Clinical trial results:
A Double-Blind, Placebo-Controlled, Parallel-Group Study of Rufinamide Given as Adjunctive Therapy in Patients with Refractory Partial Seizures

Summary

EudraCT number	2016-004944-12
Trial protocol	Outside EU/EEA
Global end of trial date	20 May 2009

Results information

Result version number	v2 (current)
This version publication date	03 July 2019
First version publication date	18 May 2019
Version creation reason	• Correction of full data set Contact details will be updated for this study.

Trial information

Trial identification

Sponsor protocol code	E2080-A001-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00334958
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Inc.
Sponsor organisation address	155 Tice Boulevard, Woodcliff Lake, United States,
Public contact	Eisai Medical Information, Eisai Inc., 1 8882472378, esi_oncmedinfo@eisai.com
Scientific contact	Eisai Medical Information, Eisai Inc., 1 8882472378, esi_oncmedinfo@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	20 May 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 May 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of rufinamide on total partial seizure frequency in adolescent and adult participants (12 to 80 years, inclusive) with refractory partial onset seizures maintained on a maximum of 3 stable antiepileptic 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 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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 February 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	United States: 343
Country: Number of subjects enrolled	Canada: 13
Worldwide total number of subjects	356
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)	36
Adults (18-64 years)	308
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were screened at 75 centers (69 in the United States and 6 in Canada). Participants were enrolled at 65 centers (61 in the United States and 4 in Canada).

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Rufinamide

Arm description:

For the 12-day Titration Phase, rufinamide was administered orally in doses starting with 400 mg twice daily and increased every 3 days in 400 mg twice daily increments up to 1600 mg twice daily (total daily dose 3200 mg). For the Maintenance Phase, maintenance doses of 1600 mg twice daily (3200 mg total daily dose) were administered. Subjects unable to tolerate the target dose (3200 mg/day) were allowed only during the Titration Phase to have the dose reduced to 3 tablets twice daily (corresponding to a dose of 2400 mg/day in the rufinamide group).

Arm type	Experimental
Investigational medicinal product name	Rufinamide
Investigational medicinal product code	E2080
Other name	BANZEL
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Rufinamide was administered orally in doses starting with 400 mg twice daily and increased every 3 days in 400 mg twice daily increments up to 1600 mg twice daily (total daily dose 3200 mg). For the Maintenance Phase, maintenance doses of 1600 mg twice daily (3200 mg total daily dose) were administered. Subjects unable to tolerate the target dose (3200 mg/day) were allowed only during the Titration Phase to have the dose reduced to 3 tablets twice daily (corresponding to a dose of 2400 mg/day in the rufinamide group).

Arm title	Placebo

Arm description:

For the 12-day Titration Phase and the Maintenance Phase, rufinamide matching-placebo orally, twice daily was administered.

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

Dosage and administration details:

Rufinamide matching placebo was administered orally, twice daily.

Number of subjects in period 1	Rufinamide	Placebo
Started	176	180
Completed	139	156
Not completed	37	24
Consent withdrawn by subject	7	4
Request of investigator or sponsor	-	1
Adverse event, non-fatal	27	12
Protocol violation	2	2
Not specified	1	2
Medication noncompliance	-	3

Baseline characteristics

Reporting groups	
Reporting group title	Rufinamide
Reporting group description:	
For the 12-day Titration Phase, rufinamide was administered orally in doses starting with 400 mg twice daily and increased every 3 days in 400 mg twice daily increments up to 1600 mg twice daily (total daily dose 3200 mg). For the Maintenance Phase, maintenance doses of 1600 mg twice daily (3200 mg total daily dose) were administered. Subjects unable to tolerate the target dose (3200 mg/day) were allowed only during the Titration Phase to have the dose reduced to 3 tablets twice daily (corresponding to a dose of 2400 mg/day in the rufinamide group).	
Reporting group title	Placebo
Reporting group description:	
For the 12-day Titration Phase and the Maintenance Phase, rufinamide matching-placebo orally, twice daily was administered.	

Reporting group values	Rufinamide	Placebo	Total
Number of subjects	176	180	356
Age categorical Units: Subjects			
Adolescents (12-17 years)	15	21	36
Adults (18-64 years)	155	153	308
Adults (greater than or equal to 65)	6	6	12
Gender categorical Units: Subjects			
Female	92	97	189
Male	84	83	167
Race/Ethnicity Units: Subjects			
Black	14	19	33
White	145	140	285
Hispanic	13	14	27
Native American	0	2	2
Asian/Pacific Islander	4	2	6
Other	0	3	3

End points

End points reporting groups

Reporting group title	Rufinamide

Reporting group description:

For the 12-day Titration Phase, rufinamide was administered orally in doses starting with 400 mg twice daily and increased every 3 days in 400 mg twice daily increments up to 1600 mg twice daily (total daily dose 3200 mg). For the Maintenance Phase, maintenance doses of 1600 mg twice daily (3200 mg total daily dose) were administered. Subjects unable to tolerate the target dose (3200 mg/day) were allowed only during the Titration Phase to have the dose reduced to 3 tablets twice daily (corresponding to a dose of 2400 mg/day in the rufinamide group).

Reporting group title	Placebo

Reporting group description:

For the 12-day Titration Phase and the Maintenance Phase, rufinamide matching-placebo orally, twice daily was administered.

Primary: Percentage change in Total Partial Seizure Frequency per 28 Days During Maintenance Phase Relative to the Baseline Phase

End point title	Percentage change in Total Partial Seizure Frequency per 28 Days During Maintenance Phase Relative to the Baseline Phase[1]

End point description:

Seizure data was collected via patient diary, which was used to record daily seizure count and type. Intent-to-treat (ITT) population: All randomized subjects who had baseline Patient Seizure Diary data and had at least completed the titration period.

End point type	Primary

End point timeframe:

Baseline, Days 13 to 96

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: Only descriptive data was planned to be analyzed for this endpoint.

End point values	Rufinamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	175		
Units: Percentage change				
median (full range (min-max))	-23.25 (-100 to 725.6)	-9.8 (-100 to 864.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with 50% or Greater Reduction in Total Partial Seizure Frequency per 28 Days During the Maintenance Phase Relative to the Baseline Phase

End point title	Percentage of Participants with 50% or Greater Reduction in Total Partial Seizure Frequency per 28 Days During the Maintenance Phase Relative to the Baseline Phase

End point description:

Seizure data was collected via patient diary, which was used to record daily seizure count and type. ITT population: All randomized subjects who had baseline Patient Seizure Diary data and had at least completed the titration period.

End point type	Secondary

End point timeframe:

Baseline, Days 13 to 96

End point values	Rufinamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	175		
Units: Percentage of Participants				
number (not applicable)	32.5	14.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Log10 Transformed Total Partial Seizure Frequency per 28 Days during the Baseline Phase and Maintenance Phase

End point title	Log10 Transformed Total Partial Seizure Frequency per 28 Days during the Baseline Phase and Maintenance Phase

End point description:

Total partial seizure frequencies per 28 days during the double-blind Maintenance and Baseline Phases were transformed using logarithms to the base 10 (log10), because it was expected from previous studies that the results would not be normally distributed. ITT population: All randomized subjects who had baseline Patient Seizure Diary data and had at least completed the titration period.

End point type	Secondary

End point timeframe:

Days 13 to 96

End point values	Rufinamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	175		
Units: Seizures per 28-days (log-transformed)				
arithmetic mean (standard deviation)	0.98 (± 0.675)	1.13 (± 0.52)		

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction from Baseline in Total Partial Seizure Frequency Rate (RRATIO) during Maintenance Phase

End point title	Reduction from Baseline in Total Partial Seizure Frequency Rate (RRATIO) during Maintenance Phase

End point description:

RRATIO= 100*(T-B)/(T+B) where T= total seizure frequency per 28 days during the Maintenance Phase, and B=total seizure frequency per 28 days during the Baseline Phase. ITT population: All randomized subjects who had baseline Patient Seizure Diary data and had at least completed the titration period.

End point type	Secondary

End point timeframe:

Baseline, Days 13 to 96

End point values	Rufinamide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	175		
Units: RRATIO				
arithmetic mean (standard deviation)	-18.76 (± 37.841)	-6.9 (± 24.869)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All serious AEs (SAEs) were collected throughout the study from the time of consent to follow-up visit or 30 days after study drug discontinuation, whichever was longer. Serious adverse events (SAEs), regardless of causality assessment, were collected thr

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Rufinamide

Reporting group description:

For the 12-day Titration Phase, rufinamide was administered orally in doses starting with 400 mg twice daily and increased every 3 days in 400 mg twice daily increments up to 1600 mg twice daily (total daily dose 3200 mg). For the Maintenance Phase, maintenance doses of 1600 mg twice daily (3200 mg total daily dose) were administered. Subjects unable to tolerate the target dose (3200 mg/day) were allowed only during the Titration Phase to have the dose reduced to 3 tablets twice daily (corresponding to a dose of 2400 mg/day in the rufinamide group).

Reporting group title	Placebo

Reporting group description:

For the 12-day Titration Phase and the Maintenance Phase, rufinamide matching-placebo orally, twice daily was administered.

Serious adverse events	Rufinamide	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 176 (3.41%)	7 / 180 (3.89%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Weight decreased			
subjects affected / exposed	1 / 176 (0.57%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Drug toxicity			
subjects affected / exposed	0 / 176 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			

subjects affected / exposed	1 / 176 (0.57%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 176 (0.57%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Complex partial seizures			
subjects affected / exposed	1 / 176 (0.57%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	2 / 176 (1.14%)	2 / 180 (1.11%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coordination abnormal			
subjects affected / exposed	1 / 176 (0.57%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	1 / 176 (0.57%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 176 (0.57%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 176 (0.57%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	1 / 176 (0.57%)	0 / 180 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Adenomyosis			
subjects affected / exposed	0 / 176 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 176 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	0 / 176 (0.00%)	1 / 180 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 176 (0.00%)	1 / 180 (0.56%)	
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	Rufinamide	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	101 / 176 (57.39%)	66 / 180 (36.67%)	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	9 / 176 (5.11%)	5 / 180 (2.78%)	
occurrences (all)	10	5	
Nervous system disorders			

Dizziness			
subjects affected / exposed	47 / 176 (26.70%)	15 / 180 (8.33%)	
occurrences (all)	59	19	
Headache			
subjects affected / exposed	29 / 176 (16.48%)	23 / 180 (12.78%)	
occurrences (all)	36	26	
Somnolence			
subjects affected / exposed	22 / 176 (12.50%)	13 / 180 (7.22%)	
occurrences (all)	22	14	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	27 / 176 (15.34%)	18 / 180 (10.00%)	
occurrences (all)	31	19	
Eye disorders			
Diplopia			
subjects affected / exposed	14 / 176 (7.95%)	2 / 180 (1.11%)	
occurrences (all)	18	3	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	22 / 176 (12.50%)	9 / 180 (5.00%)	
occurrences (all)	23	11	
Vomiting			
subjects affected / exposed	13 / 176 (7.39%)	9 / 180 (5.00%)	
occurrences (all)	15	9	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	6 / 176 (3.41%)	15 / 180 (8.33%)	
occurrences (all)	6	15	

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

None reported