# Clinical trial results:
# A double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy and safety of adjunctive zonisamide in paediatric partial onset seizures.

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines

## Summary

| | |
|---|---|
| EudraCT number | 2006-002515-27 |
| Trial protocol | BE HU FR LV EE PL IT ES GB |
| Global end of trial date | 15 March 2011 |

**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-E044-312 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00566254 |
| 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 | 15 March 2011 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 March 2011 |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 March 2011 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To assess the efficacy of zonisamide in paediatric epilepsy subjects with partial onset seizures 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 | 27 December 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: 21 |
| Country: Number of subjects enrolled | Spain: 3 |
| Country: Number of subjects enrolled | United Kingdom: 3 |
| Country: Number of subjects enrolled | Belgium: 3 |
| Country: Number of subjects enrolled | Estonia: 2 |
| Country: Number of subjects enrolled | France: 3 |
| Country: Number of subjects enrolled | Hungary: 42 |
| Country: Number of subjects enrolled | Italy: 4 |
| Country: Number of subjects enrolled | Latvia: 21 |
| Country: Number of subjects enrolled | Ukraine: 70 |

| | |
|---|---|
| Country: Number of subjects enrolled | India: 35 |
| Worldwide total number of subjects | 207 |
| EEA total number of subjects | 102 |

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) | 110 |
| Adolescents (12-17 years) | 97 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Out of 242 participants screened, 35 participants were screen failures and 207 participants were randomized into the study. Reasons for screen failure included; protocol deviation (10), participant withdrew consent (8), lack of diary eligibility (7), and other-reason not specified (10).

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer |

Blinding implementation details:

All study medication was packaged and labeled so as to be indistinguishable between treatment groups. Zonisamide is a carbonic anhydrase inhibitor and may result in a decrease in bicarbonate in some participants. To maintain the blind, bicarbonate results from the lab were blinded from the investigator, but continued to be reviewed by an independent medical monitor for safety.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo |

Arm description:

Participants had a starting dose of 1 mg/kg/day of placebo matching zonisamide. Dose was titrated upwards with weekly dose increases until a dose of 8 mg/kg/day was reached at the end of the Titration Period (Week 8). Dose during the Maintenance Period remained unchanged from Week 8.

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Zonisamide-matching placebo capsule was taken orally once daily in the evening. The dose was titrated upwards from the 1 mg/kg/day starting dose, with weekly dose increases in increments of 1 mg/kg/day until a dose of 8 mg/kg/day was reached at the end of Week 8. No changes in dose were allowed during the Maintenance Period, after which, for participants not entering the extension study, the dose was down-titrated for 3 or 4 weeks. In the event of dose-limiting adverse events, during the Titration Period, one down-titration to a lower dose was permitted. For participants who undertook the single allowable down-titration during the Titration Period, the daily dose could be less than 8 mg/kg during the Maintenance Period. Participants who were withdrawn from the study early had their study medication down-titrated. The dose at Week 8 remained unchanged during the 12-Week Maintenance Period.

| | |
|---|---|
| **Arm title** | Zonisamide |

Arm description:

Participants had a starting dose of 1 mg/kg/day of Zonisamide. Dose was titrated upwards with weekly dose increases until a dose of 8 mg/kg/day was reached at the end of the Titration Period (Week 8). Dose during the Maintenance Period remained unchanged from Week 8.

| | |
|---|---|
| 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:

Zonisamide capsule was taken orally once daily in the evening. The dose was titrated upwards from the 1 mg/kg/day starting dose, with weekly dose increases in increments of 1 mg/kg/day until a dose of 8 mg/kg/day was reached at the end of Week 8. No changes in dose were allowed during the Maintenance Period, after which, for participants not entering the extension study, the dose was down-titrated for 3 or 4 weeks. In the event of dose-limiting adverse events, during the Titration Period, one down-titration to a lower dose was permitted. For participants who undertook the single allowable down-titration during the Titration Period, the daily dose could be less than 8 mg/kg during the Maintenance Period. Participants who were withdrawn from the study early had their study medication down-titrated. The dose at Week 8 remained unchanged during the 12-Week Maintenance Period.

| **Number of subjects in period 1** | Placebo | Zonisamide |
|---|---|---|
| Started | 100 | 107 |
| Completed | 90 | 93 |
| Not completed | 10 | 14 |
| Consent withdrawn by subject | 1 | 2 |
| Adverse event, non-fatal | 3 | 1 |
| Protocol violation | 1 | 3 |
| Not specified | - | 2 |
| Lack of efficacy | 5 | 6 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants had a starting dose of 1 mg/kg/day of placebo matching zonisamide. Dose was titrated upwards with weekly dose increases until a dose of 8 mg/kg/day was reached at the end of the Titration Period (Week 8). Dose during the Maintenance Period remained unchanged from Week 8. | |
| Reporting group title | Zonisamide |
| Reporting group description: | |
| Participants had a starting dose of 1 mg/kg/day of Zonisamide. Dose was titrated upwards with weekly dose increases until a dose of 8 mg/kg/day was reached at the end of the Titration Period (Week 8). Dose during the Maintenance Period remained unchanged from Week 8. | |

| Reporting group values | Placebo | Zonisamide | Total |
|---|---|---|---|
| Number of subjects | 100 | 107 | 207 |
| Age categorical<br>Units: Subjects | | | |
| 6 - 11 Years Old | 55 | 55 | 110 |
| 12 - 17 Years Old | 45 | 52 | 97 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 45 | 54 | 99 |
| Male | 55 | 53 | 108 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description:

Participants had a starting dose of 1 mg/kg/day of placebo matching zonisamide. Dose was titrated upwards with weekly dose increases until a dose of 8 mg/kg/day was reached at the end of the Titration Period (Week 8). Dose during the Maintenance Period remained unchanged from Week 8.

| | |
|---|---|
| Reporting group title | Zonisamide |

Reporting group description:

Participants had a starting dose of 1 mg/kg/day of Zonisamide. Dose was titrated upwards with weekly dose increases until a dose of 8 mg/kg/day was reached at the end of the Titration Period (Week 8). Dose during the Maintenance Period remained unchanged from Week 8.

### Primary: Percentage of Participants with a Decrease from Baseline in 28-day Seizure Frequency of greater than or equal to 50% (Responder) in the Maintenance Period (LOCF)

| | |
|---|---|
| End point title | Percentage of Participants with a Decrease from Baseline in 28-day Seizure Frequency of greater than or equal to 50% (Responder) in the Maintenance Period (LOCF) |

End point description:

A participant with a decrease from baseline in 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 in the Maintenance Period (28- day seizure frequency in Week 8 to Week 20 compared to Week -8 to Week 0 at Last Observation Carried Forward (LOCF)). Seizure frequency of simple partial, complex partial, and partial seizures with secondary generalization were assessed.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

Baseline (Week -8 to Week 0), and Week 8 to Week 20

| End point values | Placebo | Zonisamide | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 100[1] | 107[2] | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 31 | 50 | | |

Notes:

[1] - Intent-to-treat population - randomized participants who received at least one dose of study drug.

[2] - Intent-to-treat population - randomized participants who received at least one dose of study drug.

### Statistical analyses

| Statistical analysis title | P-value |
|---|---|

Statistical analysis description:

The primary comparison of interest was the zonisamide treatment group versus the placebo treatment group in the intent-to-treat population on last observation carried forward data during the Maintenance Period. A 5% significance level was used throughout. If the data were not normally distributed, then transformations or, if unsuccessful, non-parametric methods were used as appropriate.

| | |
|---|---|
| Comparison groups | Placebo v Zonisamide |

| | |
|---|---|
| Number of subjects included in analysis | 207 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0044 [3] |
| Method | Chi-squared |

Notes:

[3] - From the Pearson's chi-square test which was used on categorical data where no stratification factors were included in the analysis.

## Secondary: Median Percent Change from Baseline in the 28-day Seizure Frequency During the Maintenance Period (LOCF)

| | |
|---|---|
| End point title | Median Percent Change from Baseline in the 28-day Seizure Frequency During the Maintenance Period (LOCF) |

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.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Baseline (Week -8 to Week 0) and Week 8 to Week 20

| End point values | Placebo | Zonisamide | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 100[4] | 107[5] | | |
| Units: Percentage Change in Seizure Frequency | | | | |
| median (full range (min-max)) | -24.5 (-100 to 1055) | -50 (-100 to 374) | | |

Notes:

[4] - Intent-to-treat population - randomized participants who received at least one dose of study drug.

[5] - Intent-to-treat population - randomized participants who received at least one dose of study drug.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percent of Participants with greater than or equal to 50% to less than 75% and greater than or equal to 75% Decrease from Baseline in 28-day Seizure Frequency During the Maintenance Period (LOCF)

| | |
|---|---|
| End point title | Percent of Participants with greater than or equal to 50% to less than 75% and greater than or equal to 75% Decrease from Baseline in 28-day Seizure Frequency During the Maintenance Period (LOCF) |

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.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Baseline (Week -8 to Week 0) and Week 8 to Week 20

| End point values | Placebo | Zonisamide | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 100[6] | 107[7] | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Greater than or equal to 75% decrease | 12 | 27.1 | | |
| Great than or equal to50% to less than75% decrease | 19 | 23.4 | | |

Notes:

[6] - Intent-to-treat population - randomized participants who received at least one dose of study drug.

[7] - Intent-to-treat population - randomized participants who received at least one dose of study drug.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percent of Participants with greater than or equal to 25% and greater than or equal to 100% Increase from Baseline in 28-day Seizure Frequency During the Maintenance Period (LOCF)

| End point title | Percent of Participants with greater than or equal to 25% and greater than or equal to 100% Increase from Baseline in 28-day Seizure Frequency During the Maintenance Period (LOCF) |
|---|---|

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.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (Week -8 to Week 0) and Week 8 to Week 20

| End point values | Placebo | Zonisamide | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 100[8] | 107[9] | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Greater than or equal to 25% increase | 21 | 10 | | |
| Greater than or equal to 100% increase | 9 | 5 | | |

Notes:

[8] - Intent-to-treat population - randomized participants who received at least one dose of study drug.

[9] - Intent-to-treat population - randomized participants who received at least one dose of study drug.

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the time the subject signed the informed consent form through the Final Visit/Early Termination Visit and for 15 days following study drug discontinuation.

Adverse event reporting additional description:

Adverse events (AEs) were assessed at clinical visits based on the subject's diary, vitals, weight, physical examination, neurological exam, and laboratory evaluations; and by telephone interviews/contact.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 11.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description:

Participants had a starting dose of 1 mg/kg/day of placebo matching Zonisamide. Dose was titrated upwards with weekly dose increases until a dose of 8 mg/kg/day was reached at the end of the Titration Period (Week 8). Dose during the Maintenance Period remained unchanged from Week 8.

| | |
|---|---|
| Reporting group title | Zonisamide |

Reporting group description:

Participants had a starting dose of 1 mg/kg/day of Zonisamide. Dose was titrated upwards with weekly dose increases until a dose of 8 mg/kg/day was reached at the end of the Titration Period (Week 8). Dose during the Maintenance Period remained unchanged from Week 8.

| Serious adverse events | Placebo | Zonisamide | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 100 (2.00%) | 4 / 107 (3.74%) | |
| number of deaths (all causes) | 1 | 1 | |
| number of deaths resulting from adverse events | 0 | 1 | |
| Investigations | | | |
| Blood glucose decreased | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Complex partial seizures | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 107 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 107 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Status epilepticus | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 107 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 107 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Placebo | Zonisamide | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 21 / 100 (21.00%) | 19 / 107 (17.76%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 7 / 100 (7.00%) | 7 / 107 (6.54%) | |
| occurrences (all) | 12 | 15 | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 6 / 100 (6.00%) | 2 / 107 (1.87%) | |
| occurrences (all) | 8 | 3 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 9 / 100 (9.00%) | 6 / 107 (5.61%) | |
| occurrences (all) | 14 | 8 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 4 / 100 (4.00%) | 7 / 107 (6.54%) | |
| occurrences (all) | 4 | 7 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 25 January 2008 | Extended the scope of EC 27 to include hypersensitivity to excipients of the investigative medicinal product (IMP). Added additional criteria which were to lead to stopping treatment i.e., unexplained rash; symptoms, clinical and biological signs of pancreatitis; muscle pain and or weakness and elevated serum creatinine phosphokinase (CPK) and aldolase levels in the absence of another obvious cause such as trauma or grand mal seizures. |
| 04 February 2008 | Added furosemide to EC 28. Shortening of down-titration period to 3 weeks for subjects of lower weight ranges. Change to rules for reporting of pregnancies. A provision for intercurrent short-lasting illnesses was inserted to allow minor decreases of IMP dosing of not more than 4 days. Adjustment of rules for collection of SAEs. |
| 26 March 2009 | Change of Sponsors registered United Kingdom (UK) address. Clarification of rules for withdrawal of pregnant subjects to allow for a risk/benefit decision. Addition of investigator guidance/safety texts specifically to cover a safety update of the Summary of Product Characteristics (SmPC) pertaining to new safety text on suicidality, Stevens-Johnson Syndrome (SJS), Toxic epidermal necrolysis (TEN), and metabolic acidosis. |
| 21 July 2009 | Harmonisation of pregnancy withdrawal criteria with other ongoing zonisamide (ZNS) studies including removed of caveat in Amendment 02 allowing for a risk/benefit decision concerning withdrawal of pregnant subjects. Blinding of bicarbonate lab results (see Section 9.4.6) |
| 18 February 2010 | Reduced the Screening Period from 8 weeks to 4 weeks. The 8 week Baseline Phase had been a significant disincentive to enrolment. The 4 weeks seizure data collected was supplemented with 4 weeks of historical data captured before the start of the clinical study in well-documented seizure diaries maintained by the subjects as part of standard clinical practice. Only subjects with a stable Baseline Phase were entered into the study. If data quality was poor, the subject was not randomized and failed screening.<br>IC7: Extended the period subjects had to take a stable regimen of 1 or 2 other AEDs from at least 1 month before Visit 1 to at least 2 months before Visit 1, and extended the period for which vagal nerve stimulator parameters had to remain unchanged from at least 1 month before Visit 1 to at least 2 months before Visit 1.<br>EC19: Changed the allowed use of benzodiazepines as rescue medication, from once per month to once per week. The original criterion, allowing the usage of one benzodiazepine dose per month, was set as a consequence of an overly conservative study design. It is not commonly used in epilepsy study designs or linked to any defined differences in subject groups.11,12,13 Exploratory analysis to assess whether there were any differences between the two subject groups was performed as outlined in Section 9.7.1.4. |

| | |
|---|---|
| 18 February 2010 | Amendment continued:<br>EC20: Extended the period for concomitant use of felbamate or use of felbamate from within 2 months before Visit 1, to within 3 months before Visit 1.<br>EC23: Extended the period for subjects with clinically significant active hepatic disease, cardiovascular, metabolic, respiratory, renal, endocrinological and gastrointestinal diseases or any other clinically significant organic disease, from within 30 to 60 days prior to Screening.<br>Amended EC27 in line with Amendment A France.<br>Addition of EC30 and EC31.<br>Made completion of the school performance questionnaire optional rather than mandatory. This was to account for the social stigma associated with childhood epilepsy that exists in India and Europe, which was a significant disincentive to completion of the school performance questionnaire and to enrolment. Reduced the statistical power of the study from 90% to 80%. This meant that fewer subjects were required to complete the study (204 instead of 266), which allowed recruitment to be completed earlier. Stipulated that primary efficacy parameter will be analyzed stratified by country, and that the other efficacy parameters will be analyzed using ANCOVA on rank transformed data for seizure data, or chi-square as appropriate. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported