



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 |
|-----------------------|----------------|

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:

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

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 |
| Arm title | 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.

| | |
|------------------|---|
| Arm title | Zonisamide (zonisamide during core study) |
|------------------|---|

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) |
|-----------------------|--|

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.

| 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 ^[1] |
| 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 ^[2] | 72 ^[3] | | |
| 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 |
|-----------------|--|

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 |
|----------------|-----------|

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 ^[4] | 72 ^[5] | | |
| 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 |
|-----------------|---|

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 |
|----------------|-----------|

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 ^[6] | 72 ^[7] | | |
| 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 |
|-----------------|--|

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 |
|----------------|-----------|

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 ^[8] | 72 ^[9] | | |
| 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 |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 11 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Zonisamide (placebo during core study) |
|-----------------------|--|

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) |
|-----------------------|---|

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 %

| Non-serious adverse events | 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">• A criterion was added to stipulate that if a female subject became pregnant she must be withdrawn from the study.• 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. |
| 21 July 2009 | <ul style="list-style-type: none">• 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.• 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. |
| 19 March 2010 | <ul style="list-style-type: none">• 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">- 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.- 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.- The number of subjects was reduced from 266 to 204.- 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.- The exclusion criterion for concomitant use of felbamate was amended to within 3 months of Visit 1 from within 2 months of Visit 1.- The frequency of visits and scheduled assessments/events in the double-blind Transition Period and the Open-label Period was reduced.- 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.- The vital signs assessment was no longer to be performed.- Pregnancy status was to be established using a urine pregnancy test.- 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.- The definition of baseline, for the purposes of the efficacy parameters, and for the purposes of the safety parameters was clarified.- 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. |

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| 19 March 2010 | <p>Amendment 3 continued.</p> <ul style="list-style-type: none"> • 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. • The guidelines for monitoring/managing hyperchloremic, non-anion gap metabolic acidosis were modified to ensure consistency with the current version of the SmPC. • 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. |
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported