



Clinical trial results:

A double-blind, randomised, placebo-controlled, multicentre study to assess the efficacy and safety of adjunctive zonisamide in primary generalised tonic clonic seizures.

Summary

EudraCT number	2007-003557-91
Trial protocol	DE HU LT FI CZ EE
Global end of trial date	09 January 2009

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-E044-315
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00692003
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Limited
Sponsor organisation address	European Knowledge Centre, Mosquito Way, Hatfield, Herts, , Woodcliff Lake, United States, AL10 9SN
Public contact	Eisai Call Center, Eisai Limited (Eisai Inc.), 888 422-4743,
Scientific contact	Eisai Call Center, Eisai Limited (Eisia 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 July 2009
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	09 January 2009
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to assess the efficacy of adjunctive zonisamide in idiopathic generalised epilepsy (IGE) in reducing the frequency of tonic-clonic seizures in subjects with continuing primary generalised tonic clonic seizures (PGTCS) despite treatment 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 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	01 August 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	Hungary: 1
Country: Number of subjects enrolled	Lithuania: 1
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Romania: 3
Worldwide total number of subjects	6
EEA total number of subjects	5

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)	1
Adults (18-64 years)	5
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was recruited at 6 centers (3 in Romania and 1 in Australia, Hungary, and Lithuania) during the period of 01 August 2008 to 28 January 2009.

Pre-assignment

Screening details:

Twenty-one subjects were screened and 14 subjects did not continue the study after screening. Seven subjects entered the study but 1 subject did not receive any treatment. Consequently, 6 subjects were enrolled and treated during the study. None of the 6 subjects completed treatment & all discontinued due to the Sponsor's decision.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Zonisamide

Arm description:

25-400 mg zonisamide capsules orally once daily in the evening. Maximum study duration of 28 weeks comprising: Baseline Period (Week -8/-4 to Week 0) no treatment; Titration Period (Week 0 to Week 4) <12 years old: 1 mg/kg zonisamide and ≥12 years old: 50 mg zonisamide daily titrated weekly until a dose of 5 mg/kg or 300 mg was reached by Week 4; Maintenance Period (Week 4 to Week 16) dose from Week 4 to be maintained (4 mg/kg or 200 mg in the event of dose limiting adverse events); Down Titration Period (4 weeks).

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

Dosage and administration details:

25-400 mg zonisamide capsules orally once daily in the evening. Maximum study duration of 28 weeks comprising: Baseline Period (Week -8/-4 to Week 0) no treatment; Titration Period (Week 0 to Week 4) <12 years old: 1 mg/kg zonisamide and ≥12 years old: 50 mg zonisamide daily titrated weekly until a dose of 5 mg/kg or 300 mg was reached by Week 4; Maintenance Period (Week 4 to Week 16) dose from Week 4 to be maintained (4 mg/kg or 200 mg in the event of dose limiting adverse events); Down Titration Period (4 weeks).

Arm title	Placebo
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Arm description:

25-400 mg zonisamide placebo capsules orally once daily in the evening. Maximum study duration of 28 weeks comprising: Baseline Period (Week -8/-4 to Week 0) no treatment; Titration Period (Week 0 to Week 4) <12 years old: 1 mg/kg zonisamide placebo and ≥12 years old: 50 mg zonisamide placebo daily titrated weekly until a dose of 5 mg/kg or 300 mg was reached by Week 4; Maintenance Period (Week 4 to Week 16) dose from Week 4 to be maintained (4 mg/kg or 200 mg in the event of dose limiting adverse events); Down Titration Period (4 weeks).

Arm type	Placebo
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Investigational medicinal product name	Placebo matched zonisamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

25-400 mg zonisamide placebo capsules orally once daily in the evening. Maximum study duration of 28 weeks comprising: Baseline Period (Week-8/-4 to Week 0) no treatment; Titration Period (Week 0 to Week 4) <12 years old: 1 mg/kg zonisamide placebo and ≥12 years old: 50 mg zonisamide placebo daily titrated weekly until a dose of 5 mg/kg or 300 mg was reached by Week 4; Maintenance Period (Week 4 to Week 16) dose from Week 4 to be maintained (4 mg/kg or 200 mg in the event of dose limiting adverse events); Down Titration Period (4 weeks).

Number of subjects in period 1	Zonisamide	Placebo
Started	5	1
Completed	0	0
Not completed	5	1
Sponsor decision	5	1

Baseline characteristics

Reporting groups

Reporting group title	Zonisamide
Reporting group description:	
25-400 mg zonisamide capsules orally once daily in the evening. Maximum study duration of 28 weeks comprising: Baseline Period (Week-8/-4 to Week 0) no treatment; Titration Period (Week 0 to Week 4) <12 years old: 1 mg/kg zonisamide and ≥12 years old: 50 mg zonisamide daily titrated weekly until a dose of 5 mg/kg or 300 mg was reached by Week 4; Maintenance Period (Week 4 to Week 16) dose from Week 4 to be maintained (4 mg/kg or 200 mg in the event of dose limiting adverse events); Down Titration Period (4 weeks).	
Reporting group title	Placebo
Reporting group description:	
25-400 mg zonisamide placebo capsules orally once daily in the evening. Maximum study duration of 28 weeks comprising: Baseline Period (Week-8/-4 to Week 0) no treatment; Titration Period (Week 0 to Week 4) <12 years old: 1 mg/kg zonisamide placebo and ≥12 years old: 50 mg zonisamide placebo daily titrated weekly until a dose of 5 mg/kg or 300 mg was reached by Week 4; Maintenance Period (Week 4 to Week 16) dose from Week 4 to be maintained (4 mg/kg or 200 mg in the event of dose limiting adverse events); Down Titration Period (4 weeks).	

Reporting group values	Zonisamide	Placebo	Total
Number of subjects	5	1	6
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	38.4	27	
standard deviation	± 18.66	± 27	-
Gender categorical Units: Subjects			
Female	3	0	3
Male	2	1	3

End points

End points reporting groups

Reporting group title	Zonisamide
Reporting group description: 25-400 mg zonisamide capsules orally once daily in the evening. Maximum study duration of 28 weeks comprising: Baseline Period (Week -8/-4 to Week 0) no treatment; Titration Period (Week 0 to Week 4) <12 years old: 1 mg/kg zonisamide and ≥12 years old: 50 mg zonisamide daily titrated weekly until a dose of 5 mg/kg or 300 mg was reached by Week 4; Maintenance Period (Week 4 to Week 16) dose from Week 4 to be maintained (4 mg/kg or 200 mg in the event of dose limiting adverse events); Down Titration Period (4 weeks).	
Reporting group title	Placebo
Reporting group description: 25-400 mg zonisamide placebo capsules orally once daily in the evening. Maximum study duration of 28 weeks comprising: Baseline Period (Week -8/-4 to Week 0) no treatment; Titration Period (Week 0 to Week 4) <12 years old: 1 mg/kg zonisamide placebo and ≥12 years old: 50 mg zonisamide placebo daily titrated weekly until a dose of 5 mg/kg or 300 mg was reached by Week 4; Maintenance Period (Week 4 to Week 16) dose from Week 4 to be maintained (4 mg/kg or 200 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 from baseline in Primary Generalised Tonic-Clonic Seizures (PGTCS) frequency of ≥ 50% (i.e. 28-day PGTC seizure frequency in the period from Week 4 to the Week 16 visit compared to Week -8 to randomization at Week 0). Each participant's response to treatment was assessed on the basis of their seizure diaries. The diary was dispensed at the Screening Visit and maintained by the participant (parent/caregiver) through out the titration and maintenance treatment periods until the Early termination Visit at Week 16. 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/-4 to Week 0) and Maintenance Phase (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: Due to early termination of the study by the Sponsor, no formal analyses were conducted.	

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] - Due to early termination of the study by the Sponsor, no formal analyses were conducted.

[3] - Due to early termination of the study by the Sponsor, no formal analyses were conducted.

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in 28-day PGTC Seizure Frequency

End point title	Absolute Change From Baseline in 28-day PGTC Seizure Frequency
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End point description:

Absolute Change from Baseline in 28-day PGTC Seizure Frequency 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
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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: Absolute Change				
number (not applicable)				

Notes:

[4] - Due to early termination of the study by the Sponsor, no formal analyses were conducted.

[5] - Due to early termination of the study by the Sponsor, no formal analyses were conducted.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected for approximately 3 months.

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
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Reporting group description:

25-400 mg zonisamide capsules orally once daily in the evening. Maximum study duration of 28 weeks comprising: Baseline Period (Week-8/-4 to Week 0) no treatment; Titration Period (Week 0 to Week 4) <12 years old: 1 mg/kg zonisamide and ≥12 years old: 50 mg zonisamide daily titrated weekly until a dose of 5 mg/kg or 300 mg was reached by Week 4; Maintenance Period (Week 4 to Week 16) dose from Week 4 to be maintained (4 mg/kg or 200 mg in the event of dose limiting adverse events); Down Titration Period (4 weeks).

Reporting group title	Placebo
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Reporting group description:

25-400 mg zonisamide placebo capsules orally once daily in the evening. Maximum study duration of 28 weeks comprising: Baseline Period (Week-8/-4 to Week 0) no treatment; Titration Period (Week 0 to Week 4) <12 years old: 1 mg/kg zonisamide placebo and ≥12 years old: 50 mg zonisamide placebo daily titrated weekly until a dose of 5 mg/kg or 300 mg was reached by Week 4; Maintenance Period (Week 4 to Week 16) dose from Week 4 to be maintained (4 mg/kg or 200 mg in the event of dose limiting adverse events); Down Titration Period (4 weeks).

Serious adverse events	Zonisamide	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	0 / 1 (0.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	

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 / 5 (40.00%)	0 / 1 (0.00%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Postictal headache			

subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 1 (0.00%) 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Gait disturbance			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	

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	This study was terminated early at the Sponsor's discretion. When this study was discontinued, only 6 subjects had been treated. Data from the 5 subjects treated with zonisamide were insufficient to draw firm conclusions regarding efficacy.	-

Notes:

Limitations and caveats

None reported