Clinical trial results:
Comparative Study of Zonisamide and Carbamazepine as an Initial Monotherapy: Efficacy and Safety Evaluation

Summary

EudraCT number	2016-004957-33
Trial protocol	Outside EU/EEA
Global end of trial date	05 May 2010

Results information

Result version number	v1 (current)
This version publication date	12 July 2017
First version publication date	12 July 2017

Trial information

Trial identification

Sponsor protocol code	E2090-S082-405

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01127256
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Korea Inc.
Sponsor organisation address	10F Revessant, Bongeunsa-ro 86 gil 6, Gangnam-gu, Seoul, Korea, Republic of, 06163
Public contact	Eisai Korea Inc. Medical Department, Eisai Korea Inc., 82-2 34515538,
Scientific contact	Eisai Korea Inc. Medical Department, Eisai Korea Inc., 82-2 34515538,

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	05 May 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 May 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study was conducted to help with the therapeutic guideline of epileptic participants by establishing the efficacy and safety of Zonisamide in Korean participants through its comparison with Carbamazepine which is widely used as the first line drug in epileptic participants, and establishing the use of titration of Zonisamide to deduce the maximum efficacy while increasing the safety on participants.

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 Council for 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	19 July 2006
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	Korea, Republic of: 200
Worldwide total number of subjects	200
EEA total number of subjects	0

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)	0
Adults (18-64 years)	200
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was recruited at 12 centers in Korea during the period of May 2006 to May 2009.

Pre-assignment

Screening details:

A total of 200 participants enrolled; 96 participants were in the zonisamide group and 104 in the carbamazepine group. The zonisamide participants was divided into 52 participants in the slow titration group and 44 participants in the fast titration group.

Period 1

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

Blinding implementation details:

Open-label trial

Arms

Are arms mutually exclusive?	Yes
Arm title	Zonisamide

Arm description:

Initial dose was 100 mg/day, increased by 100 mg. The maximum dose was 600 mg/day.

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

Dosage and administration details:

Initial dose was 100 mg/day, increased by 100 mg. The maximum dose was 600 mg/day.

Arm title	Carbamazepine

Arm description:

Initial dose was 100 mg/day, increased by 200 mg every 1 week to 600 mg/day. The maximum dose was 1200 mg/day.

Arm type	Active comparator
Investigational medicinal product name	Carbamazepine
Investigational medicinal product code	
Other name	Tegretol, Carbatrol, Equetro, Epitol
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Initial dose was 100 mg/day, increased by 200 mg every 1 week to 600 mg/day. The maximum dose was 1200 mg/day.

Number of subjects in period 1	Zonisamide	Carbamazepine
Started	96	104
Completed	57	65
Not completed	39	39
Consent withdrawn by subject	5	9
Adverse event, non-fatal	13	13
Protocol violation	1	-
Lost to follow-up	16	17
Lack of efficacy	4	-

Baseline characteristics

Reporting groups	
Reporting group title	Zonisamide
Reporting group description:	
Initial dose was 100 mg/day, increased by 100 mg. The maximum dose was 600 mg/day.	
Reporting group title	Carbamazepine
Reporting group description:	
Initial dose was 100 mg/day, increased by 200 mg every 1 week to 600 mg/day. The maximum dose was 1200 mg/day.	

Reporting group values	Zonisamide	Carbamazepine	Total
Number of subjects	96	104	200
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	39.8	35.7	
standard deviation	± 15.9	± 15.1	-
Gender categorical			
Units: Subjects			
Female	49	53	102
Male	47	51	98
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	96	104	200
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	0	0	0
More than one race	0	0	0
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Zonisamide
Reporting group description:	
Initial dose was 100 mg/day, increased by 100 mg. The maximum dose was 600 mg/day.	
Reporting group title	Carbamazepine
Reporting group description:	
Initial dose was 100 mg/day, increased by 200 mg every 1 week to 600 mg/day. The maximum dose was 1200 mg/day.	

Primary: The Percentage of Participants With Seizure Free Rate

End point title	The Percentage of Participants With Seizure Free Rate[1]
End point description:	
The percentage of participants who had no seizure during the trial.	
End point type	Primary
End point timeframe:	
24 weeks	

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: Did not perform the Statistics Analysis for this endpoint.

End point values	Zonisamide	Carbamazepine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Percentage of participants				
number (not applicable)	73.7	83.1		

Statistical analyses

No statistical analyses for this end point

Secondary: The Percentage of Participants With Retention Rate

End point title	The Percentage of Participants With Retention Rate
End point description:	
The percentage of participants who completed the trial.	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	Zonisamide	Carbamazepine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Percentage of participants				
number (not applicable)	59.4	62.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life in Epilepsy (QoL-QOLIE31)

End point title	Quality of Life in Epilepsy (QoL-QOLIE31)

End point description:

Quality of life assessment tool. Overall scores is calculated by summing subsections, and it ranges from 0 to 100. Higher score presents higher quality of life.

End point type	Secondary

End point timeframe:

24 weeks

End point values	Zonisamide	Carbamazepine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Pre-QOLIE 31	60.72 (± 14.69)	61.96 (± 16.67)		
Post-QOLIE 31	67.27 (± 16.34)	69.51 (± 17.61)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the first dose of study drug, to approximately up to approximately 3 years 1 month.	
Assessment type	Systematic

Dictionary used	
Dictionary name	WHO-ART
Dictionary version	061

Reporting groups	
Reporting group title	Zonisamide
Reporting group description:	
Initial dose was 100 mg/day, increased by 100 mg. The maximum dose was 600 mg/day.	
Reporting group title	Carbamazepine
Reporting group description:	
Initial dose was 100 mg/day, increased by 200 mg every 1 week to 600 mg/day. The maximum dose was 1200 mg/day.	

Serious adverse events	Zonisamide	Carbamazepine	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 96 (5.21%)	9 / 104 (8.65%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Sgot Increased			
subjects affected / exposed	0 / 96 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sgpt Increased			
subjects affected / exposed	0 / 96 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Cervical Sprain			
subjects affected / exposed	1 / 96 (1.04%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right Shoulder Injury			

subjects affected / exposed	1 / 96 (1.04%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 96 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine Fibroid			
subjects affected / exposed	0 / 96 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 96 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 96 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	0 / 96 (0.00%)	4 / 104 (3.85%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depressive Mood			
subjects affected / exposed	1 / 96 (1.04%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Memory And Judgement Disturbance			

subjects affected / exposed	1 / 96 (1.04%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental Torpor			
subjects affected / exposed	0 / 96 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual Hallucination			
subjects affected / exposed	1 / 96 (1.04%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Worsening Insomnia			
subjects affected / exposed	1 / 96 (1.04%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 96 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic Ketoacidosis			
subjects affected / exposed	1 / 96 (1.04%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Zonisamide	Carbamazepine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	74 / 96 (77.08%)	70 / 104 (67.31%)	
Investigations			
Weight Decrease			
subjects affected / exposed	16 / 96 (16.67%)	2 / 104 (1.92%)	
occurrences (all)	17	2	

Nervous system disorders			
Dizziness			
subjects affected / exposed	28 / 96 (29.17%)	23 / 104 (22.12%)	
occurrences (all)	30	24	
Headache			
subjects affected / exposed	14 / 96 (14.58%)	14 / 104 (13.46%)	
occurrences (all)	14	14	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 96 (7.29%)	6 / 104 (5.77%)	
occurrences (all)	7	6	
Pyrexia			
subjects affected / exposed	6 / 96 (6.25%)	8 / 104 (7.69%)	
occurrences (all)	6	9	
Gastrointestinal disorders			
Anorexia			
subjects affected / exposed	20 / 96 (20.83%)	5 / 104 (4.81%)	
occurrences (all)	21	5	
Constipation			
subjects affected / exposed	1 / 96 (1.04%)	7 / 104 (6.73%)	
occurrences (all)	1	7	
Diarrhoea			
subjects affected / exposed	5 / 96 (5.21%)	2 / 104 (1.92%)	
occurrences (all)	6	2	
Dyspepsia			
subjects affected / exposed	1 / 96 (1.04%)	6 / 104 (5.77%)	
occurrences (all)	1	7	
Gastrointestinal Pain			
subjects affected / exposed	7 / 96 (7.29%)	2 / 104 (1.92%)	
occurrences (all)	7	2	
Nausea			
subjects affected / exposed	11 / 96 (11.46%)	12 / 104 (11.54%)	
occurrences (all)	11	14	
Skin and subcutaneous tissue disorders			
Pruritus			

subjects affected / exposed	7 / 96 (7.29%)	4 / 104 (3.85%)	
occurrences (all)	7	5	
Rash			
subjects affected / exposed	6 / 96 (6.25%)	4 / 104 (3.85%)	
occurrences (all)	6	4	
Urticaria			
subjects affected / exposed	0 / 96 (0.00%)	5 / 104 (4.81%)	
occurrences (all)	0	5	
Psychiatric disorders			
Depression			
subjects affected / exposed	4 / 96 (4.17%)	2 / 104 (1.92%)	
occurrences (all)	4	2	
Drowsiness			
subjects affected / exposed	25 / 96 (26.04%)	24 / 104 (23.08%)	
occurrences (all)	25	25	
Memory Impairment			
subjects affected / exposed	9 / 96 (9.38%)	5 / 104 (4.81%)	
occurrences (all)	9	5	
Mental Torpor			
subjects affected / exposed	7 / 96 (7.29%)	12 / 104 (11.54%)	
occurrences (all)	7	12	
Sleep Disorder			
subjects affected / exposed	6 / 96 (6.25%)	4 / 104 (3.85%)	
occurrences (all)	6	4	

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? No

Limitations and caveats

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

Early termination leading to small numbers of subjects analyzed

Notes: