

**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
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**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
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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
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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
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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)
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Subject analysis set type	Intention-to-treat
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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)
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Subject analysis set type	Safety analysis
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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) <sup>[1]</sup>
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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
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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
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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
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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
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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
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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

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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:

The 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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	13.1
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### Reporting groups

Reporting group title	Arm 1
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Reporting group description: -

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

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

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

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

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

subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Obsessive thoughts</b>			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Personality change due to a general medical condition</b>			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Postictal psychosis</b>			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Investigations</b>			
<b>Clostridium test positive</b>			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Heart rate irregular</b>			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Weight decreased</b>			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Injury, poisoning and procedural complications</b>			
<b>Head injury</b>			
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		
<b>Laceration</b>			
subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Lower limb fracture</b>			
subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Rib fracture</b>			
subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Subdural haematoma</b>			
subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Tibia fracture</b>			
subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Traumatic intracranial haemorrhage</b>			
subjects affected / exposed	2 / 1216 (0.16%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Abdominal injury</b>			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Animal bite</b>			

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

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

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		
<b>Subdural haemorrhage</b>			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
<b>Traumatic iritis</b>			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Wound</b>			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Congenital, familial and genetic disorders</b>			
<b>Hypertrophic cardiomyopathy</b>			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Skull malformation</b>			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Cardiac disorders</b>			
<b>Acute coronary syndrome</b>			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Angina pectoris</b>			
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		
<b>Myocardial infarction</b>			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Sick sinus syndrome</b>			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Nervous system disorders</b>			
<b>Convulsion</b>			
subjects affected / exposed	43 / 1216 (3.54%)		
occurrences causally related to treatment / all	15 / 49		
deaths causally related to treatment / all	1 / 2		
<b>Status epilepticus</b>			
subjects affected / exposed	16 / 1216 (1.32%)		
occurrences causally related to treatment / all	6 / 17		
deaths causally related to treatment / all	0 / 0		
<b>Epilepsy</b>			
subjects affected / exposed	15 / 1216 (1.23%)		
occurrences causally related to treatment / all	2 / 19		
deaths causally related to treatment / all	0 / 0		
<b>Dizziness</b>			
subjects affected / exposed	6 / 1216 (0.49%)		
occurrences causally related to treatment / all	3 / 6		
deaths causally related to treatment / all	0 / 0		
<b>Grand mal convulsion</b>			
subjects affected / exposed	6 / 1216 (0.49%)		
occurrences causally related to treatment / all	3 / 7		
deaths causally related to treatment / all	0 / 0		
<b>Seizure cluster</b>			

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

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

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

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		
<b>Blood and lymphatic system disorders</b>			
Anaemia			
subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Ear and labyrinth disorders</b>			
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		
<b>Eye disorders</b>			

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

subjects affected / exposed	1 / 1216 (0.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Hepatobiliary disorders</b>			
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		
<b>Skin and subcutaneous tissue disorders</b>			
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		
<b>Renal and urinary disorders</b>			
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		
<b>Endocrine disorders</b>			
Goitre			

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

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

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

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		
<b>Hypovolaemia</b>			
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 %

<b>Non-serious adverse events</b>	Arm 1		
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	1018 / 1216 (83.72%)		
<b>Investigations</b>			
Weight increased			
subjects affected / exposed	161 / 1216 (13.24%)		
occurrences (all)	204		
<b>Injury, poisoning and procedural complications</b>			
Fall			
subjects affected / exposed	116 / 1216 (9.54%)		
occurrences (all)	246		
Laceration			
subjects affected / exposed	67 / 1216 (5.51%)		
occurrences (all)	120		
<b>Nervous system disorders</b>			
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 occurrences (all)	78 / 1216 (6.41%) 126		
Dysarthria subjects affected / exposed occurrences (all)	61 / 1216 (5.02%) 84		
Headache subjects affected / exposed occurrences (all)	246 / 1216 (20.23%) 506		
Somnolence subjects affected / exposed occurrences (all)	266 / 1216 (21.88%) 449		
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	182 / 1216 (14.97%) 281		
Gait disturbance subjects affected / exposed occurrences (all)	80 / 1216 (6.58%) 127		
Irritability_ subjects affected / exposed occurrences (all)	69 / 1216 (5.67%) 85		
Pyrexia subjects affected / exposed occurrences (all)	79 / 1216 (6.50%) 135		
Ear and labyrinth disorders			
Vertigo subjects affected / exposed occurrences (all)	78 / 1216 (6.41%) 147		
Eye disorders			
Diplopia subjects affected / exposed occurrences (all)	64 / 1216 (5.26%) 92		
Gastrointestinal disorders			
Diarrhoea			

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



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 October 2008	<p>Amendment 01 – 17 Oct 2008</p> <ul style="list-style-type: none"><li>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.</li><li>Removed the 2-week titration designation to allow greater flexibility, thereby accommodating individual subject tolerability.</li><li>Clarified that felbamate is allowed as a concomitant medication to maintain consistency with the preceding double-blind studies.</li><li>Made minor editorial, grammatical, consistency, and formatting corrections.</li></ul> <p>Note: this list is not exhaustive.</p>
26 November 2008	<p>Amendment A-Germany: 26 Nov 2008</p> <ul style="list-style-type: none"><li>Administrative changes such as to update with the name of the current Study Director.</li><li>Added precautions to be followed while on the study drug,</li><li>Addressed the exclusion of subjects who cannot consent to participate in the study as per local regulations.</li><li>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.</li></ul> <p>Note: this list is not exhaustive.</p>
05 December 2008	<p>Amendment B-Lithuania: 05 December 2008</p> <ul style="list-style-type: none"><li>Administrative changes such as to update with the name of the current Study Director.</li><li>Corrected the hyperlink reference, etc.</li><li>Revise the inclusion criteria, concomitant therapy, etc.</li></ul> <p>Note: this list is not exhaustive.</p>
12 January 2009	<p>Amendment C – Germany: 12 January 2009</p> <ul style="list-style-type: none"><li>Increase the study duration.</li><li>Removed the 2-week titration designation.</li><li>Clarify that felbamate is allowed as a concomitant medication.</li><li>Made editorial, grammatical, consistency, and formatting corrections.</li><li>Administrative changes such as to update with the name of the current Study Director, etc.</li><li>Added precautions to be followed while on the study drug.</li><li>Addressed the exclusion of subjects who cannot consent to participate in the study as per local regulations.</li></ul> <p>Note: this list is not exhaustive.</p>
17 February 2009	<p>Amendment D-Republic of South Africa: 17 February 2009</p> <ul style="list-style-type: none"><li>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).</li></ul>

20 March 2009	<p>Amendment 02: 20 March 2009</p> <ul style="list-style-type: none"> <li>• The exploratory objective was added to evaluate the potential withdrawal symptoms of perampanel vs. placebo in subjects with refractory partial seizures.</li> <li>• Update the protocol with information regarding an additional safety questionnaire on study drug withdrawal symptoms.</li> <li>• Administrative changes such as sponsor company's registered office address change, etc.</li> <li>• Correction of typographical errors.</li> <li>• Define database lock as end of study.</li> <li>• Clarified the treatment for subjects rolling over into the OLE study.</li> <li>• Concomitant medication section was revised. Changes in concomitant therapy are allowed (ie, they are not considered deviations); therefore, no discussion regarding changes are needed.</li> <li>• Amended text surrounding how subjects should handle light related skin changes that occur during the study.</li> <li>• Defined Bazett as the QT interval correction method to be reported by the central lab.</li> <li>• Included information about safety monitoring via the Data Monitoring Committee.</li> </ul> <p>Note: this list is not exhaustive.</p>
28 September 2009	<p>Amendment 03: 28 September 2009, v1.0</p> <ul style="list-style-type: none"> <li>• Update the protocol with the Sponsor's new legal name and address.</li> <li>• 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.</li> <li>• Removed inconsistency, as subjects will not receive placebo in this study.</li> <li>• Extended the study duration for a total duration of approximately 5 years, until the marketing of perampanel, or until perampanel development is terminated.</li> <li>• Treatment administered section was revised as gaps between the core study and OLE are no longer allowed.</li> <li>• Administrative changes such as update in sponsor address, study director, clarifications, etc.</li> </ul> <p>Note: this list is not exhaustive.</p>
24 June 2010	<p>Amendment E (United Kingdom [UK] and India): 24 Jun 2010, v2.0</p> <ul style="list-style-type: none"> <li>• Updated the protocol with the Sponsor's new legal name and address, updated references, etc.</li> <li>• Included objectives related to the addition of adolescent-specific growth and development assessments (pharmacokinetic samples, height, thyroid and IGF-1 testing, and Tanner Staging).</li> <li>• Removed inconsistency, as subjects will not receive placebo in this study.</li> <li>• Corrected an inconsistency in the presentation of the number of weeks in the Conversion Period.</li> <li>• Extend the study duration for a total duration of approximately 5 years.</li> <li>• Update the protocol for consistency with the extension of the study duration.</li> <li>• Added analysis of additional adolescent-specific safety, PK and PK/PD analysis.</li> <li>• Treatment administered section was revised as gaps between the core study and OLE are no longer allowed.</li> </ul> <p>Note: this list is not exhaustive.</p>

27 June 2012	<p>Amendment F: 27 June 2012</p> <ul style="list-style-type: none"> <li>• 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</li> <li>• Revision to Schedule Regarding the EOT Visit: To accommodate the implementation of this protocol amendment resulting in the closure of the study protocol</li> <li>• Revision to Follow-up visit Procedures To provide subjects the option to continue accessing perampanel treatment if they are benefiting from the study drug</li> <li>• 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</li> <li>• Revision to Monitoring Schedule: To accurately reflect the current interim monitoring visit schedule</li> </ul>
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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: