Clinical trial results:
An Open-Label Extension Phase of the Double-Blind, Placebo-Controlled, Dose-Escalation, Parallel-Group Studies to Evaluate the Efficacy and Safety of E2007 (Perampanel) Given as Adjunctive Therapy in Subjects With Refractory Partial Seizures

Summary

EudraCT number	2007-006170-28
Trial protocol	CZ ES AT BE PT LT NL HU FR GB SE EE LV DK IT DE FI BG GR
Global end of trial date	18 September 2014

Results information

Result version number	v1 (current)
This version publication date	13 April 2016
First version publication date	13 April 2016

Trial information

Trial identification

Sponsor protocol code	E2007-G000-307

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00735397
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 0845 676 1400, LMedInfo@eisai.net
Scientific contact	Medical Information, Eisai Europe Limited, +44 0845 676 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	26 November 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the safety and tolerability of perampanel (up to 12 mg/day) given as adjunctive treatment in subjects with refractory partial seizures and to evaluate the maintenance of effect of perampanel for the control of refractory partial seizures.

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	17 October 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 39
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Portugal: 7
Country: Number of subjects enrolled	Spain: 42
Country: Number of subjects enrolled	Sweden: 19
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Austria: 13
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Bulgaria: 37
Country: Number of subjects enrolled	Czech Republic: 6
Country: Number of subjects enrolled	Estonia: 26

Country: Number of subjects enrolled	Finland: 6
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 59
Country: Number of subjects enrolled	Greece: 12
Country: Number of subjects enrolled	Hungary: 35
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Latvia: 14
Country: Number of subjects enrolled	Lithuania: 17
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	Chile: 32
Country: Number of subjects enrolled	China: 54
Country: Number of subjects enrolled	Hong Kong: 22
Country: Number of subjects enrolled	India: 71
Country: Number of subjects enrolled	Israel: 32
Country: Number of subjects enrolled	Korea, Republic of: 44
Country: Number of subjects enrolled	Mexico: 20
Country: Number of subjects enrolled	Malaysia: 5
Country: Number of subjects enrolled	Philippines: 6
Country: Number of subjects enrolled	Serbia: 42
Country: Number of subjects enrolled	Thailand: 21
Country: Number of subjects enrolled	Taiwan: 16
Country: Number of subjects enrolled	Ukraine: 18
Country: Number of subjects enrolled	United States: 241
Country: Number of subjects enrolled	South Africa: 8
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	Russian Federation: 58
Country: Number of subjects enrolled	Argentina: 80
Country: Number of subjects enrolled	Australia: 47
Worldwide total number of subjects	1218
EEA total number of subjects	383

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)	124
Adults (18-64 years)	1076
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was an open-label Extension (OLE) study for participants who completed one of the following double-blind (DB), placebo-controlled, Phase 3 studies: E2007-G000-304 (NCT00699972), E2007-G000-305(NCT00699582), and E2007-G000-306 (NCT00700310).

Pre-assignment

Screening details:

From a total of 1218 participants who provided informed consent, 2 participants were lost to follow-up and did not have any postbaseline safety data after the first OLE dose.

Period 1

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

Blinding implementation details:

During the Conversion Period, subjects and investigators remained blinded to the treatment received in the previous DB study. To achieve this, all subjects continued to take 6 tablets of study medication (2 mg perampanel or matching placebo) or fewer as they were instructed during the core DB study. During the open-label Maintenance Period, subjects were treated with the perampanel dose that provided the best combination of individual efficacy and tolerability.

Arms

Arm title	Perampanel

Arm description:

Participants previously receiving perampanel/placebo in the DB study, were titrated to receive perampanel 2 mg to 12 mg, once daily in the OLE study up to approximately 5 years.

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 tablet, once daily orally in the Open-Label Extension (OLE) study up to approximately 5 years.

Number of subjects in period 1	Perampanel
Started	1218
Completed	35
Not completed	1183
Adverse events	194
Subject Choice	252
Administrative/Other	502
Lost to follow-up	33
Inadequate therapeutic effect	202

Baseline characteristics

Reporting groups

Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	1218	1218	
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			
median	33		
full range (min-max)	12 to 76	-	
Gender categorical Units: Subjects			
Female	607	607	
Male	611	611	

End points

End points reporting groups

Reporting group title	Perampanel

Reporting group description:

Participants previously receiving perampanel/placebo in the DB study, were titrated to receive perampanel 2 mg to 12 mg, once daily in the OLE study up to approximately 5 years.

Subject analysis set title	Perampanel (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intent-to-treat (ITT) was defined as participants who provided informed consent for the OLE, received at least 1 dose of perampanel in the OLE study, and had valid seizure data during the perampanel treatment duration (DB and/or OLE studies).

Subject analysis set title	Perampanel (SAS)
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set (SAS) was defined as subjects who provided informed consent for the OLE study, received at least 1 dose of perampanel in the OLE study, and had at least 1 postdose safety assessment in the OLE study.

Primary: Number of participants with Treatment-emergent non-serious adverse events (AEs) and Treatment-emergent serious adverse events (SAEs)

End point title	Number of participants with Treatment-emergent non-serious adverse events (AEs) and Treatment-emergent serious adverse events (SAEs)[1]

End point description:

An AE was defined as any untoward medical occurrence in a clinical investigation participant administered with 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.

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 5 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 (SAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	1216			
Units: Participants				
Treatment-emergent non serious AEs	1018			
Treatment-emergent SAEs	288			

Statistical analyses

No statistical analyses for this end point

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

End point title	Median 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 pre-perampanel baseline was assessed for all partial-onset seizure types. The pre-perampanel baseline was defined as: (1) for participants who had been assigned to placebo treatment in the core DB study, the pre-perampanel baseline was computed from all data during the core DB study, and (2) for participants who had been assigned to perampanel in the core DB study, the pre-perampanel baseline was computed from the pre-randomization phase of the core DB study.

End point type	Secondary

End point timeframe:

Pre-perampanel Baseline and Weeks (1-13, 14-26, 27-39, 40-52, 53-65, 66-78, 79-91, 92-104, 105-117, 118-130, 131-143, 144-156, 157-169, 170-182, 183-195, 196-208, 209-221, 222-234, 235-247, and 248-260)

End point values	Perampanel (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	1217			
Units: Percent change				
median (full range (min-max))				
Weeks 1-13	-29.14 (-100 to 737.1)			
Weeks 14-26; N=1159	-38.54 (-100 to 866.6)			
Weeks 27-39; N=1088	-42.81 (-100 to 780.6)			
Weeks 40-52; N=969	-46.22 (-100 to 685.7)			
Weeks 53-65; N=882	-49.34 (-100 to 526.4)			
Weeks 66-78; N=822	-51.65 (-100 to 861.5)			
Weeks 79-91; N=762	-53.06 (-100 to 697.5)			
Weeks 92-104; N=720	-56.59 (-100 to 660.9)			
Weeks 105-117; N=676	-59.07 (-100 to 627.9)			
Weeks 118-130; N=642	-60.89 (-100 to 540)			
Weeks 131-143; N=583	-60.67 (-100 to 716)			
Weeks 144-156; N=517	-61.45 (-100 to 570.2)			
Weeks 157-169; N=429	-65.46 (-100 to 418.3)			
Weeks 170-182; N=323	-64.29 (-100 to 367.4)			

Weeks 183-195; N=210	-66.63 (-100 to 698.7)			
Weeks 196-208; N=119	-73.3 (-100 to 671.8)			
Weeks 209-221; N=59	-72.47 (-100 to 226.4)			
Weeks 222-234; N=37	-81.36 (-100 to 175.3)			
Weeks 235-247; N=14	-78.1 (-100 to 200.4)			
Weeks 248-260; N=5	-97.16 (-100 to 250.4)			

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 pre-perampanel Baseline (responders) was assessed. The pre-perampanel baseline was defined as: (1) for participants who had been assigned to placebo treatment in the core DB study, the Pre-perampanel baseline was computed from all data during the core DB study, and (2) for participants who had been assigned to perampanel in the core DB study, the pre-perampanel baseline was computed from the pre-randomization phase of the core DB study. The data is presented as percent responders.

End point type	Secondary

End point timeframe:

Pre-perampanel Baseline and Weeks (1-13, 14-26, 27-39, 40-52, 53-65, 66-78, 79-91, 92-104, 105-117, 118-130, 131-143, 144-156, 157-169, 170-182, 183-195, 196-208, 209-221, 222-234, 235-247, and 248-260)

End point values	Perampanel (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	1217			
Units: Percent responders				
number (not applicable)				
Weeks 1-13	30.8			
Weeks 14-26; N=1159	40.9			
Weeks 27-39; N=1088	44.2			
Weeks 40-52; N=969	45.6			
Weeks 53-65; N=882	49.5			
Weeks 66-78; N=822	51.5			
Weeks 79-91; N=762	52.9			
Weeks 92-104; N=720	57.2			

Weeks 105-117; N=676	57.1			
Weeks 118-130; N=642	58.9			
Weeks 131-143; N=583	59.3			
Weeks 144-156; N=517	60.9			
Weeks 157-169; N=429	63.2			
Weeks 170-182; N=323	60.1			
Weeks 183-195; N=210	62.9			
Weeks 196-208; N=119	64.7			
Weeks 209-221; N=59	67.8			
Weeks 222-234; N=37	73			
Weeks 235-247; N=14	64.3			
Weeks 248-260; N=5	80			

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 5 years

Adverse event reporting additional description:

Tha analysis was performed using the Safety Analysis Set (SAS), defined as subjects who provided informed consent for the OLE study, received at least 1 dose of perampanel in the OLE study, and had at least 1 postdose safety assessment in the OLE study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Arm 1

Reporting group description: -

Serious adverse events	Arm 1		
Total subjects affected by serious adverse events			
subjects affected / exposed	288 / 1216 (23.68%)		
number of deaths (all causes)	11		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Benign lung neoplasm			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer metastatic			

subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endometrial adenocarcinoma				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Glioma				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Papillary thyroid cancer				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tumour pain				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Uterine leiomyoma				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypertension				
subjects affected / exposed	2 / 1216 (0.16%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Aortic aneurysm				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				

subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	6 / 1216 (0.49%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Medical device removal			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Abortion spontaneous incomplete			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Gait disturbance			
subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pain			

subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cyst			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Drug ineffective			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperthermia			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			

subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sudden death				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Reproductive system and breast disorders				
Dysfunctional uterine bleeding				
subjects affected / exposed	2 / 1216 (0.16%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bartholinitis				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Breast enlargement				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic ovarian cyst				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Menstrual disorder				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ovarian cyst				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ovarian mass				

subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ovarian rupture				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Polycystic ovaries				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Uterine cyst				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Uterine haemorrhage				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Uterine polyp				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	3 / 1216 (0.25%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	2 / 1216 (0.16%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Acute respiratory failure				

subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Nasal septum deviation				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Psychiatric disorders				
Aggression				
subjects affected / exposed	14 / 1216 (1.15%)			
occurrences causally related to treatment / all	12 / 15			
deaths causally related to treatment / all	0 / 0			
Psychotic disorder				
subjects affected / exposed	8 / 1216 (0.66%)			
occurrences causally related to treatment / all	6 / 8			
deaths causally related to treatment / all	0 / 0			
Suicidal ideation				
subjects affected / exposed	6 / 1216 (0.49%)			
occurrences causally related to treatment / all	6 / 6			
deaths causally related to treatment / all	0 / 0			
Affective disorder				

subjects affected / exposed	5 / 1216 (0.41%)			
occurrences causally related to treatment / all	4 / 5			
deaths causally related to treatment / all	0 / 0			
Depression				
subjects affected / exposed	5 / 1216 (0.41%)			
occurrences causally related to treatment / all	3 / 6			
deaths causally related to treatment / all	0 / 0			
Acute psychosis				
subjects affected / exposed	4 / 1216 (0.33%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Suicide attempt				
subjects affected / exposed	4 / 1216 (0.33%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Disorientation				
subjects affected / exposed	3 / 1216 (0.25%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Paranoia				
subjects affected / exposed	3 / 1216 (0.25%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Abnormal behavior				
subjects affected / exposed	2 / 1216 (0.16%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Agitation				
subjects affected / exposed	2 / 1216 (0.16%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Adjustment disorder				

subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anger			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 0		
Catatonia			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Delirium			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Delusion			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Delusion of grandeur			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epileptic psychosis			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hallucination, auditory			

subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Homicidal ideation			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Insomnia			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Irritability			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Major depression			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mental disorder due to a general medical condition			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Mental status changes			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Mood altered			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Negativism			

subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Obsessive thoughts				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Personality change due to a general medical condition				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Postictal psychosis				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Clostridium test positive				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Heart rate irregular				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Weight decreased				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Head injury				
subjects affected / exposed	12 / 1216 (0.99%)			
occurrences causally related to treatment / all	0 / 12			
deaths causally related to treatment / all	0 / 1			

Ankle fracture			
subjects affected / exposed	7 / 1216 (0.58%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	5 / 1216 (0.41%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	5 / 1216 (0.41%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 1		
Toxicity to various agents			
subjects affected / exposed	5 / 1216 (0.41%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Contusion			
subjects affected / exposed	4 / 1216 (0.33%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Facial bones fracture			
subjects affected / exposed	4 / 1216 (0.33%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Craniocerebral injury			
subjects affected / exposed	3 / 1216 (0.25%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Foot fracture			
subjects affected / exposed	3 / 1216 (0.25%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Lumbar vertebral fracture			

subjects affected / exposed	3 / 1216 (0.25%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Accidental overdose			
subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Brain contusion			
subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Clavicle fracture			
subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Extradural haematoma			
subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Fibula fracture			
subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hand fracture			
subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Jaw fracture			

subjects affected / exposed	2 / 1216 (0.16%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Laceration				
subjects affected / exposed	2 / 1216 (0.16%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	2 / 1216 (0.16%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	2 / 1216 (0.16%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	2 / 1216 (0.16%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	2 / 1216 (0.16%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Traumatic intracranial haemorrhage				
subjects affected / exposed	2 / 1216 (0.16%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Abdominal injury				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Animal bite				

subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Burns second degree			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Burns third degree			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cartilage injury			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cervical vertebral fracture			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Concussion			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Epidural haemorrhage			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Excoriation			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Forearm fracture			

subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal stoma complication			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intentional overdose			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Joint dislocation			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Limb injury			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Limb traumatic amputation			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscle strain			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neck injury			

subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post concussion syndrome			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural intestinal perforation			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin laceration			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skull fracture			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skull fractured base			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Subcutaneous haematoma			

subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subdural haemorrhage				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Traumatic iritis				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				
Hypertrophic cardiomyopathy				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skull malformation				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute coronary syndrome				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	3 / 1216 (0.25%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			

Angina unstable			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	3 / 1216 (0.25%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Atrioventricular dissociation			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiovascular insufficiency			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery stenosis			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mitral valve incompetence			

subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sick sinus syndrome				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Convulsion				
subjects affected / exposed	43 / 1216 (3.54%)			
occurrences causally related to treatment / all	15 / 49			
deaths causally related to treatment / all	1 / 2			
Status epilepticus				
subjects affected / exposed	16 / 1216 (1.32%)			
occurrences causally related to treatment / all	6 / 17			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	15 / 1216 (1.23%)			
occurrences causally related to treatment / all	2 / 19			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	6 / 1216 (0.49%)			
occurrences causally related to treatment / all	3 / 6			
deaths causally related to treatment / all	0 / 0			
Grand mal convulsion				
subjects affected / exposed	6 / 1216 (0.49%)			
occurrences causally related to treatment / all	3 / 7			
deaths causally related to treatment / all	0 / 0			
Seizure cluster				

subjects affected / exposed	6 / 1216 (0.49%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Ataxia			
subjects affected / exposed	3 / 1216 (0.25%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Partial seizures			
subjects affected / exposed	3 / 1216 (0.25%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Partial seizures with secondary generalisation			
subjects affected / exposed	3 / 1216 (0.25%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Cerebral haemorrhage			
subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Cerebrovascular accident			
subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Drug withdrawal convulsions			
subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dysarthria			
subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hemiparesis			

subjects affected / exposed	2 / 1216 (0.16%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hypoaesthesia				
subjects affected / exposed	2 / 1216 (0.16%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Somnolence				
subjects affected / exposed	2 / 1216 (0.16%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	2 / 1216 (0.16%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Carotid artery dissection				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Carpal tunnel syndrome				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Central nervous system lesion				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cognitive disorder				

subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Coma				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Complex partial seizures				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dementia Alzheimer's type				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Incoherent				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Memory impairment				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multifocal motor neuropathy				

subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral sensorimotor neuropathy				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Postictal paralysis				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychomotor hyperactivity				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Simple partial seizures				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Speech disorder				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal cord compression				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stupor				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Subarachnoid haemorrhage				

subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Temporal lobe epilepsy			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tremor			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vertebral artery dissection			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Conductive deafness			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			

Conjunctivitis allergic				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Iritis				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Visual impairment				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Gastritis				
subjects affected / exposed	3 / 1216 (0.25%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	3 / 1216 (0.25%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis ischaemic				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis microscopic				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer				

subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenitis			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enterocolitis			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			

subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	4 / 1216 (0.33%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rash maculo-papular			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Goitre			

subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	5 / 1216 (0.41%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bursitis			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Periarthritis			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pseudarthrosis			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Scoliosis			

subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Soft tissue necrosis				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pneumonia				
subjects affected / exposed	13 / 1216 (1.07%)			
occurrences causally related to treatment / all	0 / 15			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	6 / 1216 (0.49%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	5 / 1216 (0.41%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	2 / 1216 (0.16%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Postoperative wound infection				
subjects affected / exposed	2 / 1216 (0.16%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Tooth abscess				
subjects affected / exposed	2 / 1216 (0.16%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Wound infection staphylococcal				

subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Abscess limb			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis perforated			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacterial disease carrier			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Klebsiella infection			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meningitis			

subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oral infection			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pharyngitis			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural pneumonia			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal cyst infection			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			

subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tuberculosis				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Typhoid fever				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound infection				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hyponatraemia				
subjects affected / exposed	3 / 1216 (0.25%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diabetic ketoacidosis				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypernatraemia				
subjects affected / exposed	1 / 1216 (0.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypochloraemia				

subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypovolaemia			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Arm 1		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1018 / 1216 (83.72%)		
Investigations			
Weight increased			
subjects affected / exposed	161 / 1216 (13.24%)		
occurrences (all)	204		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	116 / 1216 (9.54%)		
occurrences (all)	246		
Laceration			
subjects affected / exposed	67 / 1216 (5.51%)		
occurrences (all)	120		
Nervous system disorders			
Dizziness			
subjects affected / exposed	591 / 1216 (48.60%)		
occurrences (all)	1401		
Ataxia			
subjects affected / exposed	84 / 1216 (6.91%)		
occurrences (all)	136		
Balance disorder			
subjects affected / exposed	74 / 1216 (6.09%)		
occurrences (all)	129		
Convulsion			

subjects affected / exposed	78 / 1216 (6.41%)		
occurrences (all)	126		
Dysarthria			
subjects affected / exposed	61 / 1216 (5.02%)		
occurrences (all)	84		
Headache			
subjects affected / exposed	246 / 1216 (20.23%)		
occurrences (all)	506		
Somnolence			
subjects affected / exposed	266 / 1216 (21.88%)		
occurrences (all)	449		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	182 / 1216 (14.97%)		
occurrences (all)	281		
Gait disturbance			
subjects affected / exposed	80 / 1216 (6.58%)		
occurrences (all)	127		
Irritability_			
subjects affected / exposed	69 / 1216 (5.67%)		
occurrences (all)	85		
Pyrexia			
subjects affected / exposed	79 / 1216 (6.50%)		
occurrences (all)	135		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	78 / 1216 (6.41%)		
occurrences (all)	147		
Eye disorders			
Diplopia			
subjects affected / exposed	64 / 1216 (5.26%)		
occurrences (all)	92		
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	84 / 1216 (6.91%)		
occurrences (all)	121		
Nausea			
subjects affected / exposed	115 / 1216 (9.46%)		
occurrences (all)	154		
Vomiting			
subjects affected / exposed	95 / 1216 (7.81%)		
occurrences (all)	119		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	79 / 1216 (6.50%)		
occurrences (all)	101		
Depression			
subjects affected / exposed	82 / 1216 (6.74%)		
occurrences (all)	102		
Insomnia			
subjects affected / exposed	86 / 1216 (7.07%)		
occurrences (all)	124		
Irritability			
subjects affected / exposed	125 / 1216 (10.28%)		
occurrences (all)	166		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	86 / 1216 (7.07%)		
occurrences (all)	111		
Infections and infestations			
Influenza			
subjects affected / exposed	70 / 1216 (5.76%)		
occurrences (all)	100		
Nasopharyngitis			
subjects affected / exposed	142 / 1216 (11.68%)		
occurrences (all)	239		
Upper respiratory tract infection			
subjects affected / exposed	107 / 1216 (8.80%)		
occurrences (all)	188		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 October 2008	Amendment 01 – 17 Oct 2008 • Increased the study duration (from 14 months to 26 months) to obtain additional on-drug and off-drug safety information in subjects with longer durations of perampanel exposure. • Removed the 2-week titration designation to allow greater flexibility, thereby accommodating individual subject tolerability. • Clarified that felbamate is allowed as a concomitant medication to maintain consistency with the preceding double-blind studies. • Made minor editorial, grammatical, consistency, and formatting corrections. Note: this list is not exhaustive.
26 November 2008	Amendment A-Germany: 26 Nov 2008 • Administrative changes such as to update with the name of the current Study Director. • Added precausions to be followed while on the study drug, • Addressed the exclusion of subjects who cannot consent to participate in the study as per local regulations. • Defined the conditions under which the study may be terminated: The program is intended to continue until the investigational drug is licensed in Germany, or until it is terminated. At present, there are no other foreseeable reasons for termination of the study. However, the study could be terminated due to safety concerns or for other reasons. Note: this list is not exhaustive.
05 December 2008	Amendment B-Lithuania: 05 December 2008 • Administrative changes such as to update with the name of the current Study Director. • Corrected the hyperlink reference, etc. • Revise the inclusion criteria, concomitant therapy, etc. Note: this list is not exhaustive.
12 January 2009	Amendment C – Germany: 12 January 2009 • Increase the study duration. • Removed the 2-week titration designation. • Clarify that felbamate is allowed as a concomitant medication. • Made editorial, grammatical, consistency, and formatting corrections. • Administrative changes such as to update with the name of the current Study Director, etc. • Added precausions to be followed while on the study drug. • Addressed the exclusion of subjects who cannot consent to participate in the study as per local regulations. Note: this list is not exhaustive.
17 February 2009	Amendment D-Republic of South Africa: 17 February 2009 • Revised the version of the Declaration of Helsinki from the 1996 version to the latest 2008 version as per the request of the South African Medical Association Research Ethics Committee (SAMAREC).

20 March 2009	Amendment 02: 20 March 2009 • The exploratory objective was added to evaluate the potential withdrawal symptoms of perampanel vs. placebo in subjects with refractory partial seizures. • Update the protocol with information regarding an additional safety questionnaire on study drug withdrawal symptoms. • Administrative changes such as sponsor company's registered office address change, etc. • Correction of typographical errors. • Define database lock as end of study. • Clarified the treatment for subjects rolling over into the OLE study. • Concomitant medication section was revised. Changes in concomitant therapy are allowed (ie, they are not considered deviations); therefore, no discussion regarding changes are needed. • Amended text surrounding how subjects should handle light related skin changes that occur during the study. • Defined Bazett as the QT interval correction method to be reported by the central lab. • Included information about safety monitoring via the Data Monitoring Committee. Note: this list is not exhaustive.
28 September 2009	Amendment 03: 28 September 2009, v1.0 • Update the protocol with the Sponsor’s new legal name and address. • Included objectives related to the addition of adolescent-specific growth and development assessments (pharmacokinetic samples, height, thyroid and IGF-1 testing, and Tanner Staging) and PK/PD analysis. • Removed inconsistency, as subjects will not receive placebo in this study. • Extended the study duration for a total duration of approximately 5 years, until the marketing of perampanel, or until perampanel development is terminated. • Treatment administered section was revised as gaps between the core study and OLE are no longer allowed. • Administrative changes such as update in sponsor address, study director, clarifications, etc. Note: this list is not exhaustive.
24 June 2010	Amendment E (United Kingdom [UK] and India): 24 Jun 2010, v2.0 • Updated the protocol with the Sponsor’s new legal name and address, updated references, etc. • Included objectives related to the addition of adolescent-specific growth and development assessments (pharmacokinetic samples, height, thyroid and IGF-1 testing, and Tanner Staging). • Removed inconsistency, as subjects will not receive placebo in this study. • Corrected an inconsistency in the presentation of the number of weeks in the Conversion Period. • Extend the study duration for a total duration of approximately 5 years. • Update the protocol for consistency with the extension of the study duration. • Added analysis of additional adolescent-specific safety, PK and PK/PD analysis. • Treatment administered section was revised as gaps between the core study and OLE are no longer allowed. Note: this list is not exhaustive.

27 June 2012	Amendment F: 27 June 2012 • Closure of Study Protocol: 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 and regions. Positive Opinion has been received from CHMP. Therefore, Study E2007 G000 307 will be closed • Revision to Schedule Regarding the EOT Visit: To accommodate the implementation of this protocol amendment resulting in the closure of the study protocol • Revision to Follow-up visit Procedures To provide subjects the option to continue accessing perampanel treatment if they are benefiting from the study drug • Revision to Questionnaire Procedures: These questionnaires are no longer deemed necessary for subjects who will continue to receive perampanel therapy after the conclusion of the study • Revision to Monitoring Schedule: To accurately reflect the current interim monitoring visit schedule

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
02 January 2012	The sponsor terminated the study in 2012 following receipt of a positive opinion for perampanel from the Committee for Medicinal Products for Human Use. An end-of-treatment (EOT) visit was scheduled within 2 to 6 weeks for all subjects who remained in the Maintenance Period. If it was the opinion of the treating physician that a subject would benefit significantly from further treatment with perampanel after the trial concluded, perampanel treatment was made available under Eisai's compassionate use policy in accordance with local country legislative provisions until the time that perampanel was commercially available in the country in which the subject resided.	-

Notes:

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: