Clinical trial results:
A Double-blind, Randomized, Placebo-controlled, Multicenter, Parallel-group Study with an Open-label Extension Phase to Evaluate the Efficacy and Safety of Adjunctive Perampanel in Primary Generalized Tonic-Clonic Seizures

Summary

EudraCT number	2011-000265-12
Trial protocol	HU DE LV GR AT CZ NL PL LT
Global end of trial date	13 November 2015

Results information

Result version number	v2 (current)
This version publication date	10 November 2016
First version publication date	22 June 2016
Version creation reason	• Correction of full data set single data point revised

Trial information

Trial identification

Sponsor protocol code	E2007-G000-332

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01393743
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai
Sponsor organisation address	100 Tice Boulevard, Woodcliff Lake, United States, 07677
Public contact	Medical Information, Eisai Limited, 44 2086001400, LMedInfo@eisai.net
Scientific contact	Medical Information, Eisai Limited, 44 2086001400, LMedInfo@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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 May 2014
Global end of trial reached?	Yes
Global end of trial date	13 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of adjunctive perampanel therapy, compared to placebo, on primary generalized tonic-clonic (PGTC) seizures

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 Conference 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 Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan’s GCP Subject Information and Informed Consent.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	13 July 2011
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	Poland: 6
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Latvia: 8
Country: Number of subjects enrolled	Lithuania: 4
Country: Number of subjects enrolled	Australia: 17
Country: Number of subjects enrolled	China: 36

Country: Number of subjects enrolled	India: 13
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Japan: 11
Country: Number of subjects enrolled	Korea, Republic of: 7
Country: Number of subjects enrolled	Serbia: 2
Country: Number of subjects enrolled	United States: 39
Worldwide total number of subjects	163
EEA total number of subjects	35

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	22
Adults (18-64 years)	140
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Out of 138 participants who entered the extension phase, 78 participants completed and 60 participants discontinued the extension phase. Reasons for participant discontinuation was as follows: adverse event (12); lost to follow-up (2); participant choice (16); lack of efficacy (7); withdrawal of consent (8); pregnancy (1); and not specified (14).

Pre-assignment

Screening details:

Of the 307 participants who were screened, 143 participants were screen failures and 164 participants were eligible to continue in the study but 1 participant withdrew from the perampanel group prior to receiving treatment.

Period 1

Period 1 title	Core Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Everyone in the Core Study took a total of 6 tablets of study drug, (combination of placebo alone or active drug plus placebo) in order to maintain the blind during the open-label Extension Blinded Conversion Period, which allowed participants to titrate a total daily dose of 12 mg (2 mg x 6 tablets). Participants whose dose was reduced due to intolerable adverse events was allocated a different kit that contained more placebo tablets in order to maintain the same total number of tablets (n=6).

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo (Core Study)

Arm description:

Participants received 6 tablets of perampanel matched placebo, once a day, before bedtime and with food.

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

Dosage and administration details:

Participants received 6 tablets of perampanel-matched placebo, once a day, before bedtime and with food.

Arm title	Perampanel (Core Study)

Arm description:

Participants received 6 tablets (initially,1 tablet of 2 mg perampanel plus 5 tablets of perampanel matched placebo) and up-titrated weekly in 2 mg increments to a target dose range of 8 mg per day maintaining the blind with administration of 6 tablets per day of either perampanel/perampanel matched placebo.

Arm type	Experimental
Investigational medicinal product name	Perampanel
Investigational medicinal product code	E2007
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received 6 tablets (initially ,1 tablet of 2 mg perampanel plus 5 tablets of perampanel matched placebo) and up-titrated weekly in 2 mg increments to a target dose range of 8 mg per day maintaining the blind with administration of 6 tablets per day of either perampanel/perampanel matched placebo.

Number of subjects in period 1	Placebo (Core Study)	Perampanel (Core Study)
Started	82	81
Completed	72	68
Not completed	10	13
Adverse event, non-fatal	5	9
Participant's choice	2	3
Lost to follow-up	1	1
Inadequate therapeutic effect	2	-

Baseline characteristics

Reporting groups

Reporting group title	Placebo (Core Study)
Reporting group description:	
Participants received 6 tablets of perampanel matched placebo, once a day, before bedtime and with food.	
Reporting group title	Perampanel (Core Study)
Reporting group description:	
Participants received 6 tablets (initially,1 tablet of 2 mg perampanel plus 5 tablets of perampanel matched placebo) and up-titrated weekly in 2 mg increments to a target dose range of 8 mg per day maintaining the blind with administration of 6 tablets per day of either perampanel/perampanel matched placebo.	

Reporting group values	Placebo (Core Study)	Perampanel (Core Study)	Total
Number of subjects	82	81	163
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
The full analysis set included all randomized participants who received at least 1 dose of study drug and had any postbaseline seizure frequency data.			
Units: years			
median	26	26	
full range (min-max)	14 to 70	12 to 58	-
Gender categorical Units: Subjects			
Female	46	46	92
Male	36	35	71

Subject analysis sets

Subject analysis set title	Perampanel Extension Phase
Subject analysis set type	Full analysis
Subject analysis set description:	
Eligible participants from the Core Study had the option of entering into the Extension Phase. A total of 138 participants entered into the Extension Phase, 70 participants from the placebo arm of the Core Study and 68 participants from the perampanel arm of the Core Study. The Extension Phase Full Analysis Set (FAS) included all participants who were eligible to participate in the Extension Phase, received at least 1 dose of study drug in this phase, and had baseline seizure frequency data and at least 1 observation of valid seizure diary data during study drug treatment duration.	
Subject analysis set title	Perampanel Extension Phase PGTC Seizures

Subject analysis set type	Sub-group analysis

Subject analysis set description:

The median percent change from the Pre-perampanel baseline in PGTC seizure frequency per 28 days by 13-week intervals through greater than or equal to Week 144.

Subject analysis set title	Perampanel Extension Phase All Seizures
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The median percent change from the Pre-perampanel baseline in the seizure frequency per 28 days of all seizures by 13-week intervals through greater than or equal to Week 144.

Reporting group values	Perampanel Extension Phase	Perampanel Extension Phase PGTC Seizures	Perampanel Extension Phase All Seizures
Number of subjects	138	138	138
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
The full analysis set included all randomized participants who received at least 1 dose of study drug and had any postbaseline seizure frequency data.			
Units: years median full range (min-max)	 25 12 to 70		
Gender categorical Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	Placebo (Core Study)

Reporting group description:

Participants received 6 tablets of perampanel matched placebo, once a day, before bedtime and with food.

Reporting group title	Perampanel (Core Study)

Reporting group description:

Participants received 6 tablets (initially,1 tablet of 2 mg perampanel plus 5 tablets of perampanel matched placebo) and up-titrated weekly in 2 mg increments to a target dose range of 8 mg per day maintaining the blind with administration of 6 tablets per day of either perampanel/perampanel matched placebo.

Subject analysis set title	Perampanel Extension Phase
Subject analysis set type	Full analysis

Subject analysis set description:

Eligible participants from the Core Study had the option of entering into the Extension Phase. A total of 138 participants entered into the Extension Phase, 70 participants from the placebo arm of the Core Study and 68 participants from the perampanel arm of the Core Study. The Extension Phase Full Analysis Set (FAS) included all participants who were eligible to participate in the Extension Phase, received at least 1 dose of study drug in this phase, and had baseline seizure frequency data and at least 1 observation of valid seizure diary data during study drug treatment duration.

Subject analysis set title	Perampanel Extension Phase PGTC Seizures
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The median percent change from the Pre-perampanel baseline in PGTC seizure frequency per 28 days by 13-week intervals through greater than or equal to Week 144.

Subject analysis set title	Perampanel Extension Phase All Seizures
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The median percent change from the Pre-perampanel baseline in the seizure frequency per 28 days of all seizures by 13-week intervals through greater than or equal to Week 144.

Primary: Median Percent Change in Primary Generalized Tonic Clonic Seizure Frequency (PGTC) Per 28 Days During the Titration and Maintenance Periods (Combined) Relative to Baseline (Prerandomization) - (for Core Study)

End point title	Median Percent Change in Primary Generalized Tonic Clonic Seizure Frequency (PGTC) Per 28 Days During the Titration and Maintenance Periods (Combined) Relative to Baseline (Prerandomization) - (for Core Study)

End point description:

Seizure frequency per 28 days was derived from the information recorded in the participant diaries. PGTC seizure frequency per 28 days (as determined from participant diaries) was calculated as the number of PGTC seizures divided by the number of days in the interval and multiplied by 28. The percent change from baseline in PGTC seizure was analyzed over the Titration and Maintenance Periods combined, while baseline was defined as seizure frequency per 28 days based on all valid diary data during the Prerandomization Phase.

End point type	Primary

End point timeframe:

Baseline (4 or 8 weeks), Titration (4 weeks), and Maintenance (13 weeks)

End point values	Placebo (Core Study)	Perampanel (Core Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	81		
Units: Percent change				
median (full range (min-max))	-38.38 (-100 to 1546.3)	-76.47 (-100 to 184.5)		

Statistical analyses

Statistical analysis title	Median Difference to Placebo

Statistical analysis description:

The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.

Comparison groups	Placebo (Core Study) v Perampanel (Core Study)
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	-30.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-45.49
upper limit	-15.244

Notes:

[1] - The P-value is based on a rank analysis of covariance with treatment and pooled country as factors, and prerandomization seizure frequency as a covariate.

Primary: 50% Responder Rate for Primary Generalized Tonic Clonic Seizure During Maintenance-LOCF - (for Core Study)

End point title	50% Responder Rate for Primary Generalized Tonic Clonic Seizure During Maintenance-LOCF - (for Core Study)

End point description:

A responder was a participant who experienced a 50% or greater reduction in seizure frequency per 28 days during Maintenance-last observation carried forward (LOCF) from prerandomization. The data was presented as the percentage of participants.

End point type	Primary

End point timeframe:

Baseline (4 or 8 weeks) and Maintenance (13 weeks)

End point values	Placebo (Core Study)	Perampanel (Core Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	81		
Units: Percentage of participants				
number (not applicable)	39.5	64.2		

Statistical analyses

Statistical analysis title	P Value Compared to Placebo

Statistical analysis description:

The P value is based on non-missing values and is from a Cochran-Mantel-Haenszel test stratified by pooled country.

Comparison groups	Perampanel (Core Study) v Placebo (Core Study)
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0019
Method	Cochran-Mantel-Haenszel

Primary: 50% Responder Rate in Primary Generalized Tonic-Clonic Seizure Frequency per 28 days Relative to the Core Study Prerandomization Phase – (for Extension Phase)

End point title	50% Responder Rate in Primary Generalized Tonic-Clonic Seizure Frequency per 28 days Relative to the Core Study Prerandomization Phase – (for Extension Phase)[2]

End point description:

Responder rate was defined as the percentage of participants who experienced a 50% or greater reduction in PGTC and total seizure frequency during treatment per 28 days relative to baseline (responder). Week 1 began on the date of first dose of the perampanel treatment regardless of whether it occurred in the Core Study or Extension Phase and continued to and included the date of the last dose of perampanel in the Extension Phase. For any given analysis window and seizure type(s), a 50% response from Core Study Prerandomization is a participant whose seizure frequency per 28 days for that seizure type(s) during that analysis window is 50% to 100% lower than his or her Core Study Prerandomization baseline seizure frequency per 28 days for that same seizure type(s). In Part B of the Extension Phase (after Visit 15), the seizure diary is only completed for days on which a seizure occurred and missing days were imputed as non-seizure days.

End point type	Primary

End point timeframe:

Week 1 of perampanel treatment to date of last dose of perampanel in the Extension Phase

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistics were not calculated for this endpoint.

End point values	Perampanel Extension Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	138			
Units: Percentage of participants				
number (not applicable)				
Core Study Maintenance Period	55.1			
Extension Conversion Period	74.6			
Extension Phase Maintenance Period Weeks 1 to 13	75.9			
Extension Phase Maintenance Period Weeks 14 to 26	78.4			
Extension Phase Maintenance Period Weeks 27 to 39	78.1			
Extension Phase Maintenance Period Weeks 40 to 52	79.8			
Extension Phase Maintenance Period Weeks 53 to 65	81.8			
Extension Phase Maintenance Period Weeks 66 to 78	76.5			
Extension Phase Maintenance Period Weeks 79 to 91	80.3			
Extension Phase Maintenance Period Weeks 92 to 104	91.4			

Statistical analyses

No statistical analyses for this end point

Secondary: 50% Responder Rate for All Seizures During Maintenance-LOCF - (for Core Study)

End point title	50% Responder Rate for All Seizures During Maintenance-LOCF - (for Core Study)

End point description:

All seizures included PGTC, myoclonic, absence and all other seizures that occur during the study. A responder was a participant who experienced a 50% or greater reduction in seizure frequency per 28 days during Maintenance- LOCF from prerandomization. The data was presented as percentage of participants.

End point type	Secondary

End point timeframe:

Baseline (4 or 8 weeks) and Maintenance (13 weeks)

End point values	Placebo (Core Study)	Perampanel (Core Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	81		
Units: Percentage of participants				
number (not applicable)	34.6	45.7		

Statistical analyses

Statistical analysis title	P value compared to placebo

Statistical analysis description:

The P value is based on non-missing values and is from a Cochran-Mantel-Haenszel test stratified by pooled country.

Comparison groups	Placebo (Core Study) v Perampanel (Core Study)
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1826
Method	Cochran-Mantel-Haenszel

Secondary: Median Percent Change in all Seizure Frequency per 28 days during the Titration and Maintenance Periods (combined) Relative to Baseline (Prerandomization) - (for Core Study)

End point title	Median Percent Change in all Seizure Frequency per 28 days during the Titration and Maintenance Periods (combined) Relative to Baseline (Prerandomization) - (for Core Study)

End point description:

Seizure frequency per 28 days was derived from the information recorded in the participant diaries. PGTC seizure frequency per 28 days was calculated as the number of PGTC seizures divided by the number of days in the interval and multiplied by 28. The percent change in seizure frequency relative to baseline (prerandomization) for all seizures (PGTC, myoclonic, absence and all other seizures that occur during the study) per 28 days during the Titration and Maintenance Periods combined was analyzed.

End point type	Secondary

End point timeframe:

Baseline (4 or 8 weeks), Titration (4 weeks), and Maintenance (13 weeks)

End point values	Placebo (Core Study)	Perampanel (Core Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	81		
Units: Percent Change				
median (full range (min-max))	-22.87 (-100 to 125.7)	-43.4 (-100 to 1366.7)		

Statistical analyses

Statistical analysis title	Median Difference to Placebo

Statistical analysis description:

The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.

Comparison groups	Perampanel (Core Study) v Placebo (Core Study)
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0018 [3]
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	-23.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.668
upper limit	-8.518

Notes:

[3] - The P value is based on a rank analysis of covariance with treatment and pooled country as factors, and prerandomization seizure frequency as a covariate.

Secondary: Median Percent Change in Primary Generalized Seizure Subtype Frequency per 28 days during the Titration and Maintenance Periods (combined) Relative to Baseline (Prerandomization) - (for Core Study)

End point title	Median Percent Change in Primary Generalized Seizure Subtype Frequency per 28 days during the Titration and Maintenance Periods (combined) Relative to Baseline (Prerandomization) - (for Core Study)

End point description:

Seizure frequency per 28 days was derived from the information recorded in the participant diaries. PGTC seizure frequency per 28 days was calculated as the number of PGTC seizures divided by the number of days in the interval and multiplied by 28. The percent change in seizure frequency relative to baseline (prerandomization) for primary generalized seizure subtype (myoclonic and absence) per 28 days during the Titration and Maintenance Periods combined was analyzed.

End point type	Secondary

End point timeframe:

Baseline (4 or 8 weeks), Titration (4 weeks), and Maintenance (13 weeks)

End point values	Placebo (Core Study)	Perampanel (Core Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	81		
Units: Percent Change				
median (full range (min-max))				
Absence	-7.58 (-100 to 592.4)	-41.18 (-100 to 8088.2)		
Myoclonic	-52.54 (-100 to 321.2)	-24.47 (-100 to 482.4)		

Statistical analyses

Statistical analysis title	Median Difference to Placebo for Absence Seizures

Statistical analysis description:

The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.

Comparison groups	Placebo (Core Study) v Perampanel (Core Study)
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3478 [4]
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	-12.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-53.054
upper limit	26.989

Notes:

[4] - The P value is based on a rank analysis of covariance with treatment and pooled country as factors, and prerandomization seizure frequency as a covariate.

Statistical analysis title	Median Difference to Placebo for Myoclonic Seizure

Statistical analysis description:

The median difference to placebo and the 95% confidence interval are based on the Hodges-Lehmann method.

Comparison groups	Placebo (Core Study) v Perampanel (Core Study)
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.61
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	24.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.338
upper limit	59.938

Secondary: 50% Responder Rate for Primary Generalized Seizure Subtype During Maintenance - LOCF - (for Core Study)

End point title	50% Responder Rate for Primary Generalized Seizure Subtype During Maintenance - LOCF - (for Core Study)

End point description:

Primary generalized seizure subtype included absence and myoclonic seizures. A responder was a participant who experienced a 50% or greater reduction in seizure frequency per 28 days during Maintenance - (last observation carried forward LOCF) from prerandomization. The data was presented as the percentage of participants.

End point type	Secondary

End point timeframe:

Baseline (4 or 8 weeks) and Maintenance (13 weeks)

End point values	Placebo (Core Study)	Perampanel (Core Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	81		
Units: Percentage of participants				
number (not applicable)				
Absence	39.4	48.1		
Myoclonic	60.9	41.7		

Statistical analyses

Statistical analysis title	P Value Compared to Placebo for Absence Seizures

Statistical analysis description:

The P value is based on non-missing values and is from a Cochran-Mantel-Haenszel test stratified by pooled country.

Comparison groups	Placebo (Core Study) v Perampanel (Core Study)
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4653
Method	Cochran-Mantel-Haenszel

Statistical analysis title	P Value Compared to Placebo for Myoclonic Seizures

Statistical analysis description:

The P value is based on non-missing values and is from a Cochran-Mantel-Haenszel test stratified by pooled country.

Comparison groups	Placebo (Core Study) v Perampanel (Core Study)
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3694
Method	Cochran-Mantel-Haenszel

Secondary: Percent Change from Core Study Prerandomization Phase in Primary Generalized Tonic-Clonic (PGTC) Seizure Frequency per 28 Days - (for Extension Phase)

End point title	Percent Change from Core Study Prerandomization Phase in Primary Generalized Tonic-Clonic (PGTC) Seizure Frequency per 28 Days - (for Extension Phase)

End point description:

Week 1 began on the date of first dose of the perampanel treatment regardless of whether it occurred in the Core Study or Extension Phase and continued to and included the date of the last dose of perampanel in the Extension Phase. For any given analysis window and seizure type(s), a 50% responder from Core Study Randomization is a participant whose seizure frequency per 28 days for that seizure type(s) during that analysis window is 50% to 100% lower than his or her Core Study Prerandomization baseline seizure frequency per 28 days for that same seizure type(s). In Part B of the Extension Phase (after Visit 15), the seizure diary is only completed for days on which a seizure occurred and missing days were imputed as non-seizure days.

End point type	Secondary

End point timeframe:

Date of first dose of study drug to date of last dose of study drug in the Extension Phase

End point values	Perampanel Extension Phase			
Subject group type	Subject analysis set			
Number of subjects analysed	138			
Units: Percent change in PGTC seizure frequency				
median (full range (min-max))				
Core Study Titration Period	-57.72 (-100 to 500)			
Core Study Maintenance Period	-57.4 (-100 to 2011.6)			
Extension Phase Conversion Period	-100 (-100 to 166.7)			
Extension Phase Maintenance Period, Weeks 1 to 13	-84.62 (-100 to 594.5)			
Extension Phase Maintenance Period, Weeks 14 to 26	-86.81 (-100 to 186.2)			
Extension Phase Maintenance Period, Weeks 27 to 39	-86.62 (-100 to 250.8)			
Extension Phase Maintenance Period, Weeks 40 to 52	-100 (-100 to 146.2)			
Extension Phase Maintenance Period, Weeks 53 to 65	-100 (-100 to 150.5)			
Extension Phase Maintenance Period, Weeks 66 to 78	-100 (-100 to 108.8)			
Extension Phase Maintenance, Weeks 79 to 91	-100 (-100 to 140.1)			
Extension Phase Maintenance, Weeks 92 to 104	-100 (-100 to 171.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Percent Change from Pre-Perampanel Baseline in Seizure Frequency per 28 Days - (for Extension Phase)

End point title	Summary of Percent Change from Pre-Perampanel Baseline in Seizure Frequency per 28 Days - (for Extension Phase)

End point description:

Efficacy assessments included seizure counts from participant diaries. The percent change in seizure frequency was assessed during the perampanel treatment duration, with the pre-perampanel baseline being used for evaluating the change. The pre-perampanel baseline was defined as follows: 1) for all participants who had been assigned to placebo treatment in the Core Study, the pre-perampanel baseline was computed from all valid seizure diary data during the Core Study, and 2) for participants who had been assigned to perampanel in the Core Study, the pre-perampanel baseline was computed from all valid seizure diary data during the Prerandomization Phase plus the 4 weeks prior to the Prerandomization Phase of the Core Study. The perampanel treatment duration consisted of: 1) the Randomization Phase of the Core Study plus the Extension Phase for participants assigned to perampanel in the Core Study, and 2) the Extension Phase for participants assigned to placebo in the Core Study.

End point type	Secondary

End point timeframe:

Weeks: 1 to 13, 14 to 26, 27 to 39, 40 to 52, 53 to 65, 66 to 78, 79 to 91, 92 to 104, 105 to 117, 118 to 130, 131 to 143, greater than or equal to 144

End point values	Perampanel Extension Phase PGTC Seizures	Perampanel Extension Phase All Seizures		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	138	138		
Units: Median Percent Change				
number (not applicable)				
Weeks 1 - 13 (n = 138)	-77.45	-56.54		
Weeks 14 - 26 (n = 133)	-74.21	-63.53		
Weeks 27 - 39 (n = 125)	-84.62	-79.49		
Weeks 40 - 52 (n = 118)	-89.65	-83.38		
Weeks 53 - 65 (n = 109)	-92.45	-83.33		
Weeks 66 - 78 (n = 90)	-100	-88.71		
Weeks 79 - 91 (n = 80)	-100	-90.28		
Weeks 92 - 104 (n = 52)	-100	-98.96		
Weeks 105 - 117 (n = 41)	-100	-96.42		
Weeks 118 - 130 (n = 27)	-100	-96.58		
Weeks 131 - 143 (n = 19)	-100	-91.7		
Weeks greater than or equal to 144 (n=9)	-100	-82.09		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment Emergent Adverse events and serious adverse events as a measure of safety and tolerability of perampanel in subjects with inadequately controlled PGTC seizures - (for Core Study)

End point title	Number of Participants with Treatment Emergent Adverse events and serious adverse events as a measure of safety and tolerability of perampanel in subjects with inadequately controlled PGTC seizures - (for Core Study)

End point description:

An Adverse event (AE) was defined as any untoward medical occurrence in a clinical investigation

participant administered an investigational product. A serious adverse event (SAE) was defined as any untoward medical occurrence that at any dose resulted in death, was life-threatening (i.e., the subject was at immediate risk of death from the AE as it occurred; this did not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death), required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or was a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug). In this study, treatment emergent adverse events (TEAEs) (defined as an AE that started/increased in severity on/after the first dose of study medication up to 30 days after the final dose of study medication) were assessed.

End point type	Secondary

End point timeframe:

For each participant, from the first treatment dose till 30 days after the last dose or up to 21 weeks for core study and 142 weeks for extension phase.

End point values	Placebo (Core Study)	Perampanel (Core Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	81		
Units: Participants				
number (not applicable)				
Treatment emergent adverse events	59	67		
Treatment emergent serious adverse events	7	6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of first dose of perampanel up to 30 days after the last dose, or up to approximately 163 weeks total.

Adverse event reporting additional description:

Treatment-emergent Adverse Events (TEAEs) included AEs that occurred from the first dose of perampanel (in Core Study or Extension Phase) to 30 days after the last dose of perampanel, or that were present before the first day of perampanel administration but worsened in severity during the study. TEAEs are reported in the Safety Section.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Placebo (Core Study)

Reporting group description:

Participants received 6 tablets of perampanel matched placebo, once a day.

Reporting group title	Perampanel (Extension Phase)

Reporting group description:

The Extension Phase had two parts: Part A (6-week blinded Conversion Period plus a 32-week Maintenance Period) and Part B (maximum of 104-week Maintenance Period). Part A: Participants who received placebo in the Core Study were started on blinded oral perampanel (2 mg/day) and were up-titrated weekly in 2-mg increments to the optimal dose per investigator's discretion. Participants who were assigned to the perampanel arm in the Core Study continued to receive blinded perampanel once daily at the dose received during the Maintenance Period of the Core Study. Conversion Period: dose adjustments could be made at the investigator’s discretion. Part B: Participants were unblinded to study treatment and remained on the optimal perampanel dose established during the blinded Conversion Period (Part A). Dose adjustment in 2-mg increments (upwards or downwards) was allowed at the investigator's discretion. The maximum dose of perampanel allowed during the Extension Phase was 12 mg/day.

Reporting group title	Perampanel (Core Study)

Reporting group description:

Participants received 6 tablets (initially ,1 tablet of 2 mg perampanel plus 5 tablets of perampanel matched placebo) and up-titrated weekly in 2 mg increments to a target dose range of 8 mg per day maintaining the blind with administration of 6 tablets per day of either perampanel/perampanel matched placebo.

Serious adverse events	Placebo (Core Study)	Perampanel (Extension Phase)	Perampanel (Core Study)
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 82 (8.54%)	18 / 138 (13.04%)	6 / 81 (7.41%)
number of deaths (all causes)	1	1	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial adenocarcinoma			

subjects affected / exposed	0 / 82 (0.00%)	1 / 138 (0.72%)	0 / 81 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous incomplete			
subjects affected / exposed	0 / 82 (0.00%)	1 / 138 (0.72%)	0 / 81 (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
General disorders and administration site conditions			
Drowning			
subjects affected / exposed	0 / 82 (0.00%)	0 / 138 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 138 (0.72%)	0 / 81 (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
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 82 (0.00%)	1 / 138 (0.72%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 82 (0.00%)	2 / 138 (1.45%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aggression			
subjects affected / exposed	0 / 82 (0.00%)	1 / 138 (0.72%)	0 / 81 (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
Depression			

subjects affected / exposed	0 / 82 (0.00%)	1 / 138 (0.72%)	0 / 81 (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
Mental disorder			
subjects affected / exposed	0 / 82 (0.00%)	1 / 138 (0.72%)	0 / 81 (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
Mental status changes			
subjects affected / exposed	0 / 82 (0.00%)	1 / 138 (0.72%)	0 / 81 (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
Psychiatric symptom			
subjects affected / exposed	0 / 82 (0.00%)	1 / 138 (0.72%)	0 / 81 (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
Psychogenic seizure			
subjects affected / exposed	0 / 82 (0.00%)	1 / 138 (0.72%)	0 / 81 (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
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 82 (1.22%)	0 / 138 (0.00%)	0 / 81 (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
Thermal burn			
subjects affected / exposed	1 / 82 (1.22%)	0 / 138 (0.00%)	0 / 81 (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
Facial bones fracture			
subjects affected / exposed	0 / 82 (0.00%)	1 / 138 (0.72%)	0 / 81 (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
Fibula fracture			

subjects affected / exposed	0 / 82 (0.00%)	1 / 138 (0.72%)	0 / 81 (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
Tibia fracture			
subjects affected / exposed	0 / 82 (0.00%)	1 / 138 (0.72%)	0 / 81 (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
Wound			
subjects affected / exposed	0 / 82 (0.00%)	1 / 138 (0.72%)	0 / 81 (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
Nervous system disorders			
Convulsion			
subjects affected / exposed	2 / 82 (2.44%)	3 / 138 (2.17%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Grand Mal Convulsion			
subjects affected / exposed	1 / 82 (1.22%)	1 / 138 (0.72%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status eiplepticus			
subjects affected / exposed	1 / 82 (1.22%)	0 / 138 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sedation			
subjects affected / exposed	0 / 82 (0.00%)	1 / 138 (0.72%)	0 / 81 (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
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 82 (0.00%)	1 / 138 (0.72%)	0 / 81 (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

Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 82 (0.00%)	1 / 138 (0.72%)	0 / 81 (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
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 82 (0.00%)	1 / 138 (0.72%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 82 (1.22%)	0 / 138 (0.00%)	0 / 81 (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
Pancreatitis acute			
subjects affected / exposed	0 / 82 (0.00%)	1 / 138 (0.72%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	0 / 82 (0.00%)	0 / 138 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Invertebral disc protrusion			
subjects affected / exposed	0 / 82 (0.00%)	1 / 138 (0.72%)	0 / 81 (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
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 138 (0.72%)	0 / 81 (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
Pneumonia			

subjects affected / exposed	0 / 82 (0.00%)	1 / 138 (0.72%)	0 / 81 (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
Septic shock			
subjects affected / exposed	0 / 82 (0.00%)	1 / 138 (0.72%)	0 / 81 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 82 (0.00%)	1 / 138 (0.72%)	0 / 81 (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

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

Non-serious adverse events	Placebo (Core Study)	Perampanel (Extension Phase)	Perampanel (Core Study)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 82 (43.90%)	106 / 138 (76.81%)	56 / 81 (69.14%)
Investigations			
Weight increased			
subjects affected / exposed	3 / 82 (3.66%)	13 / 138 (9.42%)	6 / 81 (7.41%)
occurrences (all)	3	14	7
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 82 (3.66%)	12 / 138 (8.70%)	5 / 81 (6.17%)
occurrences (all)	3	15	5
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 82 (6.10%)	53 / 138 (38.41%)	26 / 81 (32.10%)
occurrences (all)	5	64	26
Headache			
subjects affected / exposed	8 / 82 (9.76%)	17 / 138 (12.32%)	10 / 81 (12.35%)
occurrences (all)	10	61	19
Somnolence			

subjects affected / exposed	3 / 82 (3.66%)	18 / 138 (13.04%)	9 / 81 (11.11%)
occurrences (all)	3	22	11
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 82 (6.10%)	14 / 138 (10.14%)	12 / 81 (14.81%)
occurrences (all)	5	16	12
Irritability			
subjects affected / exposed	2 / 82 (2.44%)	19 / 138 (13.77%)	9 / 81 (11.11%)
occurrences (all)	2	24	9
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 82 (2.44%)	15 / 138 (10.87%)	7 / 81 (8.64%)
occurrences (all)	5	19	7
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 82 (3.66%)	11 / 138 (7.97%)	5 / 81 (6.17%)
occurrences (all)	3	12	5
Vomiting			
subjects affected / exposed	2 / 82 (2.44%)	9 / 138 (6.52%)	7 / 81 (8.64%)
occurrences (all)	2	16	10
Abdominal pain			
subjects affected / exposed	1 / 82 (1.22%)	8 / 138 (5.80%)	4 / 81 (4.94%)
occurrences (all)	1	8	4
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 82 (3.66%)	7 / 138 (5.07%)	4 / 81 (4.94%)
occurrences (all)	3	8	4
Insomnia			
subjects affected / exposed	4 / 82 (4.88%)	12 / 138 (8.70%)	3 / 81 (3.70%)
occurrences (all)	4	17	3
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 82 (8.54%)	20 / 138 (14.49%)	7 / 81 (8.64%)
occurrences (all)	8	31	7
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	5 / 82 (6.10%) 7	18 / 138 (13.04%) 25	4 / 81 (4.94%) 5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 October 2011	• Clarified age level per health authority request to postpone recruitment of adolescent subjects until safety data are available from the ongoing pediatric study. • Evidence of active hepatic disease was added as an exclusion criterion per health authority request. • The Conversion Period was extended to eliminate potential unblinding. • Increased the number of PGTC seizures (from ≥2 to ≥3) required during the 8-week Baseline Period. • Added prohibited medications to exclusion criteria to meet health authority requirements.
12 April 2012	• Study duration was extended by 52 weeks to provide subjects the option to continue accessing perampanel treatment if they are benefiting from the study drug; Extension Phase was split into Part A and Part B. • To guarantee uninterrupted treatment to those subjects who benefit from perampanel, stipulated treatment until perampanel became commercially available. • Increased the maximum number of AEDs allowed to 3 to align with patient population targeted by this protocol, based on feedback from Key Opinion Leaders. • Exclusion of subjects aged ≥65 years for India per the request of the Drug Controller General of India. • Increased the number of sites changed to 95 to ensure target recruitment was met in a timely fashion. • Addition of QOLIE-31-P and HCRU to demonstrate that improving the seizure frequency impacts quality of life of these subjects, including visits to hospitals.
15 November 2013	• Extension Phase Part B extended by 52 weeks to provide continued treatment until efficacy and safety results in this indication become available. • Specified an end of treatment visit for subjects who had at least 52 weeks of treatment in the Extension Phase. • Stipulated explicitly, the termination of the Extension Phase upon commercial availability of perampanel or if a positive risk-benefit assessment in this indication was not demonstrated. • Added decision points for subjects' continued participation after completion of Extension Part A. As an added safety measure a total of 52 weeks exposure to perampanel was to be achieved before extended treatment is initiated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported