



## Clinical trial results:

**An open-label extension study following a double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy and safety of adjunctive zonisamide in paediatric partial onset seizures.**

### Summary

EudraCT number	2007-000198-53
Trial protocol	HU BE LV IT EE PL ES FR GB
Global end of trial date	08 March 2012

### Results information

Result version number	v1 (current)
This version publication date	27 July 2016
First version publication date	27 July 2016

### Trial information

#### Trial identification

Sponsor protocol code	E2090-E044-313
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01136954
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Eisai
Sponsor organisation address	100 Tice Boulevard, Woodcliff Lake, United States, 07677
Public contact	Eisai Call Center, Eisai Inc., 888 422-4743,
Scientific contact	Eisai Call Center, Eisai Inc., 888 422-4743,

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 March 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 February 2012
Global end of trial reached?	Yes
Global end of trial date	08 March 2012
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To assess the long-term safety of zonisamide used as an adjunctive treatment in paediatric subjects treated with one or two other anti-epileptic drugs (AEDs).

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 Council 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 Technical Requirements for Registration 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.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP Subject Information and Informed Consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 July 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Estonia: 2
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Hungary: 33
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Latvia: 18
Country: Number of subjects enrolled	Ukraine: 66

Worldwide total number of subjects	144
EEA total number of subjects	78

Notes:

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**Subjects enrolled per age group**

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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)	67
Adolescents (12-17 years)	77
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

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## Subject disposition

### Recruitment

Recruitment details:

Participants who completed E2090-E044-312 (NCT00566254)"Study 312" core study were invited to participate in this extension study.

### Pre-assignment

Screening details:

Of the 183 participants who completed Study 312 and were eligible to enter into this study, E2090-E044-313 (Study 313), 144 participants entered into Study 313.

### Period 1

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

Blinding implementation details:

To preserve the blind for Study 312, participants entering into Study 313 started with a double-blind Transition Period during which participants already on zonisamide continued on the same dose of zonisamide for their weight, and those who were taking placebo during Study 312 were up-titrated to an appropriate dose of zonisamide. At the end of the Transition Period, participants entered the Open-label Period, in which all participants took zonisamide at a known dose level.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Zonisamide (placebo during core study)

Arm description:

Participants previously receiving placebo in Study 312, started dosing with zonisamide with a dose of 1 mg/kg/day and titrated upwards with weekly dose increases until a dose of 8 mg/kg/day was reached at the end of the Transition Period (weeks 2 -11). Down-titration was allowed between the limits of 1 to 8 mg/kg/day during the Open-label Period. Subsequently, a 45-57 week Open-label period followed. Placebo dosing ceased in Open-label Period. In the event of dose-limiting adverse events during the Transition Period, the dose of both placebo and zonisamide could be down-titrated to one level above the minimal dose.

Arm type	Experimental
Investigational medicinal product name	Zonisamide
Investigational medicinal product code	
Other name	Zonegran, E2090
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Titration Period: Participants were started on oral zonisamide at approximately 1 mg/kg/day. The total daily dose of zonisamide was gradually increased until it equaled the maintenance dose of placebo they had been receiving at the end of Study 312. When this point was reached, the participant stopped taking placebo. Open-label Period: All participants took zonisamide at a known dose level. Participants could be down-titrated, if necessary, and as often as needed until the minimum dose at each level was reached. Participants who down-titrated could be re up-titrated, if required, to control seizures: this could be repeated until the maximum dose in that weight group was reached. At the end of the Open-label Period, participants either down-titrated or continued taking zonisamide under Eisai's Compassionate Use policy; participants who down-titrated were permitted to up-titrate a replacement AED at the same time.

<b>Arm title</b>	Zonisamide (zonisamide during core study)
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Arm description:

Participants previously receiving zonisamide in Study 312 continued taking the same dose of study drug (8 mg/kg/day),supplemented with an increasing number of placebo capsules to mirror the up-titration regimen being followed by those previously receiving placebo.Down-titration was allowed between the limits of 1 to 8 mg/kg/day during Transition Period. Subsequently, a 45-57 week Open-label period

followed. In the event of dose-limiting adverse events during the Transition Period, the dose of both placebo and zonisamide could be down-titrated to one level above the minimal dose.

Arm type	Experimental
Investigational medicinal product name	Zonisamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

**Titration Period:** Participants continued on oral zonisamide at the dose they received in Study 312, supplemented with an increasing number of placebo capsules, thereby mirroring the up-titration regimen being followed by those participants previously randomized to placebo in Study 312. **Open-label Period:** All participants took zonisamide at a known dose level. Participants could be down-titrated, if necessary, and as often as needed until the minimum dose at each level was reached. Participants who down-titrated could be re up-titrated, if required, to control seizures: this could be repeated until the maximum dose in that weight group was reached. At the end of the Open-label Period, participants either down-titrated or continued taking zonisamide under Eisai's Compassionate Use policy; participants who down-titrated were permitted to up-titrate a replacement AED at the same time.

Number of subjects in period 1	Zonisamide (placebo during core study)	Zonisamide (zonisamide during core study)
Started	72	72
Completed	48	51
Not completed	24	21
Consent withdrawn by subject	6	2
Physician decision	-	1
Adverse event, non-fatal	3	2
Not specified	1	3
Lack of efficacy	14	13

## Baseline characteristics

### Reporting groups

Reporting group title	Zonisamide (placebo during core study)
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#### Reporting group description:

Participants previously receiving placebo in Study 312, started dosing with zonisamide with a dose of 1 mg/kg/day and titrated upwards with weekly dose increases until a dose of 8 mg/kg/day was reached at the end of the Transition Period (weeks 2 -11). Down-titration was allowed between the limits of 1 to 8 mg/kg/day during the Open-label Period. Subsequently, a 45-57 week Open-label period followed. Placebo dosing ceased in Open-label Period. In the event of dose-limiting adverse events during the Transition Period, the dose of both placebo and zonisamide could be down-titrated to one level above the minimal dose.

Reporting group title	Zonisamide (zonisamide during core study)
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#### Reporting group description:

Participants previously receiving zonisamide in Study 312 continued taking the same dose of study drug (8 mg/kg/day), supplemented with an increasing number of placebo capsules to mirror the up-titration regimen being followed by those previously receiving placebo. Down-titration was allowed between the limits of 1 to 8 mg/kg/day during Transition Period. Subsequently, a 45-57 week Open-label period followed. In the event of dose-limiting adverse events during the Transition Period, the dose of both placebo and zonisamide could be down-titrated to one level above the minimal dose.

Reporting group values	Zonisamide (placebo during core study)	Zonisamide (zonisamide during core study)	Total
Number of subjects	72	72	144
Age categorical			
Units: Subjects			
6 - 11 Years	34	33	67
12 - 18 Years	38	39	77
Gender categorical			
Units: Subjects			
Female	32	41	73
Male	40	31	71

## End points

### End points reporting groups

Reporting group title	Zonisamide (placebo during core study)
Reporting group description: Participants previously receiving placebo in Study 312, started dosing with zonisamide with a dose of 1 mg/kg/day and titrated upwards with weekly dose increases until a dose of 8 mg/kg/day was reached at the end of the Transition Period (weeks 2 -11). Down-titration was allowed between the limits of 1 to 8 mg/kg/day during the Open-label Period. Subsequently, a 45-57 week Open-label period followed. Placebo dosing ceased in Open-label Period. In the event of dose-limiting adverse events during the Transition Period, the dose of both placebo and zonisamide could be down-titrated to one level above the minimal dose.	
Reporting group title	Zonisamide (zonisamide during core study)
Reporting group description: Participants previously receiving zonisamide in Study 312 continued taking the same dose of study drug (8 mg/kg/day), supplemented with an increasing number of placebo capsules to mirror the up-titration regimen being followed by those previously receiving placebo. Down-titration was allowed between the limits of 1 to 8 mg/kg/day during Transition Period. Subsequently, a 45-57 week Open-label period followed. In the event of dose-limiting adverse events during the Transition Period, the dose of both placebo and zonisamide could be down-titrated to one level above the minimal dose.	

### Primary: Treatment Emergent Non-Serious Adverse Events with greater than 5% Frequency

End point title	Treatment Emergent Non-Serious Adverse Events with greater than 5% Frequency <sup>[1]</sup>
End point description: Treatment Emergent Adverse Event (TEAE) is defined as an Adverse Event with a start date on or after Day 1 and within 15 days of last dose. For each event, each participant experiencing an event is only counted once even if they had multiple episodes.	
End point type	Primary
End point timeframe: Week 1 through Week 59	

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: Statistical analyses are not available for this data.

End point values	Zonisamide (placebo during core study)	Zonisamide (zonisamide during core study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72 <sup>[2]</sup>	72 <sup>[3]</sup>		
Units: Participants				
number (not applicable)				
Nasopharyngitis	6	9		
Bronchitis	4	3		
Respiratory tract infection	2	4		
Headache	4	7		
Weight decreased	6	6		
Abdominal pain	1	4		
Decreased appetite	5	4		

Notes:

[2] - Safety population-all participants who entered the study and received at least 1 dose of study drug

[3] - Safety population-all participants who entered the study and received at least 1 dose of study drug

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants with a Decrease from Baseline in 28-day Seizure

End point title	Percentage of Participants with a Decrease from Baseline in 28-day Seizure
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End point description:

A participant with a decrease from baseline in 28-day seizure frequency of greater than or equal to 50% was considered a responder. Participants' parent or guardian maintained a seizure diary recording the date, number, and type of seizures the subject had. The primary analysis assessed the percent of responders from Baseline in the Open Label Visit Period. Seizure frequency of simple partial, complex partial, and partial seizures with secondary generalization were assessed.

End point type	Secondary
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End point timeframe:

Baseline through Week 59

End point values	Zonisamide (placebo during core study)	Zonisamide (zonisamide during core study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72 <sup>[4]</sup>	72 <sup>[5]</sup>		
Units: Percentage of participants				
number (not applicable)	55.6	56.9		

Notes:

[4] - Safety population-all participants who entered the study and received at least 1 dose of study drug

[5] - Safety population-all participants who entered the study and received at least 1 dose of study drug

## Statistical analyses

No statistical analyses for this end point

### Secondary: Median Change from Study 312 Baseline in the 28-day Seizure Frequency

End point title	Median Change from Study 312 Baseline in the 28-day Seizure Frequency
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End point description:

Participants' parent or guardian maintained a seizure diary recording the date, number, and type of seizures the subject had. Seizure frequency of simple partial, complex partial, and partial seizures with secondary generalization were assessed from baseline of Study 312 through the Open Label Visit Period.

End point type	Secondary
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End point timeframe:

Baseline of Study 312 (Week -8 to Week 0) to Week 59 of Study 313

End point values	Zonisamide (placebo during core study)	Zonisamide (zonisamide during core study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72 <sup>[6]</sup>	72 <sup>[7]</sup>		
Units: Seizures				
median (full range (min-max))	-3.8 (-89 to 73)	-4.7 (-95 to 50)		

Notes:

[6] - Safety population-all participants who entered the study and received at least 1 dose of study drug

[7] - Safety population-all participants who entered the study and received at least 1 dose of study drug

### Statistical analyses

No statistical analyses for this end point

### Secondary: Median Percent Change from Study 312 Baseline in the 28-day Seizure Frequency during the Open Label Period

End point title	Median Percent Change from Study 312 Baseline in the 28-day Seizure Frequency during the Open Label Period
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End point description:

Participants' parent or guardian maintained a seizure diary recording the date, number, and type of seizures the subject had. Seizure frequency of simple partial, complex partial, and partial seizures with secondary generalization were assessed from baseline of Study 312 through the Open Label Visit Period. Percentage change = 100% x (seizure frequency at period - seizure frequency at Study 312 baseline)/seizure frequency at Study 312 baseline.

End point type	Secondary
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End point timeframe:

Baseline of Study 312 (Week -8 to Week 0) to Week 59 of Study 313

End point values	Zonisamide (placebo during core study)	Zonisamide (zonisamide during core study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72 <sup>[8]</sup>	72 <sup>[9]</sup>		
Units: Percentage change				
median (full range (min-max))	-64.6 (-100 to 174)	-67.9 (-100 to 262)		

Notes:

[8] - Safety population-all participants who entered the study and received at least 1 dose of study drug

[9] - Safety population-all participants who entered the study and received at least 1 dose of study drug

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

"Treatment-Emergent Adverse Events (TEAE) were collected, and includes all Adverse Events (AE) with a start date on or after Day 1 and within 15 Days of last dose, including AEs with missing start dates. Participants were followed for up to 61 weeks.

Adverse event reporting additional description:

Treatment-emergent AEs were summarized by period (Transition, Open-label, Down-titration), treatment group, body system, and preferred term (PT).

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	11
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### Reporting groups

Reporting group title	Zonisamide (placebo during core study)
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Reporting group description:

Participants previously receiving placebo in Study 312, started dosing with zonisamide at a dose of 1 mg/kg/day and titrated upwards with weekly dose increases until a dose of 8 mg/kg/day was reached at the end of the Transition Period (weeks 2 -11). Down-titration was allowed between the limits of 1 to 8 mg/kg/day during the Open-label Period. Subsequently, a 45-57 week Open-label period followed. Placebo dosing ceased in Open-label Period. In the event of dose-limiting adverse events during the Transition Period, the dose of both placebo and zonisamide could be down-titrated to one level above the minimal dose.

Reporting group title	Zonisamide (zonisamide during core study)
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Reporting group description:

Participants previously receiving zonisamide in Study 312 continued taking the same dose of study drug (8 mg/kg/day), supplemented with an increasing number of placebo capsules to mirror the up-titration regimen being followed by those previously receiving placebo. Down-titration was allowed between the limits of 1 to 8 mg/kg/day during the Open-label Period. Subsequently, a 45-57 week Open-label period followed. In the event of dose-limiting adverse events during the Transition Period, the dose of both placebo and zonisamide could be down-titrated to one level above the minimal dose.

Serious adverse events	Zonisamide (placebo during core study)	Zonisamide (zonisamide during core study)	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 72 (4.17%)	7 / 72 (9.72%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Ventricular extrasystoles			

subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Partial seizures with secondary generalisation			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Foreign body aspiration			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph gland infection			

subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Zonisamide (placebo during core study)	Zonisamide (zonisamide during core study)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 72 (25.00%)	25 / 72 (34.72%)	
Investigations			
Weight decreased			
subjects affected / exposed	6 / 72 (8.33%)	6 / 72 (8.33%)	
occurrences (all)	6	6	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 72 (5.56%)	7 / 72 (9.72%)	
occurrences (all)	4	12	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 72 (1.39%)	4 / 72 (5.56%)	
occurrences (all)	1	4	
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all)	6 / 72 (8.33%) 8	9 / 72 (12.50%) 14	
Bronchitis subjects affected / exposed occurrences (all)	4 / 72 (5.56%) 4	3 / 72 (4.17%) 3	
Respiratory tract infection subjects affected / exposed occurrences (all)	2 / 72 (2.78%) 5	4 / 72 (5.56%) 5	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	5 / 72 (6.94%) 5	4 / 72 (5.56%) 4	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 March 2009	Additional safety text was included regarding management of rashes, monitoring subjects for signs of suicidal ideation, and monitoring/managing hyperchloremic, non-anion gap metabolic acidosis. This was due to a safety update of the SmPC.
28 April 2009	<ul style="list-style-type: none"><li>• A criterion was added to stipulate that if a female subject became pregnant she must be withdrawn from the study.</li><li>• Additional safety text was included regarding management of rashes, monitoring subjects for signs of suicidal ideation, and monitoring/managing hyperchloremic, non-anion gap metabolic acidosis. This was due to a safety update of the SmPC.</li></ul>
21 July 2009	<ul style="list-style-type: none"><li>• To harmonise pregnancy withdrawal criteria with other ongoing zonisamide studies a criterion was added stipulating that if a female subject became pregnant she must be withdrawn from the study.</li><li>• To ensure adequate blinding of the study, laboratory bicarbonate results were to remain blinded to investigators unless they were of potential clinical significance. Since zonisamide is a carbonic anhydrase inhibitor and can be associated with decreased bicarbonate levels, it may have been possible for investigators to determine which treatment a subject was receiving by reviewing their bicarbonate results.</li></ul>
19 March 2010	<ul style="list-style-type: none"><li>• The following changes were made (in accordance with changes made to the Study 312 protocol) as agreed with the EMA.<ul style="list-style-type: none"><li>- The duration of the Open-label Period was reduced from up to 72 weeks to 45 through 57 weeks and the total study duration was reduced from a maximum of 87 weeks to a maximum of 59 weeks.</li><li>- At the end of the study, subjects who wished to continue taking zonisamide could apply for the treatment in accordance with Eisai's compassionate use policy; subjects for whom the treatment was stopped were down-titrated.</li><li>- The number of subjects was reduced from 266 to 204.</li><li>- The frequency of use of rescue benzodiazepines which led to exclusion was amended to greater than once a week from one or more times a month.</li><li>- The exclusion criterion for concomitant use of felbamate was amended to within 3 months of Visit 1 from within 2 months of Visit 1.</li><li>- The frequency of visits and scheduled assessments/events in the double-blind Transition Period and the Open-label Period was reduced.</li><li>- The cognitive testing battery was modified to comprise only COWAT; it was to be assessed at Study Entry and the Final Visit/Early Termination Visit. Completion of the school performance letter was made optional.</li><li>- The vital signs assessment was no longer to be performed.</li><li>- Pregnancy status was to be established using a urine pregnancy test.</li><li>- For subjects who stopped treatment at the end of the study, the Follow-Up Visit after down-titration was removed and the assessments completed during the follow-up telephone call were amended.</li><li>- The definition of baseline, for the purposes of the efficacy parameters, and for the purposes of the safety parameters was clarified.</li><li>- Vital signs and cognitive testing data (other than COWAT data) were to be analyzed only for data collected prior to the implementation of Protocol Amendment 03. Medication compliance was to be summarized. Safety parameters were to be plotted as appropriate.</li></ul></li></ul>

19 March 2010	<p>Amendment 3 continued.</p> <ul style="list-style-type: none"> <li>• Blinding of bicarbonate results to investigators was only required at the Study Entry Visit (Visit 1) since in the Open-label Period all subjects took zonisamide.</li> <li>• The guidelines for monitoring/managing hyperchloremic, non-anion gap metabolic acidosis were modified to ensure consistency with the current version of the SmPC.</li> <li>• Additional exploratory analyses were to be conducted at the end of the study to compare subjects who entered the study pre- and post- Protocol Amendment 03, to explore whether the primary and secondary efficacy endpoints were affected by the increased limit on benzodiazepine use that was introduced in Protocol Amendment 03.</li> </ul>
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Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported