



Clinical trial results: A Placebo-Controlled, Double-Blind Comparative Study of E2080 in Lennox-Gastaut Syndrome Patients

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2016-004952-30 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 12 August 2011 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 21 February 2018 |
| First version publication date | 21 February 2018 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | E2080-J081-304 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01146951 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Eisai Co., Ltd. |
| Sponsor organisation address | 4-6-10 Koishikawa, Bunkyo-ku, Tokyo, Japan, 112-8088 |
| Public contact | Customer Joy Department. EJ, Eisai Co., Ltd., Eisai Co., Ltd., 81(03) 3817-3700, |
| Scientific contact | Customer Joy Department. EJ, Eisai Co., Ltd., Eisai Co., Ltd., 81(03) 3817-3700, |

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 | 12 August 2011 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 August 2011 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate that the efficacy of E2080 in percent change in tonic-atonic seizure frequency in participants with Lennox-Gastaut Syndrome (LGS) relative to placebo.

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 | 17 June 2010 |
| 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 | Japan: 58 |
| Worldwide total number of subjects | 58 |
| 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) | 23 |
| Adolescents (12-17 years) | 13 |
| Adults (18-64 years) | 22 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of n= 66 who started Observation Period, 7 discontinued from study. Primary reasons were deviation of the inclusion/ exclusion criteria (n=5), untoward event before study treatment (n=1) & other (n=1). Of 59 participants, 58 were included in Full Analysis Set. 1 participant (E2080 group) was excluded due to inappropriate diagnosis of disease.

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 |

Arms

| | |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Rufinamide (E2080) |

Arm description:

Rufinamide : Rufinamide tablets administered orally twice daily after breakfast and dinner. Treatment was divided into a Dose Titration Period (2 weeks) and a Dose Maintenance Period (10 weeks). As a general rule, the dose was increased by 1 step every 2 days until it reached the target maintenance dose determined by body weight at the start of the Observation Period.

Target maintenance dose:

15.0 - 30.0 kilograms (kg): 1000 milligrams/day (mg/day) (5 tablets each in the morning and evening)

30.1 - 50.0 kg: 1800 mg/day (4 tablets in the morning and 5 in the evening)

50.1 - 70.0 kg: 2400 mg/day (6 tablets each in the morning and evening)

>= 70.1 kg: 3200 mg/day (8 tablets each in the morning and evening)

| | |
|--|--------------|
| 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 tablets administered orally twice daily after breakfast and dinner. Treatment was divided into a Dose Titration Period (2 weeks) and a Dose Maintenance Period (10 weeks). As a general rule, the dose was increased by 1 step every 2 days until it reached the target maintenance dose determined by body weight at the start of the Observation Period.

Target maintenance dose:

15.0 - 30.0 kg: 1000 mg/day (5 tablets each in the morning and evening)

30.1 - 50.0 kg: 1800 mg/day (4 tablets in the morning and 5 in the evening)

50.1 - 70.0 kg: 2400 mg/day (6 tablets each in the morning and evening)

>= 70.1 kg: 3200 mg/day (8 tablets each in the morning and evening)

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

Arm description:

Placebo : Rufinamide Matching Placebo tablets administered orally twice daily after breakfast and dinner for a total of 12 weeks

| | |
|----------|---------|
| 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 tablets administered orally twice daily after breakfast and dinner for a total of 12 weeks.

| Number of subjects in period 1 | Rufinamide (E2080) | Placebo |
|---------------------------------------|--------------------|---------|
| Started | 28 | 30 |
| Completed | 24 | 29 |
| Not completed | 4 | 1 |
| Adverse event, non-fatal | 4 | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Rufinamide (E2080) |
|-----------------------|--------------------|

Reporting group description:

Rufinamide : Rufinamide tablets administered orally twice daily after breakfast and dinner. Treatment was divided into a Dose Titration Period (2 weeks) and a Dose Maintenance Period (10 weeks). As a general rule, the dose was increased by 1 step every 2 days until it reached the target maintenance dose determined by body weight at the start of the Observation Period.

Target maintenance dose:

15.0 - 30.0 kilograms (kg): 1000 milligrams/day (mg/day) (5 tablets each in the morning and evening)

30.1 - 50.0 kg: 1800 mg/day (4 tablets in the morning and 5 in the evening)

50.1 - 70.0 kg: 2400 mg/day (6 tablets each in the morning and evening)

>= 70.1 kg: 3200 mg/day (8 tablets each in the morning and evening)

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

Reporting group description:

Placebo : Rufinamide Matching Placebo tablets administered orally twice daily after breakfast and dinner for a total of 12 weeks

| Reporting group values | Rufinamide (E2080) | Placebo | Total |
|--|--------------------|---------|-------|
| Number of subjects | 28 | 30 | 58 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 10 | 13 | 23 |
| Adolescents (12-17 years) | 6 | 7 | 13 |
| Adults (18-64 years) | 12 | 10 | 22 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| One participant from the Rufinamide (E2080) group was excluded from the Full Analysis Set because of the inappropriate diagnosis of the disease, dropping the total number from 29 to 28 participants. | | | |
| Units: years | | | |
| arithmetic mean | 16 | 13.9 | |
| standard deviation | ± 7.1 | ± 6.1 | - |
| Gender categorical | | | |
| One subject from the Rufinamide (E2080) group was excluded from the FAS because of the inappropriate diagnosis of the disease, dropping the total number from 29 to 28 participants. | | | |
| Units: Subjects | | | |
| Female | 11 | 11 | 22 |
| Male | 17 | 19 | 36 |

End points

End points reporting groups

| | |
|--|--------------------|
| Reporting group title | Rufinamide (E2080) |
| Reporting group description: | |
| Rufinamide : Rufinamide tablets administered orally twice daily after breakfast and dinner. Treatment was divided into a Dose Titration Period (2 weeks) and a Dose Maintenance Period (10 weeks). As a general rule, the dose was increased by 1 step every 2 days until it reached the target maintenance dose determined by body weight at the start of the Observation Period. | |
| Target maintenance dose: | |
| 15.0 - 30.0 kilograms (kg): 1000 milligrams/day (mg/day) (5 tablets each in the morning and evening) | |
| 30.1 - 50.0 kg: 1800 mg/day (4 tablets in the morning and 5 in the evening) | |
| 50.1 - 70.0 kg: 2400 mg/day (6 tablets each in the morning and evening) | |
| >= 70.1 kg: 3200 mg/day (8 tablets each in the morning and evening) | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Placebo : Rufinamide Matching Placebo tablets administered orally twice daily after breakfast and dinner for a total of 12 weeks | |

Primary: Percent Change in Tonic-Atonic Seizure Frequency from Baseline (Per 28 days)

| | |
|--|--|
| End point title | Percent Change in Tonic-Atonic Seizure Frequency from Baseline (Per 28 days) |
| End point description: | |
| The sum of the frequencies of tonic seizures and atonic seizures was defined as the “tonic-atonic seizure frequency”. The percent change in tonic-atonic seizure frequency per 28 days was assessed. The percent change in tonic-atonic seizure frequency was calculated using the tonic-atonic seizure frequency per 28 days of the Observation Period as the baseline and the tonic-atonic seizure frequency per 28 days of the Treatment Period as the post-treatment value. Percentage change in tonic-atonic seizure frequency was calculated as follows: $[100 \times (\text{post-treatment value}-\text{baseline})/\text{baseline}]$. The frequency of epileptic seizures was recorded in the seizure diary by the recorder. Seizure frequency was counted based on the classification established by the International League Against Epilepsy (ILAE). The diary recorder monitored the participant and recorded the seizure diary in a consistent manner, and continued these practices throughout the study period. Full Analysis Set (FAS) was analyzed. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline (28 day observational period) and End of Treatment (28 day treatment period) | |

| End point values | Rufinamide (E2080) | Placebo | | |
|-------------------------------|-----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 28 | 30 | | |
| Units: Percent Change | | | | |
| median (full range (min-max)) | -24.2 (-93.5 to 27.2) | -3.25 (-81.6 to 151.9) | | |

Statistical analyses

| | |
|---|-------------------------------|
| Statistical analysis title | Analysis of seizure frequency |
| Comparison groups | Placebo v Rufinamide (E2080) |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.003 |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Hodges-Lehmann |
| Point estimate | -26.65 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -40.3 |
| upper limit | -11.8 |

Secondary: Number of Participants achieving a 50% reduction in tonic-atonic

| | |
|--|--|
| End point title | Number of Participants achieving a 50% reduction in tonic-atonic |
| End point description: 50% Responder Rate in Tonic-Atonic Seizure Frequency was presented as the number of participants who achieved a 50% reduction in tonic-atonic seizure frequency. FAS was defined as participants who were registered for the Treatment Period and excludes those listed below; Participants who did not meet the inclusion criterion related the target disease, participants who did not take the study drug, participants without any evaluable efficacy data after the start of study treatment. | |
| End point type | Secondary |
| End point timeframe: 12 weeks | |

| End point values | Rufinamide (E2080) | Placebo | | |
|------------------------------|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 28 | 30 | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Yes (50% Reduction Achieved) | 7 | 2 | | |
| No | 21 | 28 | | |

Statistical analyses

| | |
|-----------------------------------|---------------------------------------|
| Statistical analysis title | Analysis of 50% reduction in seizures |
| Comparison groups | Placebo v Rufinamide (E2080) |

| | |
|---|---------------|
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.074 |
| Method | Fisher exact |

Secondary: Percent Change in Total Seizure Frequency (Per 28 days)

| | |
|--|---|
| End point title | Percent Change in Total Seizure Frequency (Per 28 days) |
| End point description: | |
| Percent change in the total seizure frequency (per 28 days) was calculated using the total seizure frequency per 28 days of the Observation Period as the baseline and the total seizure frequency per 28 days of the Treatment Period as the post-treatment value. Percentage change in total seizure frequency was calculated as follows: $[100 \times (\text{post-treatment value} - \text{baseline}) / \text{baseline}]$. Full analysis set (FAS) is defined as participants who were registered for the Treatment Period and excludes those listed below. Participants who did not meet the inclusion criterion related the target disease, participants who did not take the study drug, participants without any evaluable efficacy data after the start of study treatment. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline (28 day observational period) and End of Treatment (28 day treatment period) | |

| End point values | Rufinamide (E2080) | Placebo | | |
|-------------------------------|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 28 | 30 | | |
| Units: Percent Change | | | | |
| median (full range (min-max)) | -32.9 (-87.3 to 15.4) | -3.05 (-52.2 to 133) | | |

Statistical analyses

| | |
|---|-------------------------------------|
| Statistical analysis title | Analysis of total seizure frequency |
| Comparison groups | Rufinamide (E2080) v Placebo |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Hodges-Lehmann method |
| Point estimate | -33.3 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -47.1 |
| upper limit | -17 |

Secondary: Percentage change in the frequency of seizures other than tonic-atonic seizures (per 28 days)

| | |
|-----------------|---|
| End point title | Percentage change in the frequency of seizures other than tonic-atonic seizures (per 28 days) |
|-----------------|---|

End point description:

Percent change in the frequency of seizures other than tonic-atonic seizures (per 28 days) was calculated using the total seizure frequency per 28 days of the Observation Period as the baseline and the total seizure frequency per 28 days of the Treatment Period as the post-treatment value. Percentage change in total seizure frequency was calculated as follows: $[100 \times (\text{post-treatment value} - \text{baseline}) / \text{baseline}]$. Seizures analyzed other than tonic-atonic seizures included: Partial seizure freq. (frequency), Absence seizure, Atyp. (atypical) absence seizure, Myoclonic seizure, Clonic seizure, Tonic seizure, Tonic-clonic seizure, Atonic seizure, & Uncla. (unclassified) epileptic seizure. The frequency of epileptic seizures was recorded in the diary by the recorder. Seizure frequency was counted based on the classification established by the International League Against Epilepsy (ILAE). The diary recorder monitored the participant and recorded the seizure diary in a consistent manner.

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

End point timeframe:

Baseline (28 day observational period) and End of Treatment (28 day treatment period)

| End point values | Rufinamide (E2080) | Placebo | | |
|---|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 28 | 30 | | |
| Units: Percent change | | | | |
| median (full range (min-max)) | | | | |
| Partial Seizure Freq. % Change (n=4,6) | -52.2 (-96.2 to -26.3) | 4.5 (-28.2 to 35.9) | | |
| Absence Seizure Freq. % Change (n=1,0) | 3.4 (3.4 to 3.4) | 0 (0 to 0) | | |
| Atyp. Absence Seizure Freq. % Change (n=12,19) | -59 (-100 to 107.1) | -21.1 (-83.2 to 253.5) | | |
| Myoclonic Seizure Freq. % Change (n=10,10) | -52.35 (-100 to 53.3) | 6.6 (-46.1 to 270) | | |
| Clonic Seizure Freq. % Change (n=1,0) | -81.2 (-81.2 to -81.2) | 0 (0 to 0) | | |
| Tonic Seizure Freq. % Change (n=28,28) | -24.2 (-92.6 to 42.8) | -3.6 (-83.8 to 274.8) | | |
| Tonic-clonic Seizure Freq. % Change (n=2,10) | -57.35 (-100 to -14.7) | 2.35 (-75.8 to 450) | | |
| Atonic Seizure Freq. % Change (n=10,12) | -63.1 (-100 to 68.8) | -6.1 (-100 to 2195.7) | | |
| Uncla. Epileptic Seizure Freq. % Change (n=1,0) | -88.7 (-88.7 to -88.7) | 0 (0 to 0) | | |

Statistical analyses

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|----------------------------|--|
| Statistical analysis title | Analysis for Partial Seizure Frequency |
| Comparison groups | Rufinamide (E2080) v Placebo |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.025 |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Hodges-Lehmann method |
| Point estimate | -57.15 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -104.5 |
| upper limit | -17.3 |

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|---|--|
| Statistical analysis title | Analysis of atypical absence seizure frequency |
| Comparison groups | Placebo v Rufinamide (E2080) |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.128 |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Hodges-Lehmann method |
| Point estimate | -28.65 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -72 |
| upper limit | 0.9 |

| | |
|---|--|
| Statistical analysis title | Analysis for myoclonic seizure frequency |
| Comparison groups | Placebo v Rufinamide (E2080) |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.021 |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Hodges-Lehmann method |
| Point estimate | -54.35 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -126.6 |
| upper limit | -15.4 |

| | |
|-----------------------------------|-------------------------------------|
| Statistical analysis title | Analysis of tonic seizure frequency |
|-----------------------------------|-------------------------------------|

| | |
|---|------------------------------|
| Comparison groups | Rufinamide (E2080) v Placebo |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.031 |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Hodges-Lehmann method |
| Point estimate | -23.2 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -40.7 |
| upper limit | -5.6 |

| | |
|---|---|
| Statistical analysis title | Analysis for Tonic-clonic seizure frequency |
| Comparison groups | Placebo v Rufinamide (E2080) |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.107 |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Hodges-Lehmann method |
| Point estimate | -71.4 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -464.7 |
| upper limit | 30.5 |

| | |
|---|--------------------------------------|
| Statistical analysis title | Analysis of Atonic seizure frequency |
| Comparison groups | Placebo v Rufinamide (E2080) |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.221 |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Hodges-Lehmann method |
| Point estimate | -52.1 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -89.1 |
| upper limit | 10.8 |

Secondary: Clinical Global Impression of Change (CGIC)

| | |
|-----------------|---|
| End point title | Clinical Global Impression of Change (CGIC) |
|-----------------|---|

End point description:

CGIC in participants with Lennox-Gastaut Syndrome relative to placebo was presented as number of participants in each category at the final assessment (last observation carried forward [LOCF]) & at Week 12 of the Treatment Period. The investigator assessed the CGIC by comparing the participants' condition during the 4 weeks immediately before the completion (or discontinuation [d/c]) of the Treatment Period to his/her condition during the 4-week Observation Period (for participants who d/c'd the study during the Treatment Period, the CGIC was assessed by comparing the participant's condition from the start to discontinuation of the study treatment to his/her condition during the 4-week Observation Period).

The CGIC was assessed according to the following 7-grade scale based on the frequency & severity of seizures, adverse events, and overall conditions of daily life.

Markedly improved, Improved, Slightly improved, Unchanged, Slightly worsened, Worsened, Markedly worsened.

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

End point timeframe:

Up to Week 12 of the treatment period

| End point values | Rufinamide (E2080) | Placebo | | |
|---------------------------------------|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 28 | 30 | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| Week 12: Markedly improved (n=25, 29) | 0 | 0 | | |
| Week 12: Improved (n=25, 29) | 9 | 0 | | |
| Week 12: Slightly Improved (n=25, 29) | 4 | 9 | | |
| Week 12: Unchanged (n=25, 29) | 10 | 18 | | |
| Week 12: Slightly Worsened (n=25, 29) | 1 | 1 | | |
| Week 12: Worsened (n=25, 29) | 1 | 1 | | |
| Week 12: Markedly Worsened (n=25, 29) | 0 | 0 | | |
| LOCF: Markedly Improved (n=28, 30) | 3 | 0 | | |
| LOCF: Improved (n=28, 30) | 9 | 0 | | |
| LOCF: Slightly Improved (n=28, 30) | 4 | 9 | | |
| LOCF: Unchanged (n=28, 30) | 10 | 19 | | |
| LOCF: Slightly Worsened (n=28, 30) | 1 | 1 | | |
| LOCF: Worsened (n=28, 30) | 1 | 1 | | |
| LOCF: Markedly Worsened (n=28, 30) | 0 | 0 | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Analysis of Week 12 of the Treatment Period |
| Comparison groups | Rufinamide (E2080) v Placebo |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.041 |
| Method | Wilcoxon (Mann-Whitney) |

| | |
|---|-------------------------------------|
| Statistical analysis title | Analysis of final assessment (LOCF) |
| Comparison groups | Rufinamide (E2080) v Placebo |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.007 |
| Method | Wilcoxon (Mann-Whitney) |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of first dose until date of last dose of study treatment, up to approximately 1 year 2 months

Adverse event reporting additional description:

Treatment-emergent adverse events and treatment-emergent serious adverse events were reported for the safety analysis set, which consisted of participants who registered for the Treatment Period and excludes participants who did not take study drug and those without any evaluable safety data after the start of study treatment.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 13.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Rufinamide (E2080) |
|-----------------------|--------------------|

Reporting group description:

Rufinamide tablets administered orally twice daily after breakfast and dinner. Treatment was divided into a Dose Titration Period (2 weeks) and a Dose Maintenance Period (10 weeks). As a general rule, the dose was increased by 1 step every 2 days until it reached the target maintenance dose determined by body weight at the start of the Observation Period. Target maintenance dose: 15.0 - 30.0 kg: 1000 mg/day (5 tablets each in the morning and evening) 30.1 - 50.0 kg: 1800 mg/day (4 tablets in the morning and 5 in the evening) 50.1 - 70.0 kg: 2400 mg/day (6 tablets each in the morning and evening) ≥ 70.1 kg: 3200 mg/day (8 tablets each in the morning and evening)

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

Reporting group description:

Rufinamide Matching Placebo tablets administered orally twice daily after breakfast and dinner for a total of 12 weeks.

| Serious adverse events | Rufinamide (E2080) | Placebo | |
|---|--------------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 30 (3.33%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Drug eruption | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 30 (3.33%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Rufinamide (E2080) | Placebo | |
|---|--------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 27 / 29 (93.10%) | 21 / 30 (70.00%) | |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Stereotypy | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Investigations | | | |
| Blood Lactate Dehydrogenase Increased | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Blood Pressure Decreased | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Blood Pressure Increased | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 2 | |

| | | | |
|--|----------------|----------------|--|
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lymphocyte Count Decreased | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Platelet Count Decreased | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Excoriation | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 2 | |
| Eye injury | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Subcutaneous Haematoma | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tooth injury | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Nervous system disorders | | | |
| Autism | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Headache | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Complex partial seizures | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Psychomotor Hyperactivity | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Somnolence | | | |
| subjects affected / exposed | 6 / 29 (20.69%) | 2 / 30 (6.67%) | |
| occurrences (all) | 6 | 2 | |
| Status Epilepticus | | | |
| subjects affected / exposed | 8 / 29 (27.59%) | 5 / 30 (16.67%) | |
| occurrences (all) | 9 | 9 | |
| Tonic Convulsion | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal disorders | | | |
| Anal Fissure | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Aphthous Stomatitis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Dental Caries | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 30 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Gingival Bleeding | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Nausea | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 30 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Vomiting | | | |
| subjects affected / exposed | 5 / 29 (17.24%) | 1 / 30 (3.33%) | |
| occurrences (all) | 7 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Eczema | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Purpura | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin chapped | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Heat rash | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Hyperkeratosis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Drug eruption | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Joint Swelling | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 30 (3.33%) | |
| occurrences (all) | 0 | 1 | |
| Gastroenteritis | | | |

| | | | |
|------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 29 (0.00%) | 2 / 30 (6.67%) | |
| occurrences (all) | 0 | 2 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 9 / 29 (31.03%) | 9 / 30 (30.00%) | |
| occurrences (all) | 10 | 9 | |
| Otitis Media | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 30 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 1 / 30 (3.33%) | |
| occurrences (all) | 1 | 1 | |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 4 / 30 (13.33%) | |
| occurrences (all) | 2 | 4 | |
| Metabolism and nutrition disorders | | | |
| Decreased Appetite | | | |
| subjects affected / exposed | 6 / 29 (20.69%) | 2 / 30 (6.67%) | |
| occurrences (all) | 6 | 2 | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 30 (0.00%) | |
| occurrences (all) | 2 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 12 May 2010 | <ul style="list-style-type: none">• Description of the method for examining concomitant drugs was modified.• Date and time of taking E2080 and concomitant AEDs immediately before blood sampling for plasma drug concentration measurements were deleted from the monitoring procedure.• Explanation to the investigator and sub investigator was added. |
| 05 July 2010 | <ul style="list-style-type: none">• Check for blinding of the study drug before packaging the study drug by the allocation manager was deleted.• The study implementation structure of the sponsor and the responsible person were changed.• Matters to be described in the CRF (postponement of dose increase or reduction, and increase in the interval of tapering) were deleted from the identification of the source data. |
| 13 October 2010 | <ul style="list-style-type: none">• Phenobarbital (suppository) was added to rescue drugs for status epilepticus.• The study implementation structure of the sponsor was changed.• Monitors were changed.• Responsible persons at the case registration center, emergency key code control center, and clinical research organization were changed. |
| 11 April 2011 | <ul style="list-style-type: none">• The study implementation structure of the sponsor was changed. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported