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 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).

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 prerandomization. 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 parampanel), 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	1 / 34 (2.94%)	5 / 36 (13.89%)	8 / 58 (13.79%)
occurrences (all)	1	5	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	0 / 34 (0.00%)	3 / 36 (8.33%)	3 / 58 (5.17%)
occurrences (all)	0	3	3
Hordeolum			
subjects affected / exposed	2 / 34 (5.88%)	0 / 36 (0.00%)	2 / 58 (3.45%)
occurrences (all)	2	0	2
Influenza			
subjects affected / exposed	2 / 34 (5.88%)	0 / 36 (0.00%)	2 / 58 (3.45%)
occurrences (all)	2	0	3
Nasopharyngitis			
subjects affected / exposed	2 / 34 (5.88%)	2 / 36 (5.56%)	7 / 58 (12.07%)
occurrences (all)	4	2	15
Pneumonia			
subjects affected / exposed	2 / 34 (5.88%)	1 / 36 (2.78%)	2 / 58 (3.45%)
occurrences (all)	2	1	2
Upper respiratory tract infection			
subjects affected / exposed	4 / 34 (11.76%)	1 / 36 (2.78%)	7 / 58 (12.07%)
occurrences (all)	7	1	11
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 34 (8.82%)	0 / 36 (0.00%)	6 / 58 (10.34%)
occurrences (all)	3	0	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: