



Clinical trial results:

A Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial With an Open-Label Extension Phase of Perampanel as Adjunctive Treatment in Subjects at Least 2 Years of Age With Inadequately Controlled Seizures Associated With Lennox-Gastaut Syndrome

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2014-002321-35 |
| Trial protocol | HU BE LV PL CZ FR IT |
| Global end of trial date | 19 July 2021 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 29 January 2022 |
| First version publication date | 29 January 2022 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | E2007-G000-338 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02834793 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Eisai Ltd. |
| Sponsor organisation address | European Knowledge Centre, Mosquito Way, Hatfield, Hertfordshire, United Kingdom, AL10 9SN |
| Public contact | Eisai Medical Information, Eisai Ltd., 44 845 676 1400, EUMedInfo@eisai.net |
| Scientific contact | Eisai Medical Information, Eisai Ltd., 44 845 676 1400, EUMedInfo@eisai.net |

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? | Yes |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 19 July 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 19 July 2021 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate that perampanel given as adjunctive antiepileptic treatment was superior compared to placebo in reducing the incidence of drop seizures during 18 weeks of treatment in subjects with inadequately controlled seizures associated with Lennox-Gastaut Syndrome (LGS).

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 - European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country, and Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 13 December 2016 |
| 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: 4 |
| Country: Number of subjects enrolled | Belgium: 7 |
| Country: Number of subjects enrolled | Czechia: 1 |
| Country: Number of subjects enrolled | Japan: 19 |
| Country: Number of subjects enrolled | Korea, Republic of: 4 |
| Country: Number of subjects enrolled | United States: 35 |
| Worldwide total number of subjects | 70 |
| EEA total number of subjects | 8 |

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) | 35 |
| 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:

Subjects took part in the study at 40 investigative sites in Australia, Belgium, the Czech Republic, Japan, India, South Korea, and the United States from 13 December 2016 to 19 July 2021. A total of 101 subjects were enrolled (signed informed consent) and 70 subjects were randomized to receive study treatment in Core Study.

Pre-assignment

Screening details:

This study included a Core Study Phase and an Extension Phase, which in turn consisted of Extension A and Extension B. Study was terminated early by the sponsor due to recruitment challenges that was further impacted by the COVID-19 pandemic.

Period 1

| | |
|------------------------------|--|
| Period 1 title | Core Study (Up to 18 Weeks) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Carer, Assessor |

Arms

| | |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Core Study: Placebo |

Arm description:

Subjects received placebo matched to perampanel oral tablets or placebo matched to perampanel oral suspension (formulation was selected based on the subject's condition and at the discretion of the investigator), once daily at bedtime during the titration period. During the maintenance period, subjects continued to receive the placebo matched to perampanel tablets or placebo matched to perampanel oral suspension at dose level that was administered at the end of the titration period. The total duration of the titration period (6 weeks) and maintenance period (12 weeks) in Core Study was 18 weeks.

| | |
|--|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo matched to perampanel oral suspension |
| Investigational medicinal product code | |
| Other name | E2007 |
| Pharmaceutical forms | Oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received placebo matched to perampanel oral suspension, once daily at bedtime during Titration Period for up to 6 weeks. During the Maintenance Period, subjects continued to receive the placebo matched to perampanel oral suspension dose level that was administered at the end of the Titration Period for up to 12 weeks.

| | |
|--|--------------------------------------|
| Investigational medicinal product name | Placebo matched to perampanel tablet |
| Investigational medicinal product code | |
| Other name | E2007 |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received placebo matched to perampanel 2 mg, oral tablet, once daily at bedtime during Titration Period for up to 6 weeks. During the Maintenance Period, subjects continued to receive the placebo matched to perampanel tablet at dose level that was administered at the end of the Titration Period for up to 12 weeks.

| | |
|------------------|------------------------|
| Arm title | Core Study: Perampanel |
|------------------|------------------------|

Arm description:

Subjects received starting dose of perampanel, one 2 milligram (mg) oral tablet or 4 milliliter (mL) oral

suspension (containing 2 mg perampanel), once daily at bedtime then up-titrated weekly in 2 mg increments to a target dose of 8 milligram per day (mg/day) during titration period. During the maintenance period, subjects continued to receive the perampanel dose level that was administered at the end of the titration period. The total duration of the titration period (6 weeks) and maintenance period (12 weeks) in the Core Study was 18 weeks.

| | |
|--|----------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Perampanel oral suspension |
| Investigational medicinal product code | |
| Other name | E2007 |
| Pharmaceutical forms | Oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received starting dose of perampanel 4 mL oral suspension (containing 2 mg perampanel) once daily at bedtime then up-titrated in 2-mg increments to a target dose of 8 mg/day during Titration Period for up to 6 weeks. During the Maintenance Period, subjects continued to receive the perampanel dose level that was administered at the end of the Titration Period for up to 12 weeks.

| | |
|--|------------------------|
| Investigational medicinal product name | Perampanel oral tablet |
| Investigational medicinal product code | |
| Other name | E2007 |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received starting dose of perampanel, 2 mg, oral tablet, once daily at bedtime then up-titrated in 2-mg increments to a target dose of 8 milligram per day (mg/day) during Titration Period for up to 6 weeks. During the Maintenance Period, subjects continued to receive the perampanel dose level that was administered at the end of the Titration Period for up to 12 weeks.

| Number of subjects in period 1 | Core Study: Placebo | Core Study: Perampanel |
|---------------------------------------|---------------------|------------------------|
| Started | 36 | 34 |
| Completed | 32 | 29 |
| Not completed | 4 | 5 |
| Consent withdrawn by subject | 1 | 1 |
| Adverse event, non-fatal | - | 3 |
| Subject Choice | 1 | - |
| Study terminated by sponsor | - | 1 |
| Lost to follow-up | 1 | - |
| Lack of efficacy | 1 | - |

Period 2

| | |
|------------------------------|------------------------------------|
| Period 2 title | Extension Phase A (up to 52 Weeks) |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------|-------------------------------|
| Arm title | Extension Phase A: Perampanel |
|------------------|-------------------------------|

Arm description:

Subjects who completed the Core Study and who were eligible entered into Extension Phase A. Subjects previously assigned to perampanel arm (Core Study) continued taking study medication at the dose received during the Core maintenance period, and subjects previously assigned to a placebo arm (Core Study) started perampanel dose as one 2 mg tablet or 4 mL oral suspension (containing 2 mg perampanel) once daily at bedtime, then up-titrated weekly in 2-mg increments up to a maximum dose of 8 mg/day for 6 weeks conversion period of Extension Phase A. After the conversion period, subjects could be titrated up to 12 mg/day in 2-week intervals during the maintenance period (46 weeks) of Extension Phase A as per the investigator's discretion. The total duration of the conversion period and maintenance period in Extension Phase A was 52 weeks.

| | |
|--|----------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Perampanel oral suspension |
| Investigational medicinal product code | |
| Other name | E2007 |
| Pharmaceutical forms | Oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

During Extension Phase A conversion period, subjects previously assigned to a placebo arm (in Core Study) received perampanel 4 mL oral suspension (containing 2 mg perampanel) once daily at bedtime, then up-titrated in 2 mg increments to a target dose of 8 mg/day, and subjects previously assigned to perampanel arm (Core Study) continued taking study medication at the dose received during the Core Maintenance Period. After the 6 weeks conversion period, subjects could be titrated up to 12 mg/day in 2-week intervals during the Maintenance Period (up to 46 weeks) of Extension Phase A.

| | |
|--|------------------------|
| Investigational medicinal product name | Perampanel oral tablet |
| Investigational medicinal product code | |
| Other name | E2007 |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

During Extension Phase A conversion period, subjects previously assigned to a placebo arm (in Core Study) received perampanel, 2 mg, oral tablet, once daily at bedtime then up-titrated in 2 mg increments to a target dose of 8 milligram per day (mg/day), and subjects previously assigned to perampanel arm (Core Study) continued taking study medication at the dose received during the Core Maintenance Period. After the 6 weeks conversion period, subjects could be titrated up to 12 mg/day in 2-week intervals during the Maintenance Period (up to 46 weeks) of Extension Phase A.

| Number of subjects in period 2^[1] | Extension Phase A: Perampanel |
|---|-------------------------------|
| Started | 58 |
| Completed | 32 |
| Not completed | 26 |
| Consent withdrawn by subject | 4 |
| Adverse event, non-fatal | 5 |
| Subject Choice | 3 |
| Not Specified | 1 |
| Study terminated by sponsor | 9 |
| Lack of efficacy | 4 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Subjects who completed the Core Study had the option to roll over into Extension Phase A.

Period 3

| | |
|------------------------------|-------------------------------------|
| Period 3 title | Extension Phase B (up to 188 Weeks) |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------|-------------------------------|
| Arm title | Extension Phase B: Perampanel |
|------------------|-------------------------------|

Arm description:

Subjects who completed Extension Phase A and who were eligible entered into Extension Phase B. Subjects received perampanel at their optimal perampanel dose (that is, dose maintained at the end of Extension A) until perampanel was available commercially or accessible via extended access program (EAP) (in the country in which a subject resides) or unless study termination by the sponsor (up to 188 weeks).

| | |
|--|----------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Perampanel oral suspension |
| Investigational medicinal product code | |
| Other name | E2007 |
| Pharmaceutical forms | Oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received perampanel, oral suspension at their optimal dose (that is, dose maintained at the end of Extension A) up to 188 weeks.

| | |
|--|------------------------|
| Investigational medicinal product name | Perampanel oral tablet |
| Investigational medicinal product code | |
| Other name | E2007 |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received perampanel tablet, orally at their optimal dose (that is, dose maintained at the end of Extension A) up to 188 weeks.

| Number of subjects in period 3^[2] | Extension Phase B: Perampanel |
|---|-------------------------------|
| Started | 13 |
| Completed | 1 |
| Not completed | 12 |
| Adverse event, non-fatal | 1 |
| Subject Choice | 1 |
| Not Specified | 1 |
| Study terminated by sponsor | 8 |
| Lack of efficacy | 1 |

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Subjects who completed Extension Phase A and who were eligible entered into Extension Phase B.

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Core Study: Placebo |
|-----------------------|---------------------|

Reporting group description:

Subjects received placebo matched to perampanel oral tablets or placebo matched to perampanel oral suspension (formulation was selected based on the subject's condition and at the discretion of the investigator), once daily at bedtime during the titration period. During the maintenance period, subjects continued to receive the placebo matched to perampanel tablets or placebo matched to perampanel oral suspension at dose level that was administered at the end of the titration period. The total duration of the titration period (6 weeks) and maintenance period (12 weeks) in Core Study was 18 weeks.

| | |
|-----------------------|------------------------|
| Reporting group title | Core Study: Perampanel |
|-----------------------|------------------------|

Reporting group description:

Subjects received starting dose of perampanel, one 2 milligram (mg) oral tablet or 4 milliliter (mL) oral suspension (containing 2 mg perampanel), once daily at bedtime then up-titrated weekly in 2 mg increments to a target dose of 8 milligram per day (mg/day) during titration period. During the maintenance period, subjects continued to receive the perampanel dose level that was administered at the end of the titration period. The total duration of the titration period (6 weeks) and maintenance period (12 weeks) in the Core Study was 18 weeks.

| Reporting group values | Core Study: Placebo | Core Study: Perampanel | Total |
|---|---------------------|------------------------|-------|
| Number of subjects | 36 | 34 | 70 |
| 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) | 19 | 16 | 35 |
| Adolescents (12-17 years) | 7 | 6 | 13 |
| Adults (18-64 years) | 10 | 12 | 22 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: years | | | |
| arithmetic mean | 13.3 | 14.7 | |
| standard deviation | ± 7.80 | ± 10.37 | - |
| Sex: Female, Male Units: subjects | | | |
| Female | 13 | 17 | 30 |
| Male | 23 | 17 | 40 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 13 | 13 | 26 |
| Native Hawaiian or Other Pacific Islander | 1 | 0 | 1 |
| Black or African American | 4 | 2 | 6 |
| White | 15 | 16 | 31 |
| More than one race | 0 | 0 | 0 |

| | | | |
|-------------------------|----|----|----|
| Unknown or Not Reported | 3 | 3 | 6 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 5 | 4 | 9 |
| Not Hispanic or Latino | 31 | 30 | 61 |
| Unknown or Not Reported | 0 | 0 | 0 |

Subject analysis sets

| | |
|----------------------------|-----------------------------|
| Subject analysis set title | Extension Phase: Perampanel |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

Subjects who completed Core Study entered Extension A. Subjects who received perampanel in Core Study, continued at dose received during Core maintenance period, and subjects who received placebo in Core Study started perampanel dose as one 2 mg oral tablet or 4 mL oral suspension (containing 2 mg perampanel) once daily at bedtime, then up-titrated weekly in 2-mg increments up to dose of 8 mg/day for 6 weeks conversion period. After conversion period, subjects could be titrated up to 12 mg/day in 2-week intervals during maintenance period (46 weeks) as per investigator's discretion. Total duration of conversion and maintenance period in Extension Phase A was 52 weeks. Subjects who completed Extension A had option to enter into Extension B in countries where extended access program (EAP) could not be implemented, and received perampanel at optimal dose(dose at end of Extension A) until perampanel was available commercially or unless study termination(up to 188 weeks).

| Reporting group values | Extension Phase: Perampanel | | |
|---|--------------------------------|--|--|
| Number of subjects | 58 | | |
| 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) | 30 | | |
| Adolescents (12-17 years) | 10 | | |
| Adults (18-64 years) | 18 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 13.3 | | |
| standard deviation | ± 8.17 | | |
| Sex: Female, Male | | | |
| Units: subjects | | | |
| Female | 24 | | |
| Male | 34 | | |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | | | |
| Asian | 23 | | |
| Native Hawaiian or Other Pacific Islander | 1 | | |
| Black or African American | 5 | | |
| White | 24 | | |

| | | | |
|-------------------------|----|--|--|
| More than one race | 0 | | |
| Unknown or Not Reported | 5 | | |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 6 | | |
| Not Hispanic or Latino | 52 | | |
| Unknown or Not Reported | 0 | | |

End points

End points reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Core Study: Placebo |
|-----------------------|---------------------|

Reporting group description:

Subjects received placebo matched to perampanel oral tablets or placebo matched to perampanel oral suspension (formulation was selected based on the subject's condition and at the discretion of the investigator), once daily at bedtime during the titration period. During the maintenance period, subjects continued to receive the placebo matched to perampanel tablets or placebo matched to perampanel oral suspension at dose level that was administered at the end of the titration period. The total duration of the titration period (6 weeks) and maintenance period (12 weeks) in Core Study was 18 weeks.

| | |
|-----------------------|------------------------|
| Reporting group title | Core Study: Perampanel |
|-----------------------|------------------------|

Reporting group description:

Subjects received starting dose of perampanel, one 2 milligram (mg) oral tablet or 4 milliliter (mL) oral suspension (containing 2 mg perampanel), once daily at bedtime then up-titrated weekly in 2 mg increments to a target dose of 8 milligram per day (mg/day) during titration period. During the maintenance period, subjects continued to receive the perampanel dose level that was administered at the end of the titration period. The total duration of the titration period (6 weeks) and maintenance period (12 weeks) in the Core Study was 18 weeks.

| | |
|-----------------------|-------------------------------|
| Reporting group title | Extension Phase A: Perampanel |
|-----------------------|-------------------------------|

Reporting group description:

Subjects who completed the Core Study and who were eligible entered into Extension Phase A. Subjects previously assigned to perampanel arm (Core Study) continued taking study medication at the dose received during the Core maintenance period, and subjects previously assigned to a placebo arm (Core Study) started perampanel dose as one 2 mg tablet or 4 mL oral suspension (containing 2 mg perampanel) once daily at bedtime, then up-titrated weekly in 2-mg increments up to a maximum dose of 8 mg/day for 6 weeks conversion period of Extension Phase A. After the conversion period, subjects could be titrated up to 12 mg/day in 2-week intervals during the maintenance period (46 weeks) of Extension Phase A as per the investigator's discretion. The total duration of the conversion period and maintenance period in Extension Phase A was 52 weeks.

| | |
|-----------------------|-------------------------------|
| Reporting group title | Extension Phase B: Perampanel |
|-----------------------|-------------------------------|

Reporting group description:

Subjects who completed Extension Phase A and who were eligible entered into Extension Phase B. Subjects received perampanel at their optimal perampanel dose (that is, dose maintained at the end of Extension A) until perampanel was available commercially or accessible via extended access program (EAP) (in the country in which a subject resides) or unless study termination by the sponsor (up to 188 weeks).

| | |
|----------------------------|-----------------------------|
| Subject analysis set title | Extension Phase: Perampanel |
|----------------------------|-----------------------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Subjects who completed Core Study entered Extension A. Subjects who received perampanel in Core Study, continued at dose received during Core maintenance period, and subjects who received placebo in Core Study started perampanel dose as one 2 mg oral tablet or 4 mL oral suspension (containing 2 mg perampanel) once daily at bedtime, then up-titrated weekly in 2-mg increments up to dose of 8 mg/day for 6-week conversion period. After conversion period, subjects could be titrated up to 12 mg/day in 2-week intervals during maintenance period (46 weeks) as per investigator's discretion. Total duration of conversion and maintenance period in Extension Phase A was 52 weeks. Subjects who completed Extension A had option to enter into Extension B in countries where extended access program (EAP) could not be implemented, and received perampanel at optimal dose(dose at end of Extension A) until perampanel was available commercially or unless study termination(up to 188 weeks).

Primary: Core Study: Median Percent Change in Drop Seizure Frequency per 28 Days During Double-blind Treatment Relative to the Prerandomization Phase (Baseline)

| | |
|-----------------|---|
| End point title | Core Study: Median Percent Change in Drop Seizure Frequency per 28 Days During Double-blind Treatment Relative to the Prerandomization Phase (Baseline) |
|-----------------|---|

End point description:

Drop seizure was defined as a drop attack or spell involving the entire body, trunk, or head that led to a fall, injury, slumping in a chair, or the subject's head hitting a surface or that could have led to a fall or injury, depending on the subject's position at the time of the attack or spell. The Full Analysis Set (FAS)

was the group of randomized subjects who received at least one dose of the study drug and had at least one post-dose seizure measurement.

| | |
|-------------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Baseline up to 18 weeks | |

| End point values | Core Study: Placebo | Core Study: Perampanel | | |
|-------------------------------|------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36 | 34 | | |
| Units: percent change | | | | |
| median (full range (min-max)) | | | | |
| Prerandomization (Baseline) | 77.65 (7.5 to 481.1) | 46.56 (6.2 to 645.0) | | |
| Treatment Period | -4.51 (-86.2 to 201.8) | -23.07 (-96.4 to 371.4) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Prerandomization, Treatment Period |
| Statistical analysis description: | |
| The median difference to placebo and the 95 percent (%) confidence interval (CI) were based on the Hodges-Lehmann method. | |
| Comparison groups | Core Study: Placebo v Core Study: Perampanel |
| Number of subjects included in analysis | 70 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.107 ^[1] |
| Method | ANCOVA |
| Parameter estimate | Median difference (net) |
| Point estimate | -19.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -49.2 |
| upper limit | 4.8 |

Notes:

[1] - The p-value was based on a rank analysis of covariance (ANCOVA) with treatment, region, and age-group as factors, and prerandomization drop seizure frequency as a covariate.

Secondary: Core Study: Median Percent Change in Total Seizure Frequency per 28 Days During Double-blind Treatment Relative to the Prerandomization Phase (Baseline)

| | |
|-----------------|--|
| End point title | Core Study: Median Percent Change in Total Seizure Frequency per 28 Days During Double-blind Treatment Relative to the Prerandomization Phase (Baseline) |
|-----------------|--|

End point description:

Total seizure was the number of seizures assessed and recorded by the subject's parent(s)/caregiver(s) in the subject seizure diary. Seizure diaries was used to collect seizure counts and types. The FAS was the group of randomized subjects who received at least one dose of the study drug and had at least one

post-dose seizure measurement.

| | |
|-------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to 18 weeks | |

| End point values | Core Study: Placebo | Core Study: Perampanel | | |
|-----------------------------------|----------------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36 | 34 | | |
| Units: percent change | | | | |
| median (full range (min-max)) | | | | |
| Prerandomization Phase (Baseline) | 110.76 (17.6 to 1754.3) | 142.55 (15.3 to 6858.0) | | |
| Treatment Period | -6.53 (-63.6 to 266.8) | -18.23 (-96.9 to 103.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study: Percentage of Subjects with 50 Percent (%) Response in the Maintenance Period of the Double-blind Treatment Phase Relative to the Prerandomization Phase (Baseline) for Drop Seizures

| | |
|-----------------|---|
| End point title | Core Study: Percentage of Subjects with 50 Percent (%) Response in the Maintenance Period of the Double-blind Treatment Phase Relative to the Prerandomization Phase (Baseline) for Drop Seizures |
|-----------------|---|

End point description:

Drop seizure was defined as a drop attack or spell involving the entire body, trunk, or head that led to a fall, injury, slumping in a chair, or the subject's head hitting a surface or that could have led to a fall or injury, depending on the subject's position at the time of the attack or spell. A responder was a subject who experienced a 50% or greater reduction in drop seizure frequency per 28 days during Maintenance from prerandomization. The FAS was the group of randomized subjects who received at least one dose of the study drug and had at least one post-dose seizure measurement.

| | |
|-------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to 18 weeks | |

| End point values | Core Study: Placebo | Core Study: Perampanel | | |
|-------------------------------|------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36 | 34 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 25.0 | 44.1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study: Percentage of Subjects with 50% Response in the Maintenance Period of the Double-blind Treatment Phase Relative to the Prerandomization Phase (Baseline) for Total Seizures

| | |
|-----------------|---|
| End point title | Core Study: Percentage of Subjects with 50% Response in the Maintenance Period of the Double-blind Treatment Phase Relative to the Prerandomization Phase (Baseline) for Total Seizures |
|-----------------|---|

End point description:

Total seizure was the number of seizures assessed and recorded by the subject's parent(s)/caregiver(s) in the subject seizure diary. Seizure diaries was used to collect seizure counts and types. A responder was a subject who experienced a 50% or greater reduction in drop seizure frequency per 28 days during Maintenance from prerandomization. The FAS was the group of randomized subjects who received at least one dose of study drug and had at least one post-dose seizure measurement.

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

End point timeframe:

Baseline up to 18 weeks

| End point values | Core Study: Placebo | Core Study: Perampanel | | |
|-------------------------------|---------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36 | 34 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 16.7 | 32.4 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study: Median Percent Change in Non-drop Seizure Frequency per 28 Days During Double-blind Treatment Phase Relative to the Prerandomization Phase (Baseline)

| | |
|-----------------|---|
| End point title | Core Study: Median Percent Change in Non-drop Seizure Frequency per 28 Days During Double-blind Treatment Phase Relative to the Prerandomization Phase (Baseline) |
|-----------------|---|

End point description:

Non-drop seizures were defined as non-drop attacks or spells. Drop attacks and spells involved the entire body, trunk, or head and lead to a fall, injury, slumping in a chair, or the subject's head hitting a surface, or could lead to a fall or injury, depending on the subject's position at the time of the attack or spell. The FAS was the group of randomized subjects who received at least one dose of study drug and had at least one post-dose seizure measurement. Here number of subjects analysed were subjects who were evaluable for the end point.

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

End point timeframe:

Baseline up to 18 weeks

| End point values | Core Study: Placebo | Core Study: Perampanel | | |
|-------------------------------|---------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 27 | | |
| Units: percent change | | | | |
| median (full range (min-max)) | | | | |
| Prerandomization (Baseline) | 53.37 (1.1 to 1746.8) | 88.10 (1.0 to 6531.0) | | |
| Treatment Phase | -13.21 (-100.0 to 2288.1) | -12.33 (-98.7 to 63.2) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study: Percentage of Subjects with 75% Response in the Maintenance Period of the Double-blind Treatment Phase Relative to the Prerandomization Phase (Baseline) for Drop Seizures, Non-drop Seizures and Total Seizures

| | |
|-----------------|--|
| End point title | Core Study: Percentage of Subjects with 75% Response in the Maintenance Period of the Double-blind Treatment Phase Relative to the Prerandomization Phase (Baseline) for Drop Seizures, Non-drop Seizures and Total Seizures |
|-----------------|--|

End point description:

Drop seizure was defined as a drop attack or spell involving the entire body, trunk, or head that led to a fall, injury, slumping in a chair, or the subject's head hitting a surface or that could have led to a fall or injury, depending on the subject's position at the time of the attack or spell. Non-drop seizures were defined as non-drop attacks or spells. Total seizure was the number of seizures assessed and recorded by the subject's parent(s)/caregiver(s) in the subject seizure diary. Seizure diaries was used to collect seizure counts and types. A responder was a subject who experienced a 75% or greater reduction in drop seizure/non-drop seizure/ frequency per 28 days during Maintenance from prerandomization. Here number analysed (n) were subjects who were evaluable for the end point at given categories. The FAS was the group of randomized subjects who received at least one dose of the study drug and had at least one post-dose seizure measurement.

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

End point timeframe:

Baseline up to 18 weeks

| End point values | Core Study: Placebo | Core Study: Perampanel | | |
|--------------------------------|---------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36 | 34 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Drop Seizures (n = 36, 34) | 13.9 | 26.5 | | |
| Non-drop Seizures (n = 30, 27) | 10.0 | 18.5 | | |
| Total Seizures (n = 36, 34) | 0 | 11.8 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study: Percentage of Subjects with 100% Response in the Maintenance Period of the Double-blind Treatment Phase Relative to the Prerandomization Phase (Baseline) for Drop Seizures, Non-drop Seizures and Total Seizures

| | |
|-----------------|---|
| End point title | Core Study: Percentage of Subjects with 100% Response in the Maintenance Period of the Double-blind Treatment Phase Relative to the Prerandomization Phase (Baseline) for Drop Seizures, Non-drop Seizures and Total Seizures |
|-----------------|---|

End point description:

Drop seizure was defined as a drop attack or spell involving the entire body, trunk, or head that led to a fall, injury, slumping in a chair, or the subject's head hitting a surface or that could have led to a fall or injury, depending on the subject's position at the time of the attack or spell. Non-drop seizures were defined as non-drop attacks or spells. Total seizure was the number of seizures assessed and recorded by the subject's parent(s)/caregiver(s) in the subject seizure diary. Seizure diaries was used to collect seizure counts and types. A responder was a subject who experienced a 100% or greater reduction in drop seizure/non-drop seizure/ frequency per 28 days during Maintenance from prerandomization. Here number analysed (n) were subjects who were evaluable for the end point at given categories. The FAS was the group of randomized subjects who received at least one dose of the study drug and had at least one post-dose seizure measurement.

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

End point timeframe:

Baseline up to 18 weeks

| End point values | Core Study: Placebo | Core Study: Perampanel | | |
|-------------------------------|---------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36 | 34 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Drop Seizure (n = 36, 34) | 0 | 2.9 | | |
| Non-drop Seizure (n = 31, 28) | 6.5 | 3.6 | | |
| Total Seizures (n = 36, 34) | 0 | 2.9 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study: Percentage of Subjects with 50% Response in the Maintenance Period of the Double-blind Treatment Phase Relative to the Prerandomization Phase (Baseline) for Non-drop Seizures

| | |
|-----------------|--|
| End point title | Core Study: Percentage of Subjects with 50% Response in the Maintenance Period of the Double-blind Treatment Phase Relative to the Prerandomization Phase (Baseline) for Non-drop Seizures |
|-----------------|--|

End point description:

Non-drop seizures were defined as non-drop attacks or spells. Drop attacks and spells involved the entire body, trunk, or head and lead to a fall, injury, slumping in a chair, or the subject's head hitting a surface, or could lead to a fall or injury, depending on the subject's position at the time of the attack or spell. A responder was a subject who experienced a 50% or greater reduction in non-drop seizure

frequency per 28 days during Maintenance from prandomization. Here number of subjects analysed were subjects who were evaluable for the end point. The FAS was the group of randomized subjects who received at least one dose of the study drug and had at least one post-dose seizure measurement.

| | |
|-------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to 18 weeks | |

| End point values | Core Study: Placebo | Core Study: Perampanel | | |
|-------------------------------|---------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 27 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 16.7 | 44.4 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study: Percentage of Subjects With Clinical Global Impression of Change Scores (CGIC) in the Double-blind Treatment Phase

| | |
|-----------------|--|
| End point title | Core Study: Percentage of Subjects With Clinical Global Impression of Change Scores (CGIC) in the Double-blind Treatment Phase |
|-----------------|--|

End point description:

Assessment of disease severity utilized the CGIC scale at end of treatment to evaluate subjects change in disease status from baseline. The CGIC is a 7-point likert scale that measures a physician's global impression of a subjects clinical condition. Scale ranged from 1 to 7 with lower score indicated improvement (1=very much improved, 2=much improved, 3=minimally improved), higher score indicated worsening (5=minimally worse, 6= much worse, 7=very much worse), and a score of 4 indicated no change. Here number of subjects analysed were subjects who were evaluable for the end point. The FAS was the group of randomized subjects who received at least one dose of study drug and had at least one post-dose seizure measurement.

| | |
|-------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to 18 weeks | |

| End point values | Core Study: Placebo | Core Study: Perampanel | | |
|-------------------------------|---------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 35 | 32 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Very much improved | 0 | 9.4 | | |
| Much improved | 8.6 | 15.6 | | |
| Minimally improved | 25.7 | 18.8 | | |
| No change | 57.1 | 34.4 | | |
| Minimally worse | 5.7 | 12.5 | | |

| | | | | |
|-----------------|-----|-----|--|--|
| Much worse | 2.9 | 9.4 | | |
| Very much worse | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with any Treatment-emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

| | |
|-----------------|---|
| End point title | Number of Subjects with any Treatment-emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs) |
|-----------------|---|

End point description:

TEAE was defined as an adverse event with an onset date, or a worsening in severity from baseline (pre-treatment), on or after the first dose of study drug up to 28 days following study drug discontinuation. AE was defined as any untoward medical occurrence or clinical investigation in a subject administered an investigational product. AE does not necessarily have a causal relationship with a medicinal product. SAE was defined as any AE if resulted in death or life-threatening AE or required inpatient hospitalization or prolongation of existing hospitalization or resulted in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions or was a congenital anomaly/birth defect. Subject Analysis Set (SAS) was group of subjects who received at least one dose of study drug and had at least one post-dose safety assessment. As per the planned safety analysis, safety data for Extension A and B were reported in a single arm of Extension Phase.

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

End point timeframe:

From the date of the first administration of the study drug up to 28 days after the last dose of the study drug (up to 192 weeks)

| End point values | Core Study: Placebo | Core Study: Perampanel | Extension Phase: Perampanel | |
|-----------------------------|---------------------|------------------------|-----------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 36 | 34 | 58 | |
| Units: subjects | | | | |
| TEAEs | 26 | 29 | 50 | |
| SAEs | 1 | 6 | 11 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Markedly Abnormal Laboratory Values

| | |
|-----------------|--|
| End point title | Number of Subjects With Treatment-emergent Markedly Abnormal Laboratory Values |
|-----------------|--|

End point description:

Treatment-emergent markedly abnormal value for laboratory values was based Common Terminology Criteria for Adverse events (CTCAE) Version 4.0, and determined as if the post baseline CTCAE Version 4.0 grade increases from baseline and the post baseline grade was ≥ 2 (≥ 3 for phosphate).

Laboratory tests included: Hematology count with differential, Chemistry (Electrolytes, Liver function tests, Renal function parameters, Other: albumin, cholesterol, glucose. SAS was group of subjects who received at least one dose of study drug and had at least one post-dose safety assessment.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From the date of the first administration of the study drug up to 28 days after the last dose of the study drug (up to 192 weeks) | |

| End point values | Core Study: Placebo | Core Study: Perampanel | Extension Phase: Perampanel | |
|--|---------------------|------------------------|-----------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 36 | 34 | 58 | |
| Units: subjects | | | | |
| Markedly Abnormal Low: Platelets | 1 | 0 | 0 | |
| Markedly Abnormal Low: Neutrophils | 0 | 1 | 7 | |
| Markedly Abnormal High: Gamma Glutamyl Transferase | 1 | 1 | 2 | |
| Markedly Abnormal Low: Bicarbonate | 0 | 1 | 1 | |
| Markedly Abnormal High: Sodium | 0 | 1 | 1 | |
| Markedly Abnormal Low: Albumin | 0 | 1 | 0 | |
| Markedly Abnormal High: Cholesterol | 0 | 1 | 1 | |
| Markedly Abnormal High: Triglycerides | 2 | 1 | 4 | |
| Markedly Abnormal Low: Haemoglobin | 0 | 0 | 1 | |
| Markedly Abnormal Low: Lymphocytes | 0 | 0 | 2 | |
| Markedly Abnormal Low: Leukocytes | 0 | 0 | 1 | |
| Markedly Abnormal High: Alanine Aminotransferase | 0 | 0 | 1 | |
| Markedly Abnormal Low: Glucose | 0 | 0 | 1 | |
| Markedly Abnormal High: Alkaline Phosphatase | 0 | 0 | 1 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Vital Signs

| | |
|--|--|
| End point title | Number of Subjects With Clinically Significant Vital Signs |
| End point description: | |
| Clinically significant means that a value must have met both the criterion value and satisfied the magnitude of change relative to baseline. Vital sign parameters included systolic blood pressure (BP), diastolic BP, pulse rate. SAS was group of subjects who received at least one dose of the study drug and had at least one post-dose safety assessment. | |
| End point type | Secondary |
| End point timeframe: | |
| From the date of the first administration of the study drug up to 28 days after the last dose of the study drug (up to 192 weeks) | |

| End point values | Core Study: Placebo | Core Study: Perampanel | Extension Phase: Perampanel | |
|--------------------------------|------------------------|---------------------------|-----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 36 | 34 | 58 | |
| Units: subjects | | | | |
| Systolic Blood Pressure: Low | 4 | 2 | 7 | |
| Systolic Blood Pressure: High | 0 | 0 | 0 | |
| Diastolic Blood Pressure: Low | 5 | 1 | 13 | |
| Diastolic Blood Pressure: High | 0 | 0 | 0 | |
| Pulse Rate: Low | 1 | 0 | 2 | |
| Pulse Rate: High | 4 | 5 | 11 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Core Study: Model Predicted Average Perampanel Concentrations at Steady State (Cav,ss) During the Maintenance Period of Core Study

| | |
|------------------------|--|
| End point title | Core Study: Model Predicted Average Perampanel Concentrations at Steady State (Cav,ss) During the Maintenance Period of Core Study |
| End point description: | Due to the early termination of the study resulting in reduced sample size and the variability in treatment response, population PK analysis and population PK/PD modeling planned for this study were not conducted and hence data was not collected and analyzed for this end point. |
| End point type | Secondary |
| End point timeframe: | Up to Week 18 |

| End point values | Core Study: Placebo | Core Study: Perampanel | | |
|---|------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[2] | 0 ^[3] | | |
| Units: nanogram*hour per milliliter (ng*h/mL) | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[2] - Pharmacokinetic analysis for this study was not conducted due to the early termination of the study.

[3] - Pharmacokinetic analysis for this study was not conducted due to the early termination of the study.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of first administration of study drug up to 28 days after last dose of study drug (up to 192 weeks)

Adverse event reporting additional description:

Subjects received varying doses in Extension Phase depending on tolerance but as target dose was defined as 12 mg/day for all subjects, AEs were summarized as a single arm. As per the planned safety analysis of Extension Phase, safety data for Extension A and Extension B was reported together in a single arm of Extension Phase.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 24.0 |

Reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | Core Study: Perampanel |
|-----------------------|------------------------|

Reporting group description:

Subjects received starting dose of perampanel, one 2 mg oral tablet or 4 mL oral suspension (containing 2 mg perampanel), once daily at bedtime then up-titrated weekly in 2 mg increments to a target dose of 8 mg/day during titration period. During the maintenance period, subjects continued to receive the perampanel dose level that was administered at the end of the titration period. The total duration of the titration period (6 weeks) and maintenance period (12 weeks) in the Core Study was 18 weeks.

| | |
|-----------------------|---------------------|
| Reporting group title | Core Study: Placebo |
|-----------------------|---------------------|

Reporting group description:

Subjects received placebo matched to perampanel oral tablets or placebo matched to perampanel oral suspension (formulation was selected based on the subject's condition and at the discretion of the investigator), once daily at bedtime during the titration period. During the maintenance period, subjects continued to receive the placebo matched to perampanel tablets or placebo matched to perampanel oral suspension at dose level that was administered at the end of the titration period. The total duration of the titration period (6 weeks) and maintenance period (12 weeks) in Core Study was 18 weeks.

| | |
|-----------------------|-----------------------------|
| Reporting group title | Extension Phase: Perampanel |
|-----------------------|-----------------------------|

Reporting group description:

Subjects who completed Core Study entered Extension A. Subjects who received perampanel in Core Study, continued at dose received during Core maintenance period, and subjects who received placebo in Core Study started perampanel dose as one 2 mg oral tablet or 4 mL oral suspension (containing 2 mg perampanel) once daily at bedtime, then up-titrated weekly in 2 mg increments up to dose of 8 mg/day for 6 weeks conversion period. After conversion period, subjects could be titrated up to 12 mg/day in 2-week intervals during maintenance period (46 weeks) as per investigator's discretion. Total duration of conversion and maintenance period in Extension Phase A was 52 weeks. Subjects who completed Extension A had option to enter into Extension B in countries where extended access program (EAP) could not be implemented, and received perampanel at optimal dose(dose at end of Extension A) until perampanel was available commercially or unless study termination(up to 188 weeks).

| Serious adverse events | Core Study: Perampanel | Core Study: Placebo | Extension Phase: Perampanel |
|---|---------------------------|---------------------|--------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 34 (17.65%) | 1 / 36 (2.78%) | 11 / 58 (18.97%) |
| number of deaths (all causes) | 0 | 0 | 2 |
| number of deaths resulting from adverse events | 0 | 0 | 2 |
| Nervous system disorders | | | |
| Epilepsy | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 36 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 36 (0.00%) | 2 / 58 (3.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lethargy | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 36 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Quadriplegia | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 36 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure cluster | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 36 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Microcytic anaemia | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 36 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cytogenetic abnormality | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 36 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| General disorders and administration site conditions | | | |
| Sudden unexplained death in epilepsy | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 36 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |

| | | | |
|---|----------------|----------------|----------------|
| Gastrointestinal disorders | | | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 36 (2.78%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 36 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 36 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dental caries | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 36 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumatosis intestinalis | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 36 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 36 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 36 (2.78%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 36 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Cough | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 36 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 36 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 36 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 36 (2.78%) | 3 / 58 (5.17%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory syncytial virus infection | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 36 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 36 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infected skin ulcer | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 36 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 36 (0.00%) | 2 / 58 (3.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Lower respiratory tract infection viral subjects affected / exposed | 0 / 34 (0.00%) | 0 / 36 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis subjects affected / exposed | 0 / 34 (0.00%) | 0 / 36 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed | 1 / 34 (2.94%) | 0 / 36 (0.00%) | 1 / 58 (1.72%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration subjects affected / exposed | 1 / 34 (2.94%) | 0 / 36 (0.00%) | 0 / 58 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Core Study: Perampanel | Core Study: Placebo | Extension Phase: Perampanel |
|---|---------------------------|---------------------|--------------------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 29 / 34 (85.29%) | 26 / 36 (72.22%) | 50 / 58 (86.21%) |
| Investigations Weight increased subjects affected / exposed | 2 / 34 (5.88%) | 0 / 36 (0.00%) | 2 / 58 (3.45%) |
| occurrences (all) | 2 | 0 | 2 |
| Injury, poisoning and procedural complications Skin laceration subjects affected / exposed | 2 / 34 (5.88%) | 1 / 36 (2.78%) | 3 / 58 (5.17%) |
| occurrences (all) | 2 | 3 | 4 |
| Contusion subjects affected / exposed | 0 / 34 (0.00%) | 0 / 36 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 0 | 0 | 3 |
| Nervous system disorders | | | |

| | | | |
|--|-----------------|----------------|------------------|
| Balance disorder | | | |
| subjects affected / exposed | 3 / 34 (8.82%) | 0 / 36 (0.00%) | 5 / 58 (8.62%) |
| occurrences (all) | 3 | 0 | 5 |
| Drooling | | | |
| subjects affected / exposed | 3 / 34 (8.82%) | 1 / 36 (2.78%) | 5 / 58 (8.62%) |
| occurrences (all) | 4 | 1 | 5 |
| Lethargy | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 0 / 36 (0.00%) | 2 / 58 (3.45%) |
| occurrences (all) | 3 | 0 | 3 |
| Sedation | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 0 / 36 (0.00%) | 2 / 58 (3.45%) |
| occurrences (all) | 2 | 0 | 2 |
| Somnolence | | | |
| subjects affected / exposed | 8 / 34 (23.53%) | 2 / 36 (5.56%) | 11 / 58 (18.97%) |
| occurrences (all) | 8 | 2 | 12 |
| Ataxia | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 36 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 0 | 0 | 3 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 36 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 0 | 0 | 3 |
| Seizure | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 36 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 0 | 0 | 4 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 3 / 34 (8.82%) | 1 / 36 (2.78%) | 4 / 58 (6.90%) |
| occurrences (all) | 3 | 1 | 4 |
| Gait disturbance | | | |
| subjects affected / exposed | 3 / 34 (8.82%) | 0 / 36 (0.00%) | 4 / 58 (6.90%) |
| occurrences (all) | 3 | 0 | 6 |
| Peripheral swelling | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 0 / 36 (0.00%) | 2 / 58 (3.45%) |
| occurrences (all) | 2 | 0 | 2 |
| Pyrexia | | | |

| | | | |
|--|---------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 34 (2.94%) 1 | 5 / 36 (13.89%) 5 | 8 / 58 (13.79%) 9 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 34 (8.82%) | 1 / 36 (2.78%) | 3 / 58 (5.17%) |
| occurrences (all) | 3 | 1 | 3 |
| Nausea | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 0 / 36 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 2 | 0 | 4 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 5 / 36 (13.89%) | 3 / 58 (5.17%) |
| occurrences (all) | 1 | 5 | 3 |
| Constipation | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 0 / 36 (0.00%) | 6 / 58 (10.34%) |
| occurrences (all) | 2 | 0 | 6 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 2 / 36 (5.56%) | 3 / 58 (5.17%) |
| occurrences (all) | 2 | 3 | 3 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 3 / 34 (8.82%) | 0 / 36 (0.00%) | 4 / 58 (6.90%) |
| occurrences (all) | 3 | 0 | 4 |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 2 / 36 (5.56%) | 3 / 58 (5.17%) |
| occurrences (all) | 1 | 2 | 3 |
| Irritability | | | |
| subjects affected / exposed | 5 / 34 (14.71%) | 1 / 36 (2.78%) | 7 / 58 (12.07%) |
| occurrences (all) | 5 | 1 | 8 |
| Aggression | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 36 (0.00%) | 4 / 58 (6.90%) |
| occurrences (all) | 0 | 0 | 4 |
| Insomnia | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 0 / 36 (0.00%) | 3 / 58 (5.17%) |
| occurrences (all) | 0 | 0 | 3 |

| | | | |
|--|----------------------|---------------------|-----------------------|
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) | 0 / 34 (0.00%) 0 | 3 / 36 (8.33%) 3 | 3 / 58 (5.17%) 3 |
| Hordeolum subjects affected / exposed occurrences (all) | 2 / 34 (5.88%) 2 | 0 / 36 (0.00%) 0 | 2 / 58 (3.45%) 2 |
| Influenza subjects affected / exposed occurrences (all) | 2 / 34 (5.88%) 2 | 0 / 36 (0.00%) 0 | 2 / 58 (3.45%) 3 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 2 / 34 (5.88%) 4 | 2 / 36 (5.56%) 2 | 7 / 58 (12.07%) 15 |
| Pneumonia subjects affected / exposed occurrences (all) | 2 / 34 (5.88%) 2 | 1 / 36 (2.78%) 1 | 2 / 58 (3.45%) 2 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 4 / 34 (11.76%) 7 | 1 / 36 (2.78%) 1 | 7 / 58 (12.07%) 11 |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 3 / 34 (8.82%) 3 | 0 / 36 (0.00%) 0 | 6 / 58 (10.34%) 6 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 06 December 2016 | Protocol amendment 01: Revised exclusion criterion #17 to remove double-barrier contraception from set of acceptable methods, and to add recently updated safety language, added criteria for Hy's Law and video electroencephalogram (EEG) to assessments, added Columbia Suicide Severity Rating Scale (C-SSRS) and language pertaining to suicidal behavior, and revised numbering of study weeks during extension phase and corrected the numbering of the study day at the end of Week 74. |
| 04 January 2017 | Protocol amendment 02: Added suicidal ideation to the list of exclusion criteria. Added instructions for laboratory abnormalities that might meet criteria for Hy's Law (elevated aspartate aminotransferase [AST] or alanine aminotransferase [ALT] greater than or equal to 3*upper limit of normal [ULN] and elevated total bilirubin greater than or equal to 2*ULN with an alkaline phosphatase laboratory value that is less than 2*ULN) to be reported as serious adverse events. Added language allowing for discontinuation if the C-SSRS and/or clinical impression indicates a high risk of suicidal behavior. Corrected numbering of study weeks during Conversion Period of Extension Phase. |
| 24 February 2017 | Protocol amendment 03: Added that subjects with laboratory results that include elevated AST or ALT greater than or equal to 3*ULN and elevated total bilirubin greater than or equal to 2*ULN with an ALP laboratory value that is less than 2*ULN, that is, that meet criteria for Hy's law will be withdrawn from the study. Added that subjects who appear to have a high risk of suicidal behavior according to results of the Columbia Suicide Severity Rating Scale (C-SSRS) and/or clinical impression will be withdrawn from the study. |
| 19 October 2018 | Protocol amendment 04: Added an additional extension phase (Extension B) for subjects in Japan or subjects in countries where an extended access program (EAP) cannot be implemented or has not yet been implemented, clarified inclusion criterion that subjects must have an average of at least 2 drop seizures per week during the Baseline Period, and added exclusion criterion that subjects with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption will be excluded. |
| 19 November 2018 | Protocol amendment 05: Adjust the timing of Visit 8 from Week 20 to Week 21, and Visit 9 from Week 22 to Week 23. Update Study Day numbering for these two visits accordingly. |

Notes:

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.

Study was terminated early by sponsor due to recruitment challenge, further impacted by COVID19, resulting in reduced sample size and variability in treatment response. Planned population PK analysis were not conducted and data not collected/analysed.

Notes: