has been completed, and Regulatory submissions to seek approval for marketing have been made to several countries. Therefore, Study E2007-A001-207 will be closed and the protocol was revised to schedule the EOT visit. • Miscellaneous changes such as update abbreviation table.

11 February 2013	Protocol amendment 9 dated 11 Feb 2013 • Revised definition of study end in the United States- Upon implementation of Amendment 08, the sponsor will be closing the study protocol. The study will end after European Union (EU) Marketing Authorization Application (MAA) approval (EU countries) and after United States (US) launch (US). However, if it is the opinion of the treating physician that the patient would benefit significantly from further treatment with perampanel after the trial concludes, then it is Eisai's intent to make perampanel available under Eisai's compassionate use policy (available upon request) and according to local country legislative provision. Perampanel treatment via local country legislative provision will be available until the time perampanel is commercially available in the country in which the patient resides.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Results were ready but could not be released before 21 July 2015 due to EudraCT System issues.

Notes: