



Clinical trial results:

A double-blind, randomised, placebo-controlled, multi-centre study to assess the efficacy and safety of adjunctive zonisamide in myoclonic seizures associated with idiopathic generalised epilepsy.

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2007-003556-10 |
| Trial protocol | DE HU LT CZ EE PL ES FI |
| Global end of trial date | 11 December 2008 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 29 July 2016 |
| First version publication date | 29 July 2016 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | E2090-E044-317 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00693017 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Eisai Medical Research Inc. |
| Sponsor organisation address | 100 Tice Boulevard, Woodcliff Lake, United States, 07677 |
| Public contact | Eisai Medical Information, Eisai Medical Research Inc., 888 247-2378, esi-medinfo@eisai.com |
| Scientific contact | Eisai Medical Information, Eisai Medical Research Inc., 888 247-2378, esi-medinfo@eisai.com |

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 | 22 June 2009 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 11 December 2008 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

This study is intended to provide evidence that zonisamide is safe and effective in the treatment of myoclonic seizures. The total planned trial duration will be 6.5 months. After that, participants who have completed the study will be eligible to enroll in an open-label extension study until zonisamide is marketed for this indication or further development in this indication stops. This extension study will be described in a separate protocol (E2090-E044-318).

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.
- 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 | 04 June 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 | Australia: 1 |
| Country: Number of subjects enrolled | Hungary: 3 |
| Worldwide total number of subjects | 4 |
| EEA total number of subjects | 3 |

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) | 2 |
| Adults (18-64 years) | 2 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study was recruited at three study centers (1 in Australia and 2 in Hungary). A further 39 study centers in Europe and Australia were initiated. A total of 12 study sites in the following countries were not initiated; (2 in Finland), (3 in Czech Republic), and (7 in Ukraine) during the period of 04 June 2008 to 05 January 2009.

Pre-assignment

Screening details:

Ten participants were screened for eligibility and 6 participants did not continue after the Screening Visit due to the Sponsor's decision to terminate the study. Four participants were enrolled and treated during the study.

Period 1

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

Arms

| | |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Zonisamide |

Arm description:

50-400 mg capsules once daily in the evening orally.

Maximum study duration 28 weeks comprising:

Baseline Period (Week -8 to Week 0): no treatment

Titration Period (Week 0 to Week 4): 50 mg daily titrated weekly until 300 mg was reached by Week 4

Maintenance Period (Week 5 to Week 16): 400 mg (or 350 mg in the event of dose limiting adverse events)

Down Titration Period (4 Weeks)

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Zonisamide |
| Investigational medicinal product code | E2090 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Maximum study length was 28 weeks with the following periods:

Baseline Period (Week -8 to Week 0): no treatment

Titration Period (Week 0 to Week 4): Dosing started at 50 mg zonisamide once daily in the evening. Further dose increases occurred at one week intervals until a dose of 300 mg zonisamide was reached by Week 4. In the event of a dose-limiting AE, one titration step was omitted during Weeks 0 to 3, resulting in a dose of 250 mg zonisamide at Week 4. Participants requiring further down titration during this period were to be withdrawn from the study.

Maintenance Period (Week 5 to Week 16): Participants continued with the dose of zonisamide they took during Week 4. If more seizures occurred in the first 2 weeks of this period, the dose was increased up to 400 mg zonisamide (or 350 mg zonisamide if their starting dose was 250 mg zonisamide). The dose could be reduced to 200 mg zonisamide in the case of dose-limiting AEs.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

50-400 mg Zonisamide Placebo capsules once daily in the evening orally.

Maximum study duration 28 weeks comprising:

Baseline Period (Week -8 to Week 0): no treatment

Titration Period (Week 0 to Week 4): 50 mg Zonisamide Placebo daily titrated weekly until 300 mg was reached by Week 4

Maintenance Period (Week 5 to Week 16): 400 mg Zonisamide Placebo (or 350 mg in the event of dose limiting adverse events)

Down Titration Period (4 Weeks)

| | |
|--|----------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | E2090 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Maximum study length was 28 weeks with the following periods:

Baseline Period (Week -8 to Week 0): no treatment

Titration Period (Week 0 to Week 4): Dosing started at 50 mg matched placebo once daily in the evening. Further dose increases occurred at one week intervals until a dose of 300 mg placebo was reached by Week 4. In the event of a dose-limiting AE, one titration step was omitted during Weeks 0 to 3, resulting in a dose of 250 mg placebo at Week 4. Participants requiring further down titration during this period were to be withdrawn from the study.

Maintenance Period (Week 5 to Week 16): Participants continued with the dose of placebo they took during Week 4. If more seizures occurred in the first 2 weeks of this period, the dose was increased up to 400 mg placebo (or 350 mg placebo if their starting dose was 250 mg placebo). The dose could be reduced to 200 mg placebo in the case of dose-limiting AEs.

Down Titration Period (4 Weeks)

| Number of subjects in period 1 | Zonisamide | Placebo |
|---------------------------------------|------------|---------|
| Started | 2 | 2 |
| Completed | 0 | 0 |
| Not completed | 2 | 2 |
| Death | - | 1 |
| Sponsor decision | 2 | 1 |

Baseline characteristics

Reporting groups

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

Reporting group description:

50-400 mg capsules once daily in the evening orally.

Maximum study duration 28 weeks comprising:

Baseline Period (Week -8 to Week 0): no treatment

Titration Period (Week 0 to Week 4): 50 mg daily titrated weekly until 300 mg was reached by Week 4

Maintenance Period (Week 5 to Week 16): 400 mg (or 350 mg in the event of dose limiting adverse events)

Down Titration Period (4 Weeks)

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

Reporting group description:

50-400 mg Zonisamide Placebo capsules once daily in the evening orally.

Maximum study duration 28 weeks comprising:

Baseline Period (Week -8 to Week 0): no treatment

Titration Period (Week 0 to Week 4): 50 mg Zonisamide Placebo daily titrated weekly until 300 mg was reached by Week 4

Maintenance Period (Week 5 to Week 16): 400 mg Zonisamide Placebo (or 350 mg in the event of dose limiting adverse events)

Down Titration Period (4 Weeks)

| Reporting group values | Zonisamide | Placebo | Total |
|---|------------|---------|-------|
| Number of subjects | 2 | 2 | 4 |
| 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 | | | |
| arithmetic mean | 24 | 33.5 | |
| standard deviation | ± 16.97 | ± 23.33 | - |
| Gender categorical Units: Subjects | | | |
| Female | 1 | 1 | 2 |

| | | | |
|------|---|---|---|
| Male | 1 | 1 | 2 |
|------|---|---|---|

End points

End points reporting groups

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

Reporting group description:

50-400 mg capsules once daily in the evening orally.

Maximum study duration 28 weeks comprising:

Baseline Period (Week -8 to Week 0): no treatment

Titration Period (Week 0 to Week 4): 50 mg daily titrated weekly until 300 mg was reached by Week 4

Maintenance Period (Week 5 to Week 16): 400 mg (or 350 mg in the event of dose limiting adverse events)

Down Titration Period (4 Weeks)

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

Reporting group description:

50-400 mg Zonisamide Placebo capsules once daily in the evening orally.

Maximum study duration 28 weeks comprising:

Baseline Period (Week -8 to Week 0): no treatment

Titration Period (Week 0 to Week 4): 50 mg Zonisamide Placebo daily titrated weekly until 300 mg was reached by Week 4

Maintenance Period (Week 5 to Week 16): 400 mg Zonisamide Placebo (or 350 mg in the event of dose limiting adverse events)

Down Titration Period (4 Weeks)

Primary: Number of Participants Considered Responders as Assessed During the Maintenance Period

| | |
|-----------------|---|
| End point title | Number of Participants Considered Responders as Assessed During the Maintenance Period ^[1] |
|-----------------|---|

End point description:

The number of participants who were considered responders during the 12 week Maintenance Period (Week 4 to Week 16). A responder was defined as a participant with a decrease $\geq 50\%$ from baseline in the number of days with myoclonic seizures per 28 days (i.e. 28-day myoclonic seizure frequency in Period from Week 4 to the Week 16 visit compared to Week -8 to randomization at Week 0 [Screening/Baseline Period]). Occurrence of seizures was documented in a seizure diary. The diary was dispensed at the Screening Visit and maintained by the participant (parent/caregiver) and reviewed at each following visit. The diary was completed daily. All seizures except myoclonic seizures were counted individually in the diary. Due to early termination of the study by the Sponsor, no formal analyses were conducted.

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

End point timeframe:

Baseline (Week -8 to Week 0) and Maintenance Period (Week 4 to Week 16)

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 analysis was not done.

| End point values | Zonisamide | Placebo | | |
|-----------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[2] | 0 ^[3] | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |

Notes:

[2] - Efficacy analyses were not done due to insufficient data.

[3] - Efficacy analyses were not done due to insufficient data.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline in the Monthly Number of Days with Myoclonic Seizures

| | |
|-----------------|---|
| End point title | Percentage Change from Baseline in the Monthly Number of Days with Myoclonic Seizures |
|-----------------|---|

End point description:

Percentage Change from Baseline in the monthly number of days with myoclonic seizures was assessed both for the Maintenance Period alone (Week 4 to Week 16) and for the entire double-blind treatment period (Week 0 to Week 16). Due to early termination of the study by the Sponsor, no formal analyses were conducted.

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

End point timeframe:

Baseline and up to 16 weeks

| End point values | Zonisamide | Placebo | | |
|-----------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[4] | 0 ^[5] | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |

Notes:

[4] - Efficacy analyses were not done due to insufficient data.

[5] - Efficacy analyses were not done due to insufficient data.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events were collected for up to 7 months.

Adverse event reporting additional description:

Treatment-emergent adverse events were reported for the safety population which included all participants who received at least one dose of study treatment and had at least one safety assessment.

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

Dictionary used

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

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

Reporting groups

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

Reporting group description:

Maximum study length was 28 weeks with the following periods:

Baseline Period (Week -8 to Week 0): no treatment

Titration Period (Week 0 to Week 4): Dosing started at 50 mg zonisamide once daily in the evening. Further dose increases occurred at one week intervals until a dose of 300 mg zonisamide was reached by Week 4. In the event of a dose-limiting adverse event (AE), one titration step was omitted during Weeks 0 to 3, resulting in a dose of 250 mg zonisamide at Week 4. Participants requiring further down titration during this period were to be withdrawn from the study.

Maintenance Period (Week 5 to Week 16): Participants continued with the dose of zonisamide they took during Week 4. If more seizures occurred in the first 2 weeks of this period, the dose was increased up to 400 mg zonisamide (or 350 mg zonisamide if their starting dose was 250 mg zonisamide). The dose could be reduced to 200 mg zonisamide in the case of dose-limiting AEs.

Down Titration Period (4 Weeks)

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

Reporting group description:

Maximum study length was 28 weeks with the following periods:

Baseline Period (Week -8 to Week 0): no treatment

Titration Period (Week 0 to Week 4): Dosing started at 50 mg matched placebo once daily in the evening. Further dose increases occurred at one week intervals until a dose of 300 mg placebo was reached by Week 4. In the event of a dose-limiting adverse event (AE), one titration step was omitted during Weeks 0 to 3, resulting in a dose of 250 mg placebo at Week 4. Participants requiring further down titration during this period were to be withdrawn from the study.

Maintenance Period (Week 5 to Week 16): Participants continued with the dose of placebo they took during Week 4. If more seizures occurred in the first 2 weeks of this period, the dose was increased up to 400 mg placebo (or 350 mg placebo if their starting dose was 250 mg placebo). The dose could be reduced to 200 mg placebo in the case of dose-limiting AEs.

Down Titration Period (4 Weeks)

| Serious adverse events | Zonisamide | Placebo | |
|---|---------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | |
| number of deaths (all causes) | 0 | 1 | |
| number of deaths resulting from | 0 | 0 | |

| | | | |
|--|---------------|----------------|--|
| adverse events | | | |
| General disorders and administration site conditions | | | |
| Sudden unexplained death in epilepsy | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Zonisamide | Placebo | |
|---|-----------------|-----------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 2 / 2 (100.00%) | 2 / 2 (100.00%) | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Headache | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 0 | 1 | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Eye disorders | | | |
| Vision blurred | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 1 | 1 | |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 2 (50.00%) | 0 / 2 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 2 (0.00%) | 1 / 2 (50.00%) | |
| occurrences (all) | 0 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------------------|--|--------------|
| 03 November 2008 | Early termination at the Sponsor's discretion. | - |

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|---|
| Insufficient data was collected due to early termination. Therefore no formal statistical analysis or analyses of the efficacy endpoints was performed. |
|---|

Notes: