Clinical trial results:
A Randomized, Double-blind, Placebo-controlled, Parallel-group Study With an Open-label Extension Phase to Evaluate the Effect of Perampanel (E2007) on Cognition, Growth, Safety, Tolerability, and Pharmacokinetics When Administered as an A Randomized, Double-blind, Placebo-controlled, Parallel-group Study With an Open-label Extension Phase to Evaluate the Effect of Perampanel (E2007) on Cognition, Growth, Safety, Tolerability, and Pharmacokinetics When Administered as an Adjunctive Therapy in Adolescents (12 to Less Than 18 Years of Age) With Inadequately Controlled Partial-onset Seizures

Estudio aleatorizado, doble ciego, controlado con placebo y de grupos paralelos con una fase de extensión abierta para evaluar el efecto de perampanel (E2007) en la cognición, el crecimiento, la seguridad, la tolerabilidad y la farmacocinética cuando se administra como terapia adyuvante en adolescentes (de 12 a menos de 18 años de edad) con crisis de inicio parcial insuficientemente controladas.

Summary

EudraCT number	2010-018518-56
Trial protocol	LV ES BE HU CZ
Global end of trial date	01 November 2014

Results information

Result version number	v1 (current)
This version publication date	13 April 2016
First version publication date	13 April 2016

Trial information

Trial identification

Sponsor protocol code	E2007-G000-235

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01161524
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Inc.
Sponsor organisation address	155 Tice Boulevard, Woodcliff Lake, New Jersey, United States, 07667
Public contact	Eisai Call Center, Eisai Inc., 888 422-4743,
Scientific contact	Eisai Call Center, Eisai Inc., 888 422-4743,

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	01 September 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study is designed to investigate the short- and long-term effects of perampanel on cognition, growth, and development in adolescents.

Comparar el efecto a corto plazo de perampanel y placebo en la cognición empleando el sistema Cognitive Drug Research (CDR) cuando se administra como tratamiento adjuvante a adolescentes (12 a menos de 18 años de edad) con crisis de inicio parcial controladas insuficientemente (con o sin crisis secundariamente generalizadas).

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	24 September 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Hungary: 24
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	India: 35
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Thailand: 10
Country: Number of subjects enrolled	United States: 18
Country: Number of subjects enrolled	Latvia: 19
Worldwide total number of subjects	133
EEA total number of subjects	63

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)	133
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of the 154 participants screened for entry into the Core Study, 21 were screen failures and 133 were randomized and treated. A total of 119 participants completed the Core Study, and 114 participants entered the Extension Phase.

Period 1

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

Arms

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

Arm description:

Participants received matching placebo tablets once a day (6 tablets of placebo).

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:

Perampanel matching placebo tablets taken once daily.

Arm title	Perampanel (Core Study)

Arm description:

Participants received perampanel 2 mg per day and up-titrated weekly in 2-mg increments to a target dose range of 8 to 12 mg per day.

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

Dosage and administration details:

Perampanel 2 mg titrated up to 8-12 mg maximum, taken once daily.

Number of subjects in period 1	Placebo (Core Study)	Perampanel (Core Study)
Started	48	85
Completed	43	76
Not completed	5	9
Consent withdrawn by subject	1	1
Not specified	-	1
Adverse event	-	3
Lost to follow-up	2	1
Subject choice	2	3

Period 2

Period 2 title	Extension Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

During the extension phase participants received unblinded treatment.

Arms

Arm title	Perampanel (Extension Phase)

Arm description:

During the Extension Phase, participants previously assigned to perampanel arm (Core Study) continued taking study medication at the dose achieved at the end of the Core Study once daily. Participants previously assigned to a placebo arm (Core Study) started perampanel dose at 2 mg/day and up-titrated weekly in 2-mg increments up to a maximum dose of 12 mg/day.

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

Dosage and administration details:

Perampanel 2 mg titrated up to 8-12mg maximum; taken once daily.

Number of subjects in period 2[1]	Perampanel (Extension Phase)
Started	114
Completed	90
Not completed	24
Inadequate Therapeutic Effect	4
Not specified	6

Adverse event	8
Lost to follow-up	1
Subject choice	5

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: A total of 133 subjects were randomized into the Core Study and 119 (43 in Placebo arm and 76 in Perampanel arm) subjects completed the Core Study. A total of 114 subjects entered the Extension Phase. A total of 90 subjects completed the Extension Phase.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo (Core Study)
Reporting group description:	
Participants received matching placebo tablets once a day (6 tablets of placebo).	
Reporting group title	Perampanel (Core Study)
Reporting group description:	
Participants received perampanel 2 mg per day and up-titrated weekly in 2-mg increments to a target dose range of 8 to 12 mg per day.	

Reporting group values	Placebo (Core Study)	Perampanel (Core Study)	Total
Number of subjects	48	85	133
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 Units: years			
arithmetic mean	14.3	14.3	
standard deviation	± 1.88	± 1.74	-
Gender categorical Units: Subjects			
Female	20	33	53
Male	28	52	80
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	2	3
Non-Hispanic or Latino	47	82	129
Unknown or Not Reported	0	1	1

End points

End points reporting groups

Reporting group title	Placebo (Core Study)
Reporting group description:	
Participants received matching placebo tablets once a day (6 tablets of placebo).	
Reporting group title	Perampanel (Core Study)
Reporting group description:	
Participants received perampanel 2 mg per day and up-titrated weekly in 2-mg increments to a target dose range of 8 to 12 mg per day.	
Reporting group title	Perampanel (Extension Phase)
Reporting group description:	
During the Extension Phase, participants previously assigned to perampanel arm (Core Study) continued taking study medication at the dose achieved at the end of the Core Study once daily. Participants previously assigned to a placebo arm (Core Study) started perampanel dose at 2 mg/day and up-titrated weekly in 2-mg increments up to a maximum dose of 12 mg/day.	

Primary: Change From Baseline to Week 19 in Cognition Drug Research (CDR) System Global Cognition Score (Core Study)

End point title	Change From Baseline to Week 19 in Cognition Drug Research (CDR) System Global Cognition Score (Core Study)
End point description:	
The CDR System Global Cognitive score was derived from the average of 5 CDR System cognitive domain scores (Power of Attention, Continuity of Attention, Quality of Episodic Memory, Quality of Working Memory, and Speed of Memory). The domain scores were normalized to mean of 50 and standard deviation of 10 before taking the average. The scale ranged from 0 - 100. An increase in the Global Cognitive Score indicates improvement, while a decrease indicates worsening in cognitive function.	
End point type	Primary
End point timeframe:	
Baseline (Visit 2/Week 0 Evaluation) and Week 19 LOCF (last observation carried forward)	

End point values	Placebo (Core Study)	Perampanel (Core Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[1]	79[2]		
Units: Score on a scale				
arithmetic mean (standard deviation)	1.1 (± 7.14)	-1 (± 8.86)		

Notes:

[1] - Full Analysis Set (FAS) for cognition (for Core Study)

[2] - FAS for cognition (for Core Study)

Statistical analyses

Statistical analysis title	p value (for the primary outcome measure)
Comparison groups	Placebo (Core Study) v Perampanel (Core Study)

Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.145
Method	ANCOVA

Secondary: Change From Baseline at Week 19 in the Power of Attention Score in the Randomization Phase (Core Study)

End point title	Change From Baseline at Week 19 in the Power of Attention Score in the Randomization Phase (Core Study)

End point description:

The Power of Attention domain (one of the 5 CDR System cognitive domains) was a measure of focused attention and information processing, comprised of the speed scores from the 3 CDR System attention tasks. The domain scores were normalized to mean of 50 and standard deviation (SD) of 10. The total score was derived by summing the 3 CDR system attention tasks. The standard norms for 'power of attention' score were considered as 1176 ± 130.4 (mean ± SD). A decrease in the score of Power of Attention indicated improvement in cognitive function. Change from baseline is presented as mean ± SD.

End point type	Secondary

End point timeframe:

Baseline and Week 19 LOCF

End point values	Placebo (Core Study)	Perampanel (Core Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[3]	79[4]		
Units: Score on a scale				
arithmetic mean (standard deviation)	35.1 (± 237.56)	91.1 (± 250.51)		

Notes:

[3] - FAS for cognition (Core Study)

[4] - FAS for cognition (Core Study)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 19 in the Continuity of Attention Score in the Randomization Phase (Core Study)

End point title	Change From Baseline at Week 19 in the Continuity of Attention Score in the Randomization Phase (Core Study)

End point description:

The Continuity of Attention domain (one of the 5 CDR System cognitive domains) was a measure of sustained attention, comprised of the accuracy scores from 2 of the CDR System attention tasks: choice reaction time and digit vigilance. The domain scores were normalized to mean of 50 and standard deviation of 10. The total score was derived by summing the 2 CDR system attention tasks. The

standard norms for 'Continuity of Attention' score were considered as 79.75 ± 11.25 (mean ± SD). An increase in the score of Continuity of Attention indicated improvement in cognition function. Change from baseline is presented as mean ± SD.

End point type	Secondary

End point timeframe:

Baseline and Week 19 LOCF

End point values	Placebo (Core Study)	Perampanel (Core Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[5]	79[6]		
Units: Score on a scale				
arithmetic mean (standard deviation)	1.1 (± 8.62)	-2.4 (± 9.57)		

Notes:

[5] - FAS for cognition (Core Study)

[6] - FAS for cognition (Core Study)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 19 in the Quality of Episodic Secondary Memory Score in the Randomization Phase (Core Study)

End point title	Change From Baseline at Week 19 in the Quality of Episodic Secondary Memory Score in the Randomization Phase (Core Study)

End point description:

The Quality of Episodic Secondary Memory domain was a measure of the capability of individuals to encode, store, and subsequently retrieve verbal and nonverbal information in episodic (or declarative) memory; what was meant by memory in everyday terminology. This measure was derived by summing the scores from the 4 tasks: immediate and delayed word recall, word recognition, and picture recognition. The domain scores were normalized to mean of 50 and SD of 10 before taking the sum of the subscale scores. The standard norms for 'Quality of Episodic Secondary Memory' score were considered as 180 ± 51.6 (mean ± SD). An increase in the score of Quality of Episodic Memory indicated improvement in cognition function. Change from baseline is presented as mean ± SD.

End point type	Secondary

End point timeframe:

Baseline and Week 19 LOCF

End point values	Placebo (Core Study)	Perampanel (Core Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[7]	79[8]		
Units: Score on a scale				
arithmetic mean (standard deviation)	-3.4 (± 35.77)	17.5 (± 52.34)		

Notes:

[7] - FAS for cognition (Core Study)

[8] - FAS for cognition (Core Study)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 19 in the Quality of Working Memory (Short Term) Score in the Randomization Phase (Core Study)

End point title	Change From Baseline at Week 19 in the Quality of Working Memory (Short Term) Score in the Randomization Phase (Core Study)

End point description:

The Quality of Working Memory domain (one of the 5 CDR System cognitive domains) was a measure of reflecting how well individuals can hold numeric and spatial information 'on line' in working memory. The domain scores were normalized to mean of 50 and SD of 10. The standard norms for 'Quality of Working Memory (Short Term)' score were considered as 1.67 ± 0.307 (mean ± SD). An increase in the score of Quality of Working Memory indicated improvement in cognition function. Change from baseline is presented as mean ± SD.

End point type	Secondary

End point timeframe:

Baseline and Week 19 LOCF

End point values	Placebo (Core Study)	Perampanel (Core Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[9]	79[10]		
Units: Score on a scale				
arithmetic mean (standard deviation)	0 (± 0.39)	0.1 (± 0.39)		

Notes:

[9] - FAS for cognition (Core Study)

[10] - FAS for cognition (Core Study)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 19 in the Speed of Memory Score in the Randomization Phase (Core Study)

End point title	Change From Baseline at Week 19 in the Speed of Memory Score in the Randomization Phase (Core Study)

End point description:

The Speed of Memory domain (one of the 5 CDR System cognitive domains) was a measure which reflects the time taken to accurately retrieve information from working and episodic memory. The domain scores were normalized to mean of 50 and SD of 10. The total score was derived by summing the speed scores from the two working memory tasks, plus word and picture recognition. The standard norms for 'Speed of Memory' score were considered as 3104 ± 578.8 (mean ± SD). A decrease in the score of Speed of Memory indicated improvement in cognitive function. Change from baseline is presented as mean ± SD.

End point type	Secondary

End point timeframe:

Baseline and Week 19 LOCF

End point values	Placebo (Core Study)	Perampanel (Core Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[11]	79[12]		
Units: Score on a scale				
arithmetic mean (standard deviation)	-311.4 (± 697.75)	69.6 (± 1059.75)		

Notes:

[11] - FAS for cognition (Core Study)

[12] - FAS for cognition (Core Study)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Experienced 50% or More Decrease in Seizure Frequency (Core Study)

End point title	Percentage of Participants Who Experienced 50% or More Decrease in Seizure Frequency (Core Study)

End point description:

A responder was a participant who experienced a 50% or greater reduction in seizure frequency compared to the baseline of the Randomization Phase.

End point type	Secondary

End point timeframe:

From Baseline up to Week 19 LOCF

End point values	Placebo (Core Study)	Perampanel (Core Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46[13]	83[14]		
Units: Percentage of Participants				
number (not applicable)	34.8	53		

Notes:

[13] - FAS for Efficacy

[14] - FAS for Efficacy

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Seizure Frequency per 28 Days During the Treatment Duration of the Randomization Phase (Core Study)

End point title	Percent Change From Baseline in Seizure Frequency per 28

	Days During the Treatment Duration of the Randomization Phase (Core Study)

End point description:

Seizure frequency was based on overall number of seizures obtained by summing the 4 seizure types (all partial seizure types, that is, simple partial without motor signs, simple partial with motor signs, complex partial, and complex partial with secondary generalization) collected via the patient diary over a particular time interval and re-scaled to 28 days window.

End point type	Secondary

End point timeframe:

Baseline and Week 19 LOCF

End point values	Placebo (Core Study)	Perampanel (Core Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46[15]	83[16]		
Units: Percent change				
median (full range (min-max))	-24 (-100 to 644.7)	-58 (-100 to 3404)		

Notes:

[15] - FAS for efficacy

[16] - FAS for efficacy

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Achieved Seizure-Free Status During the Maintenance Period and the Last 28 Days of the Maintenance Period During the Randomization Phase (Core Study)

End point title	Number of Participants Who Achieved Seizure-Free Status During the Maintenance Period and the Last 28 Days of the Maintenance Period During the Randomization Phase (Core Study)

End point description:

Number of Participants who were seizure free, were assessed.

End point type	Secondary

End point timeframe:

13 Week Maintenenance Period

End point values	Placebo (Core Study)	Perampanel (Core Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46[17]	83[18]		
Units: Participants				
Complete Maintenance Period	7	18		
Last 28 Days of Maintenance Period	13	31		

Notes:

[17] - FAS for efficacy

[18] - FAS for efficacy

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Seizure Frequency Per 28 Days Over the Perampanel Duration Exposure (Extension Phase)

End point title	Percent Change From Baseline in Seizure Frequency Per 28 Days Over the Perampanel Duration Exposure (Extension Phase)

End point description:

The median percent change in total partial onset seizure frequency per 28 days during the Extension Phase relative to the Pre-perampanel Baseline from Week 1 of perampanel treatment through successive 13-week intervals (Weeks 1 to 13 for subjects with any data, Weeks 1 to 26 for subjects with exposure of more than 13 weeks, Weeks 1 to 39 for subjects with exposure of more than 26 weeks, and Week 1 to 52 for subjects with exposure of more than 52 weeks) are presented. The perampanel exposure duration starts from the first perampanel dose (in the Core Study for subjects previously randomized to perampanel or Extension Phase for subjects previously randomized to placebo) to the last perampanel dose in the Extension Phase.

End point type	Secondary

End point timeframe:

Week 1-13, Week 14-26, Week 27-39, and Week 40-52

End point values	Perampanel (Extension Phase)			
Subject group type	Reporting group			
Number of subjects analysed	114[19]			
Units: Percent change				
median (full range (min-max))				
Week 1-13 (any exposure duration); N=114	-59.1 (-100 to 2909.6)			
Week 1-13 (at least 13 weeks of exposure); N=109	-60.4 (-100 to 2909.6)			
Week 1-13 (at least 26 weeks of exposure); N=107	-60.9 (-100 to 2909.6)			
Week 1-13 (at least 39 weeks of exposure); N=90	-54.2 (-100 to 2909.6)			
Week 1-13 (at least 52 weeks of exposure); N=67	-60.9 (-100 to 2909.6)			
Week 14-26 (at least 26 weeks of exposure); N=107	-63.7 (-100 to 4108.2)			
Week 14-26 (at least 39 weeks of exposure); n=90	-58.8 (-100 to 4108.2)			
Week 14-26 (at least 52 weeks of exposure); N=67	-61.3 (-100 to 4108.2)			
Week 27-39 (at least 39 weeks of exposure); N=90	-73.1 (-100 to 792.3)			
Week 27-39 (at least 52 weeks of exposure); N=67	-74.1 (-100 to 792.3)			
Week 40-52 (at least 52 weeks of exposure); N=53	-74.1 (-100 to 3160.7)			

Notes:

[19] - FAS for efficacy (Extension Phase)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Experienced 50% or More Decrease in Seizure Frequency Over the Perampanel Duration Exposure (Extension Phase)

End point title	Percentage of Participants Who Experienced 50% or More Decrease in Seizure Frequency Over the Perampanel Duration Exposure (Extension Phase)

End point description:

A responder was a participant who experienced a 50% or greater reduction in seizure frequency per 28 days from pre-perampanel. The percentage of responders from Week 1 of perampanel treatment through successive 13-week intervals (Weeks 1 to 13 for subjects with any data, Weeks 1 to 26 for subjects with exposure of more than 13 weeks, Weeks 1 to 39 for subjects with exposure of more than 26 weeks, and Week 1 to 52 for subjects with exposure of more than 52 weeks) are presented. The perampanel exposure duration starts from the first perampanel dose (in the Core Study for subjects previously randomized to perampanel or Extension Phase for subjects previously randomized to placebo) to the last perampanel dose in the Extension Phase.

End point type	Secondary

End point timeframe:

Week 1-13, Week 14-26, Week 27-39, and Week 40-52

End point values	Perampanel (Extension Phase)			
Subject group type	Reporting group			
Number of subjects analysed	114[20]			
Units: Percentage of participants				
number (not applicable)				
Week 1-13 (any exposure duration); N=114	54.4			
Week 1-13 (at least 13 weeks of exposure); N=109	55			
Week 1-13 (at least 26 weeks of exposure); N=107	56.1			
Week 1-13 (at least 39 weeks of exposure); N=90	51.1			
Week 1-13 (at least 52 weeks of exposure); N=67	53.7			
Week 14-26 (at least 26 weeks of exposure); N=107	59.8			
Week 14-26 (at least 39 weeks of exposure); N=90	56.7			
Week 14-26 (at least 52 weeks of exposure); N=67	55.2			
Week 27-39 (at least 39 weeks of exposure); N=90	58.9			
Week 27-39 (at least 52 weeks of exposure); N=67	62.7			
Week 40-52 (at least 52 weeks of exposure); N=53	66			

Notes:

[20] - FAS for Efficacy (Extension Phase)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline to End of Treatment in Cognition Drug Research (CDR) System Global Cognition Score (Extension Phase)

End point title	Mean Change From Baseline to End of Treatment in Cognition Drug Research (CDR) System Global Cognition Score (Extension Phase)

End point description:

The CDR System Global Cognitive was derived from the average of 5 CDR System cognitive domain scores (Power of Attention, Continuity of Attention, Quality of Episodic Memory, Quality of Working Memory, and Speed of Memory). Domain scores were normalized to mean of 50 and standard deviation of 10 before taking the average. The scale ranged from 0 to 100. An increase in the Global Cognitive Score indicates improvement, while a decrease indicates worsening in cognitive function. The perampanel exposure duration starts from the first perampanel dose (in the Core Study for subjects previously randomized to perampanel or Extension Phase for subjects previously randomized to placebo) to the last perampanel dose in the Extension Phase.

End point type	Secondary

End point timeframe:

Baseline, Week 9, Week 19, Week, 30, Week 39, Week 52, and End of Treatment (defined as the last nonmissing value after date of first perampanel dose up to 14 days after date of last dose)

End point values	Perampanel (Extension Phase)			
Subject group type	Reporting group			
Number of subjects analysed	112[21]			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Change from Baseline at Week 9	-3.8 (± 9.92)			
Change from Baseline at Week 19	-1.1 (± 8.16)			
Change from Baseline at Week 30	-1.3 (± 9.41)			
Change from Baseline at Week 39	-2.2 (± 10.22)			
Change from Baseline at Week 52	-0.2 (± 10.5)			
Change from Baseline at End of Treatment	-1 (± 9.91)			

Notes:

[21] - FAS for Cognition (Extension Phase)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in CDR System Global Cognition Score Over Time (Extension Phase)

End point title	Mean Change From Baseline in CDR System Global Cognition Score Over Time (Extension Phase)

End point description:

The CDR System Global Cognitive was derived from the average of 5 CDR System cognitive domain scores (Power of Attention, Continuity of Attention, Quality of Episodic Memory, Quality of Working Memory, and Speed of Memory). Domain scores were normalized to mean of 50 and SD of 10 before taking the average. The scale ranged from 0 to 100. An increase in the Global Cognitive Score indicates improvement, while a decrease indicates worsening in cognitive function. The data is presented as CDR System Global Cognitive scores at specific intervals (Week 9 for subjects with exposure of more than 9 weeks, Week 19 for subjects with exposure of more than 19 weeks, Week 30 for subjects with exposure

of more than 26 weeks, Week 39 for subjects with exposure of more than 39 weeks, and Week 52 for subjects with exposure of more than 52 weeks).

End point type	Secondary

End point timeframe:

Baseline, Week 9, Week 19, Week, 30, Week 39, and Week 52

End point values	Perampanel (Extension Phase)			
Subject group type	Reporting group			
Number of subjects analysed	112[22]			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 9 (at least 9 weeks of exposure); N=109	-3.9 (± 10.03)			
Week 9 (at least 19 weeks of exposure); N=107	-3.7 (± 9.74)			
Week 9 (at least 26 weeks of exposure); N=107	-3.7 (± 9.74)			
Week 9 (at least 39 weeks of exposure); N=90	-2.6 (± 8.73)			
Week 9 (at least 52 weeks of exposure); N=67	-3.1 (± 8.41)			
Week 19 (at least 19 weeks of exposure); N=105	-1.1 (± 8.16)			
Week 19 (at least 26 weeks of exposure); N=105	-1.1 (± 8.16)			
Week 19 (at least 39 weeks of exposure); N=88	-0.8 (± 8.45)			
Week 19 (at least 52 weeks of exposure); N=65	-1.3 (± 8.15)			
Week 30 (at least 26 weeks of exposure); N=105	-1.3 (± 9.41)			
Week 30 (at least 39 weeks of exposure); N=89	-1 (± 9.25)			
Week 30 (at least 52 weeks of exposure); N=66	-1.1 (± 9.38)			
Week 39 (at least 39 weeks of exposure); N=72	-2.3 (± 10.28)			
Week 39 (at least 52 weeks of exposure); N=52	-2.3 (± 10.23)			
Week 52 (at least 52 weeks of exposure); N=49	-0.6 (± 9.17)			

Notes:

[22] - FAS for Cognition (Extension Phase)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline by Visits in Cognition Drug Research (CDR) System Domain T-Scores (Extension Study)

End point title	Mean Change From Baseline by Visits in Cognition Drug Research (CDR) System Domain T-Scores (Extension Study)

End point description:

The Cognitive measure scores are presented as T-Scores .T-Scores were normalized standard scores with mean of 50 and SD of 10 with an absolute range of 0-100. The T-Scores are based on the norms from healthy age-matched controls from the CDR System database. Cohen's d-effect sizes were used to estimate the clinical relevance of a change in a parameter. A change in a score of 0.2 SD was defined by Cohen as a small effect size, 0.5 SD a medium effect size and 0.8 SD was considered a large effect size. An increase in the T-scores indicates improvement while a decrease in T-scores indicates worsening. Wk = Week and EOT=End of Treatment. The perampanel exposure duration starts from the first perampanel dose (in the Core Study for subjects previously randomized to perampanel or Extension Phase for subjects previously randomized to placebo) to the last perampanel dose in the Extension Phase.

End point type	Secondary

End point timeframe:

Baseline (Visit 2/Week 0 Evaluation), Week 9, Week 19, Week 30, Week 39, Week 52, and EOT (defined as the last nonmissing value after date of first dose up to 14 days after date of last dose)

End point values	Perampanel (Extension Phase)			
Subject group type	Reporting group			
Number of subjects analysed	112[23]			
Units: T-score				
arithmetic mean (standard deviation)				
Power of Attention: Week 9 (N=112)	-12.1 (± 22.24)			
Power of Attention: Week 19 (N=105)	-6.5 (± 19.39)			
Power of Attention: Week 30 (N=105)	-8.5 (± 23.77)			
Power of Attention: Week 39 (N=73)	-11.7 (± 27.04)			
Power of Attention: Week 52 (N=62)	-7.5 (± 26.4)			
Power of Attention: End of treatment (N=112)	-8 (± 25.75)			
Continuity of Attention: Week 9 (N=112)	-3.1 (± 8.99)			
Continuity of Attention: Week 19 (N=105)	-1.7 (± 8.1)			
Continuity of Attention: Week 30 (N=105)	-0.9 (± 8.44)			
Continuity of Attention: Week 39 (N=73)	-1.7 (± 8.16)			
Continuity of Attention: Week 52 (N=62)	-0.9 (± 8.97)			
Continuity of Attention: End of treatment (N=112)	-0.9 (± 7.99)			
Quality of episodic secondary Memory:Wk 9 (N=112)	1.3 (± 9.27)			
Quality of episodic secondary Memory:Wk 19 (N=105)	3 (± 9.76)			
Quality of episodic secondary Memory:Wk 30 (N=104)	2.5 (± 10.15)			
Quality of episodic secondary Memory:Wk 39 (N=73)	1.8 (± 9.78)			
Quality of episodic secondary Memory:Wk 52 (N=63)	2.4 (± 11.33)			
Quality of episodic secondary Memory: EOT (N=112)	2 (± 10)			

Quality of working memory (short term):Wk 9(N=112)	-1.8 (± 14.81)			
Quality of working memory (short term):Wk19(N=105)	1 (± 12.61)			
Quality of working memory (short term):Wk30(N=105	1.4 (± 11.63)			
Quality of working memory (short term):Wk 39 (N=73	-1.2 (± 13.31)			
Quality of working memory (short term):Wk 52(N=63)	1.4 (± 14.85)			
Quality of working memory (short term):EOT (N=112)	0.5 (± 12.85)			
Speed of memory: Week 9 (N=111)	-3.5 (± 21.26)			
Speed of memory: Week 19 (N=105)	-1.3 (± 18.23)			
Speed of memory: Week 30 (N=104)	-1.4 (± 20.63)			
Speed of memory: Week 39 (N=73)	1.8 (± 25.16)			
Speed of memory: Week 52 (N=63)	3.9 (± 25.34)			
Speed of memory: Week EOT (N=112)	1 (± 22.82)			

Notes:

[23] - FAS for cognition (Extension Phase)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in CDR System Domain T-Score Over Time: Power of Attention (Extension Phase)

End point title	Mean Change From Baseline in CDR System Domain T-Score Over Time: Power of Attention (Extension Phase)

End point description:

The Cognitive measure scores are presented as T-Scores at specific intervals (Week 9 for subjects with exposure of more than 9 weeks, Week 19 for subjects with exposure of more than 19 weeks, Week 30 for subjects with exposure of more than 26 weeks, Week 39 for subjects with exposure of more than 39 weeks, and Week 52 for subjects with exposure of more than 52 weeks). T-Scores were normalized standard scores with mean of 50 and SD of 10 with an absolute range of 0-100. The T-Scores are based on the norms from healthy age-matched controls from the CDR System database. Cohen's d-effect sizes were used to estimate the clinical relevance of a change in a parameter. A change in a score of 0.2 SD was defined by Cohen as a small effect size, 0.5 SD a medium effect size and 0.8 SD was considered a large effect size. An increase in the T-scores indicates improvement while a decrease in T-scores indicates worsening.

End point type	Secondary

End point timeframe:

Baseline, Week 9, Week 19, Week 30, Week 39, and Week 52

End point values	Perampanel (Extension Phase)			
Subject group type	Reporting group			
Number of subjects analysed	112[24]			
Units: T-score				
arithmetic mean (standard deviation)				
Week 9 (at least 9 weeks of exposure); N=109	-12.3 (± 22.47)			

Week 9 (at least 19 weeks of exposure); N=107	-11.7 (± 22.07)			
Week 9 (at least 26 weeks of exposure); N=107	-11.7 (± 22.07)			
Week 9 (at least 39 weeks of exposure); N=90	-9.5 (± 17.49)			
Week 9 (at least 52 weeks of exposure); N=67	-9.2 (± 18.13)			
Week 19 (at least 19 weeks of exposure); N=105	-6.5 (± 19.39)			
Week 19 (at least 26 weeks of exposure); N=105	-6.5 (± 19.39)			
Week 19 (at least 39 weeks of exposure); N=88	-4.9 (± 18.82)			
Week 19 (at least 52 weeks of exposure); N=65	-5.5 (± 19.37)			
Week 30 (at least 26 weeks of exposure); N=105	-8.5 (± 23.77)			
Week 30 (at least 39 weeks of exposure); N=89	-7.9 (± 21.66)			
Week 30 (at least 52 weeks of exposure); N=66	-7.6 (± 22.39)			
Week 39 (at least 39 weeks of exposure); N=72	-11.8 (± 27.22)			
Week 39 (at least 52 weeks of exposure); N=52	-12.3 (± 28.34)			
Week 52 (at least 52 weeks of exposure); N=48	-8.9 (± 25.45)			

Notes:

[24] - FAS for cognition (Extension Phase)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in CDR System Domain T-Score Over Time: Continuity of Attention (Extension Phase)

End point title	Mean Change From Baseline in CDR System Domain T-Score Over Time: Continuity of Attention (Extension Phase)

End point description:

The Cognitive measure scores are presented as T-Scores at specific intervals (Week 9 for subjects with exposure of more than 9 weeks, Week 19 for subjects with exposure of more than 19 weeks, Week 30 for subjects with exposure of more than 26 weeks, Week 39 for subjects with exposure of more than 39 weeks, and Week 52 for subjects with exposure of more than 52 weeks). T-Scores were normalized standard scores with mean of 50 and SD of 10 with an absolute range of 0-100. The T-Scores are based on the norms from healthy age-matched controls from the CDR System database. Cohen's d-effect sizes were used to estimate the clinical relevance of a change in a parameter. A change in a score of 0.2 SD was defined by Cohen as a small effect size, 0.5 SD a medium effect size and 0.8 SD was considered a large effect size. An increase in the T-scores indicates improvement while a decrease in T-scores indicates worsening.

End point type	Secondary

End point timeframe:

Baseline, Week 9, Week 19, Week, 30, Week 39, and Week 52

End point values	Perampanel (Extension Phase)			
Subject group type	Reporting group			
Number of subjects analysed	112[25]			
Units: T-score				
arithmetic mean (standard deviation)				
Week 9 (at least 9 weeks of exposure); N=109	-3.1 (± 9.11)			
Week 9 (at least 19 weeks of exposure); N=107	-3 (± 9.01)			
Week 9 (at least 26 weeks of exposure); N=107	-3 (± 9.01)			
Week 9 (at least 39 weeks of exposure); N=90	-2.8 (± 9.17)			
Week 9 (at least 52 weeks of exposure); N=67	-3.6 (± 9.53)			
Week 19 (at least 19 weeks of exposure); N=105	-1.7 (± 8.1)			
Week 19 (at least 26 weeks of exposure); N=105	-1.7 (± 8.1)			
Week 19 (at least 39 weeks of exposure); N=88	-1.7 (± 8.1)			
Week 19 (at least 52 weeks of exposure); N=65	-2.3 (± 8.49)			
Week 30 (at least 26 weeks of exposure); N=105	-0.9 (± 8.44)			
Week 30 (at least 39 weeks of exposure); N=89	-1.1 (± 8.65)			
Week 30 (at least 52 weeks of exposure); N=66	-1 (± 7.47)			
Week 39 (at least 39 weeks of exposure); N=72	-1.8 (± 8.2)			
Week 39 (at least 52 weeks of exposure); N=52	-1.4 (± 8.24)			
Week 52 (at least 52 weeks of exposure); N=48	-0.5 (± 8.6)			

Notes:

[25] - FAS for cognition (Extension Phase)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in CDR System Domain T-Score Over Time: Quality of Episodic Secondary Memory (Extension Phase)

End point title	Mean Change From Baseline in CDR System Domain T-Score Over Time: Quality of Episodic Secondary Memory (Extension Phase)

End point description:

The Cognitive measure scores are presented as T-Scores at specific intervals (Week 9 for subjects with exposure of more than 9 weeks, Week 19 for subjects with exposure of more than 19 weeks, Week 30 for subjects with exposure of more than 26 weeks, Week 39 for subjects with exposure of more than 39 weeks, and Week 52 for subjects with exposure of more than 52 weeks). T-Scores were normalized standard scores with mean of 50 and SD of 10 with an absolute range of 0-100. The T-Scores are based on the norms from healthy age-matched controls from the CDR System database. Cohen's d-effect sizes were used to estimate the clinical relevance of a change in a parameter. A change in a score of 0.2 SD was defined by Cohen as a small effect size, 0.5 SD a medium effect size and 0.8 SD was considered a

large effect size. An increase in the T-scores indicates improvement while a decrease in T-scores indicates worsening.

End point type	Secondary

End point timeframe:

Baseline, Week 9, Week 19, Week 30, Week 39, and Week 52

End point values	Perampanel (Extension Phase)			
Subject group type	Reporting group			
Number of subjects analysed	112[26]			
Units: T-score				
arithmetic mean (standard deviation)				
Week 9 (at least 9 weeks of exposure); N=109	1.2 (± 9.35)			
Week 9 (at least 19 weeks of exposure); N=107	1.4 (± 9.37)			
Week 9 (at least 26 weeks of exposure); N=107	1.4 (± 9.37)			
Week 9 (at least 39 weeks of exposure); N=90	1.9 (± 9.67)			
Week 9 (at least 52 weeks of exposure); N=67	2 (± 10.13)			
Week 19 (at least 19 weeks of exposure); N=105	3 (± 9.76)			
Week 19 (at least 26 weeks of exposure); N=105	3 (± 9.76)			
Week 19 (at least 39 weeks of exposure); N=88	2.8 (± 9.66)			
Week 19 (at least 52 weeks of exposure); N=65	2.6 (± 9.33)			
Week 30 (at least 26 weeks of exposure); N=104	2.5 (± 10.15)			
Week 30 (at least 39 weeks of exposure); N=88	2.5 (± 10.56)			
Week 30 (at least 52 weeks of exposure); N=65	2.3 (± 10.85)			
Week 39 (at least 39 weeks of exposure); N=72	1.9 (± 9.85)			
Week 39 (at least 52 weeks of exposure); N=52	2.9 (± 10.06)			
Week 52 (at least 52 weeks of exposure); N=49	2 (± 11.61)			

Notes:

[26] - FAS for cognition (Extension Phase)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in CDR System Domain T-Score Over Time: Quality of Working Memory (Short Term) (Extension Phase)

End point title	Mean Change From Baseline in CDR System Domain T-Score Over Time: Quality of Working Memory (Short Term) (Extension Phase)

End point description:

The Cognitive measure scores are presented as T-Scores at specific intervals (Week 9 for subjects with exposure of more than 9 weeks, Week 19 for subjects with exposure of more than 19 weeks, Week 30 for subjects with exposure of more than 26 weeks, Week 39 for subjects with exposure of more than 39 weeks, and Week 52 for subjects with exposure of more than 52 weeks). T-Scores were normalized standard scores with mean of 50 and SD of 10 with an absolute range of 0-100. The T-Scores are based on the norms from healthy age-matched controls from the CDR System database. Cohen's d-effect sizes were used to estimate the clinical relevance of a change in a parameter. A change in a score of 0.2 SD was defined by Cohen as a small effect size, 0.5 SD a medium effect size and 0.8 SD was considered a large effect size. An increase in the T-scores indicates improvement while a decrease in T-scores indicates worsening.

End point type	Secondary

End point timeframe:

Baseline, Week 9, Week 19, Week, 30, Week 39, and Week 52

End point values	Perampanel (Extension Phase)			
Subject group type	Reporting group			
Number of subjects analysed	112[27]			
Units: T-score				
arithmetic mean (standard deviation)				
Week 9 (at least 9 weeks of exposure); N=109	-2 (± 14.95)			
Week 9 (at least 19 weeks of exposure); N=107	-1.9 (± 14.93)			
Week 9 (at least 26 weeks of exposure); N=107	-1.9 (± 14.93)			
Week 9 (at least 39 weeks of exposure); N=90	-1.2 (± 14.58)			
Week 9 (at least 52 weeks of exposure); N=67	-0.6 (± 12.03)			
Week 19 (at least 19 weeks of exposure); N=105	1 (± 12.61)			
Week 19 (at least 26 weeks of exposure); N=105	1 (± 12.61)			
Week 19 (at least 39 weeks of exposure); N=88	1 (± 12.24)			
Week 19 (at least 52 weeks of exposure); N=65	1.1 (± 8.91)			
Week 30 (at least 26 weeks of exposure); N=105	1.4 (± 11.63)			
Week 30 (at least 39 weeks of exposure); N=89	1.5 (± 11.64)			
Week 30 (at least 52 weeks of exposure); N=66	1.1 (± 10)			
Week 39 (at least 39 weeks of exposure); N=72	-1.1 (± 13.38)			
Week 39 (at least 52 weeks of exposure); N=52	-0.1 (± 11.77)			
Week 52 (at least 52 weeks of exposure); N=49	2.9 (± 10.22)			

Notes:

[27] - FAS for cognition (Extension Phase)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in CDR System Domain T-Score Over Time: Speed of Memory (Extension Phase)

End point title	Mean Change From Baseline in CDR System Domain T-Score Over Time: Speed of Memory (Extension Phase)

End point description:

The Cognitive measure scores are presented as T-Scores at specific intervals (Week 9 for subjects with exposure of more than 9 weeks, Week 19 for subjects with exposure of more than 19 weeks, Week 30 for subjects with exposure of more than 26 weeks, Week 39 for subjects with exposure of more than 39 weeks, and Week 52 for subjects with exposure of more than 52 weeks). T-Scores were normalized standard scores with mean of 50 and SD of 10 with an absolute range of 0-100. The T-Scores are based on the norms from healthy age-matched controls from the CDR System database. Cohen's d-effect sizes were used to estimate the clinical relevance of a change in a parameter. A change in a score of 0.2 SD was defined by Cohen as a small effect size, 0.5 SD a medium effect size and 0.8 SD was considered a large effect size. An increase in the T-scores indicates improvement while a decrease in T-scores indicates worsening.

End point type	Secondary

End point timeframe:

Baseline, Week 9, Week 19, Week, 30, Week 39, and Week 52

End point values	Perampanel (Extension Phase)			
Subject group type	Reporting group			
Number of subjects analysed	112[28]			
Units: T-score				
arithmetic mean (standard deviation)				
Week 9 (at least 9 weeks of exposure); N=108	-3.7 (± 21.51)			
Week 9 (at least 19 weeks of exposure); N=106	-3.1 (± 21.31)			
Week 9 (at least 26 weeks of exposure); N=106	-3.1 (± 21.31)			
Week 9 (at least 39 weeks of exposure); N=89	-1.6 (± 20.85)			
Week 9 (at least 52 weeks of exposure); N=67	-4.3 (± 15.34)			
Week 19 (at least 19 weeks of exposure); N=105	-1.3 (± 18.23)			
Week 19 (at least 26 weeks of exposure); N=105	-1.3 (± 18.23)			
Week 19 (at least 39 weeks of exposure); N=88	-1.1 (± 18.31)			
Week 19 (at least 52 weeks of exposure); N=65	-2.4 (± 15.57)			
Week 30 (at least 26 weeks of exposure); N=104	-1.4 (± 20.63)			
Week 30 (at least 39 weeks of exposure); N=88	-0.7 (± 19.74)			
Week 30 (at least 52 weeks of exposure); N=65	-1 (± 20.06)			
Week 39 (at least 39 weeks of exposure); N=72	1.6 (± 25.29)			
Week 39 (at least 52 weeks of exposure); N=52	-0.5 (± 24.97)			

Week 52 (at least 52 weeks of exposure); N=49	1.8 (± 24.05)			

Notes:

[28] - FAS for cognition (Extension Phase)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to End of Treatment in Controlled Oral Word Association Test Scores (COWAT) (Extension Phase)

End point title	Change From Baseline to End of Treatment in Controlled Oral Word Association Test Scores (COWAT) (Extension Phase)

End point description:

The COWAT test measured the executive function of the frontal lobe and consisted of examinations of category/meaning fluency and letter/phoneme fluency. It consisted of 2 parts which included the Letter Fluency task and the Category Fluency task. For the Letter Fluency task, the participant was given one minute to list as many words as they could which began with a given letter from the following set of 3 letters: F, A, and L. The number of correct words from the 3 sets comprised the Letter Fluency score. For the Category Fluency task, the participant was given one minute to list as many words as they could which belonged to a given category. The number of correct words comprised the Category Fluency score. Total score was calculated as sum of acceptable words generated. The scale ranged from 0-90, with higher scores indicating improvement in language.

End point type	Secondary

End point timeframe:

From Baseline up to Week 52 or up to EOT (defined as the last nonmissing value after date of first dose up to 14 days after date of last dose)

End point values	Perampanel (Extension Phase)			
Subject group type	Reporting group			
Number of subjects analysed	112[29]			
Units: Scale on a score				
arithmetic mean (standard deviation)				
Letter Fluency Score; N=110	2.2 (± 7.98)			
Category Fluency Score; N=110	-0.3 (± 4.02)			

Notes:

[29] - FAS for cognition (Extension Phase).

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to End of Treatment in Time to Complete Lafayette Grooved Pegboard Test (LGPT) (Extension Phase)

End point title	Change From Baseline to End of Treatment in Time to Complete Lafayette Grooved Pegboard Test (LGPT) (Extension Phase)

End point description:

The LGPT test measured visuomotor skills. This test was a manipulative dexterity test that consisted of a metal matrix of 25 holes with randomly positioned slots. The participant was required to insert 25 grooved pegs into the holes. The task was completed once for each hand; firstly, using the dominant hand followed by the non-dominant hand. The task was timed and the scores were the time taken for the participant to complete all 25 pegs for each hand. If the test cannot be completed within 300 seconds, 300 seconds were recorded for the time. An increase in score (longer time) indicated worsening of visuomotor skills. The time to complete test is presented as mean seconds +/- SD.

End point type	Secondary

End point timeframe:

From Baseline up to Week 52 or up to EOT (defined as the last nonmissing value after date of first dose up to 14 days after date of last dose)

End point values	Perampanel (Extension Phase)			
Subject group type	Reporting group			
Number of subjects analysed	112[30]			
Units: Seconds				
arithmetic mean (standard deviation)				
Dominant Hand (N=112)	0.5 (± 18.67)			
Non-Dominant Hand (N=111)	-3.3 (± 22.49)			

Notes:

[30] - FAS for cognition (Extension Phase).

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Bone Age Minus Age (Months) From Hand X-ray (Extension Phase)

End point title	Mean Change From Baseline in Bone Age Minus Age (Months) From Hand X-ray (Extension Phase)

End point description:

Bone age was measured using hand X-ray. The mean change from Baseline in bone age (months) minus age (months) from the hand x-ray was assessed. "+" means bone age is older than age and "-" means bone age is younger than age.

End point type	Secondary

End point timeframe:

From Baseline up to Week 52 or up to EOT (defined as the last nonmissing value after date of first dose up to 14 days after date of last dose)

End point values	Perampanel (Extension Phase)			
Subject group type	Reporting group			
Number of subjects analysed	114[31]			
Units: Months				
arithmetic mean (standard deviation)				
Baseline; N=110	3.3 (± 16.21)			
Change from Baseline at EOT; N=109	-2 (± 9.83)			

Notes:

[31] - Safety Analysis Set (SAS) -Extension Phase

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to End of Treatment for the Tanner Stage

End point title	Change from Baseline to End of Treatment for the Tanner Stage

End point description:

The effect of perampanel on growth and development in adolescents (male and female), including sexual development, was measured using Tanner scale. The scale defined physical measurements of development based on external primary and secondary sex characteristics, such as the size of the breasts, genitals, testicular volume and development of pubic hair. Tanner scale consisted of 5 scales from I to V: Stage I (prepubertal); Stage II (increase in scrotum and testes, breast bud appears, sparse pubic hair growth; Stage III (increase in penis length, breast size and areola, amount and texture of pubic hair); Stage IV (continued increase in penis length, scrotum and testes, secondary mound formed above breast level, adult type pubic hair); Stage V (adult genitalia, mature breast, adult type pubic hair in texture and quantity). Data is reported as the number of participants with shifts in Tanner Stage from Baseline to End of Treatment.

End point type	Secondary

End point timeframe:

From Baseline up to Week 52 or End of treatment (EOT) (defined as the last nonmissing value after date of first dose up to 14 days after date of last dose)

End point values	Perampanel (Extension Phase)			
Subject group type	Reporting group			
Number of subjects analysed	114[32]			
Units: Participants				
Baseline Tanner stage II to EOT Tanner stage II	5			
Baseline Tanner stage II to EOT Tanner stage III	2			
Baseline Tanner stage II to EOT Tanner stage IV	3			
Baseline Tanner stage III to EOT Tanner stage III	8			
Baseline Tanner stage III to EOT Tanner stage IV	12			
Baseline Tanner stage III to EOT Tanner stage V	3			
Baseline Tanner stage IV to EOT Tanner stage IV	22			

Baseline Tanner stage IV to EOT Tanner stage V	19			
Baseline Tanner stage V to EOT Tanner stage V	40			

Notes:

[32] - SAS (Extension Phase)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of first dose of study drug up to approximately 23 weeks for the Core Study and up to approximately
83 weeks for the extension phase.

Adverse event reporting additional description:

Data are presented as treatment emergent adverse events (TEAEs), defined as an adverse event that started/increased in severity on/after the first dose of study medication up to 30 days after the final dose of study medication. Safety Analysis Set (SAS), defined as all subjects who took ≥ 1 study drug dose and had a postbaseline safety assessment.

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 matching placebo tablets once a day (6 tablets of placebo).

Reporting group title	Perampanel (Core Study)

Reporting group description:

Participants received perampanel 2 mg per day and up-titrated weekly in 2-mg increments to a target dose range of 8 to 12 mg per day.

Reporting group title	Perampanel (Extension Phase)

Reporting group description:

During the Extension Phase, participants previously assigned to perampanel arm (Core Study) continued taking study medication at the dose achieved at the end of the Core Study once daily. Participants previously assigned to a placebo arm (Core Study) started perampanel dose at 2 mg/day and up-titrated weekly in 2-mg increments up to a maximum dose of 12 mg/day.

Serious adverse events	Placebo (Core Study)	Perampanel (Core Study)	Perampanel (Extension Phase)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 48 (4.17%)	5 / 85 (5.88%)	19 / 114 (16.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Accidental overdose			

subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional overdose			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament rupture			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 48 (2.08%)	0 / 85 (0.00%)	4 / 114 (3.51%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures with secondary generalisation			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Simple partial seizures			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Gastroduodenitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Testicular necrosis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 48 (0.00%)	2 / 85 (2.35%)	4 / 114 (3.51%)
occurrences causally related to treatment / all	0 / 0	1 / 2	4 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 48 (2.08%)	0 / 85 (0.00%)	0 / 114 (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
Nasopharyngitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo (Core Study)	Perampanel (Core Study)	Perampanel (Extension Phase)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 48 (62.50%)	67 / 85 (78.82%)	95 / 114 (83.33%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pituitary tumour benign			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 48 (4.17%)	0 / 85 (0.00%)	2 / 114 (1.75%)
occurrences (all)	2	0	2
Fatigue			
subjects affected / exposed	1 / 48 (2.08%)	8 / 85 (9.41%)	13 / 114 (11.40%)
occurrences (all)	1	8	13
Local swelling			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Pyrexia			
subjects affected / exposed	1 / 48 (2.08%)	2 / 85 (2.35%)	8 / 114 (7.02%)
occurrences (all)	1	2	10
Gait disturbance			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Immune system disorders			
Multiple allergies			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Drug hypersensitivity			

subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Menstruation irregular			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Testicular torsion			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 48 (4.17%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	2	0	1
Epistaxis			
subjects affected / exposed	0 / 48 (0.00%)	2 / 85 (2.35%)	0 / 114 (0.00%)
occurrences (all)	0	4	0
Nasal congestion			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Oropharyngeal pain			
subjects affected / exposed	1 / 48 (2.08%)	1 / 85 (1.18%)	2 / 114 (1.75%)
occurrences (all)	1	1	2
Rhinitis allergic			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Rhinorrhoea			
subjects affected / exposed	1 / 48 (2.08%)	2 / 85 (2.35%)	2 / 114 (1.75%)
occurrences (all)	1	2	2
Tachypnoea			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	0 / 114 (0.00%)
occurrences (all)	0	1	0
Diaphragmatic Spasm			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Dyspnoea			

subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Snoring			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Psychiatric disorders			
Irritability			
subjects affected / exposed	1 / 48 (2.08%)	6 / 85 (7.06%)	7 / 114 (6.14%)
occurrences (all)	1	6	7
Adjustment disorder			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	0 / 114 (0.00%)
occurrences (all)	0	1	0
Aggression			
subjects affected / exposed	1 / 48 (2.08%)	6 / 85 (7.06%)	10 / 114 (8.77%)
occurrences (all)	1	10	14
Anger			
subjects affected / exposed	0 / 48 (0.00%)	2 / 85 (2.35%)	2 / 114 (1.75%)
occurrences (all)	0	3	3
Anxiety			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Bradyphrenia			
subjects affected / exposed	0 / 48 (0.00%)	3 / 85 (3.53%)	3 / 114 (2.63%)
occurrences (all)	0	3	3
Confusional state			
subjects affected / exposed	0 / 48 (0.00%)	3 / 85 (3.53%)	3 / 114 (2.63%)
occurrences (all)	0	3	3
Depressed mood			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Euphoric mood			
subjects affected / exposed	1 / 48 (2.08%)	2 / 85 (2.35%)	2 / 114 (1.75%)
occurrences (all)	1	2	2
Initial insomnia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	1	0	1

Insomnia			
subjects affected / exposed	3 / 48 (6.25%)	3 / 85 (3.53%)	5 / 114 (4.39%)
occurrences (all)	3	3	5
Intentional self-injury			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	0 / 114 (0.00%)
occurrences (all)	0	1	0
Mood altered			
subjects affected / exposed	1 / 48 (2.08%)	2 / 85 (2.35%)	1 / 114 (0.88%)
occurrences (all)	1	4	3
Mood swings			
subjects affected / exposed	1 / 48 (2.08%)	3 / 85 (3.53%)	4 / 114 (3.51%)
occurrences (all)	1	3	5
Self-injurious ideation			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Tearfulness			
subjects affected / exposed	1 / 48 (2.08%)	0 / 85 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0
Abnormal Behaviour			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Daydreaming			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Depression			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Nervousness			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	3 / 114 (2.63%)
occurrences (all)	0	0	4
Regressive behaviour			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Somnambulism			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1

Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 48 (4.17%)	3 / 85 (3.53%)	4 / 114 (3.51%)
occurrences (all)	2	3	4
Blood pressure diastolic decreased			
subjects affected / exposed	1 / 48 (2.08%)	0 / 85 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0
Platelet count decreased			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	0 / 114 (0.00%)
occurrences (all)	0	1	0
Thyroxine decreased			
subjects affected / exposed	1 / 48 (2.08%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	1	0	1
Weight decreased			
subjects affected / exposed	1 / 48 (2.08%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	1	0	1
Weight increased			
subjects affected / exposed	0 / 48 (0.00%)	5 / 85 (5.88%)	8 / 114 (7.02%)
occurrences (all)	0	5	9
White blood cell count decreased			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Alanine aminotransferase increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	2 / 114 (1.75%)
occurrences (all)	0	0	3
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	2 / 114 (1.75%)
occurrences (all)	0	0	3
Blood Cholesterol Increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Blood Glucose Decreased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Blood Pressure Decreased			

subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Blood Sodium Increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Blood Triglycerides Increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Electrocardiogram T Wave Abnormal			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	2 / 114 (1.75%)
occurrences (all)	0	1	2
Contusion			
subjects affected / exposed	0 / 48 (0.00%)	3 / 85 (3.53%)	3 / 114 (2.63%)
occurrences (all)	0	3	3
Excoriation			
subjects affected / exposed	0 / 48 (0.00%)	2 / 85 (2.35%)	2 / 114 (1.75%)
occurrences (all)	0	3	4
Joint injury			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	0 / 114 (0.00%)
occurrences (all)	0	1	0
Laceration			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Ligament rupture			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Muscle strain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Radius fracture			

subjects affected / exposed	1 / 48 (2.08%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	1	0	1
Tongue injury			
subjects affected / exposed	1 / 48 (2.08%)	0 / 85 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0
Wrist fracture			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Accidental Overdose			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	2 / 114 (1.75%)
occurrences (all)	0	0	2
Animal Bite			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	2 / 114 (1.75%)
occurrences (all)	0	0	2
Fall			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Foot fracture			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Hand fracture			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	2 / 114 (1.75%)
occurrences (all)	0	0	2
Head Injury			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	2 / 114 (1.75%)
occurrences (all)	0	0	2
Limb Injury			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Sunburn			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	3 / 114 (2.63%)
occurrences (all)	0	1	3

Angina pectoris			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Sinus bradycardia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 48 (0.00%)	4 / 85 (4.71%)	5 / 114 (4.39%)
occurrences (all)	0	5	6
Balance disorder			
subjects affected / exposed	0 / 48 (0.00%)	2 / 85 (2.35%)	3 / 114 (2.63%)
occurrences (all)	0	2	3
Clumsiness			
subjects affected / exposed	0 / 48 (0.00%)	2 / 85 (2.35%)	2 / 114 (1.75%)
occurrences (all)	0	2	2
Cognitive disorder			
subjects affected / exposed	1 / 48 (2.08%)	0 / 85 (0.00%)	2 / 114 (1.75%)
occurrences (all)	1	0	2
Convulsion			
subjects affected / exposed	4 / 48 (8.33%)	4 / 85 (4.71%)	10 / 114 (8.77%)
occurrences (all)	5	4	28
Depressed level of consciousness			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	0 / 114 (0.00%)
occurrences (all)	0	1	0
Disturbance in attention			
subjects affected / exposed	0 / 48 (0.00%)	2 / 85 (2.35%)	2 / 114 (1.75%)
occurrences (all)	0	2	2
Dizziness			
subjects affected / exposed	7 / 48 (14.58%)	26 / 85 (30.59%)	34 / 114 (29.82%)
occurrences (all)	7	43	59
Drooling			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Dysarthria			

subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	2 / 114 (1.75%)
occurrences (all)	0	1	2
Headache			
subjects affected / exposed	7 / 48 (14.58%)	9 / 85 (10.59%)	13 / 114 (11.40%)
occurrences (all)	15	12	21
Hypoaesthesia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Hypotonia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Lethargy			
subjects affected / exposed	0 / 48 (0.00%)	2 / 85 (2.35%)	4 / 114 (3.51%)
occurrences (all)	0	2	4
Memory impairment			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Partial seizures with secondary generalisation			
subjects affected / exposed	1 / 48 (2.08%)	0 / 85 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0
Simple partial seizures			
subjects affected / exposed	1 / 48 (2.08%)	1 / 85 (1.18%)	3 / 114 (2.63%)
occurrences (all)	4	1	3
Slow speech			
subjects affected / exposed	0 / 48 (0.00%)	2 / 85 (2.35%)	2 / 114 (1.75%)
occurrences (all)	0	2	2
Somnolence			
subjects affected / exposed	2 / 48 (4.17%)	13 / 85 (15.29%)	22 / 114 (19.30%)
occurrences (all)	2	13	23
Syncope			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	2 / 114 (1.75%)
occurrences (all)	0	1	2
Tremor			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	3 / 114 (2.63%)
occurrences (all)	0	1	3

Aphasia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	2 / 114 (1.75%)
occurrences (all)	0	0	2
Complex Partial Seizures			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Coordination Abnormal			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Dyskinesia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Dyspraxia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Epilepsy			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	3 / 114 (2.63%)
occurrences (all)	0	0	3
Migraine			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Partial Seizures			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Postictal Headache			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	2 / 48 (4.17%)	1 / 85 (1.18%)	3 / 114 (2.63%)
occurrences (all)	2	2	5
Monocytosis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	1	0	1
Neutropenia			

subjects affected / exposed	1 / 48 (2.08%)	0 / 85 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0
Anaemia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	2 / 114 (1.75%)
occurrences (all)	0	1	2
Leukopenia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 48 (2.08%)	0 / 85 (0.00%)	6 / 114 (5.26%)
occurrences (all)	1	0	12
Tinnitus			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 85 (0.00%)	2 / 114 (1.75%)
occurrences (all)	1	0	2
Mydriasis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Vision blurred			
subjects affected / exposed	0 / 48 (0.00%)	3 / 85 (3.53%)	2 / 114 (1.75%)
occurrences (all)	0	3	2
Visual impairment			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Myopia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Visual acuity reduced			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	2 / 48 (4.17%)	1 / 85 (1.18%)	2 / 114 (1.75%)
occurrences (all)	2	1	2
Abdominal pain upper			
subjects affected / exposed	1 / 48 (2.08%)	4 / 85 (4.71%)	4 / 114 (3.51%)
occurrences (all)	2	5	5
Constipation			
subjects affected / exposed	1 / 48 (2.08%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	1	1	1
Diarrhoea			
subjects affected / exposed	1 / 48 (2.08%)	2 / 85 (2.35%)	4 / 114 (3.51%)
occurrences (all)	1	2	4
Gastritis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 85 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	2 / 48 (4.17%)	2 / 85 (2.35%)	6 / 114 (5.26%)
occurrences (all)	5	2	9
Abdominal discomfort			
subjects affected / exposed	0 / 48 (0.00%)	2 / 85 (2.35%)	2 / 114 (1.75%)
occurrences (all)	0	2	3
Dry mouth			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Hyperchlorhydria			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	0 / 114 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	0 / 48 (0.00%)	2 / 85 (2.35%)	2 / 114 (1.75%)
occurrences (all)	0	2	2
Dyspepsia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1

Enterocolitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 48 (2.08%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	1	1	2
Dermal cyst			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Dermatitis contact			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	2 / 114 (1.75%)
occurrences (all)	0	1	2
Heat rash			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	0 / 114 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	3 / 114 (2.63%)
occurrences (all)	0	1	5
Swelling face			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Urticaria			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Acne			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	2 / 114 (1.75%)
occurrences (all)	0	0	2
Dermatitis Acneiform			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Macule			

subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Photosensitivity reaction			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Rash Maculo-Papular			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Seborrhoeic Dermatitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Miliaria			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Crystalluria			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	2
Enuresis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	2 / 114 (1.75%)
occurrences (all)	0	0	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Back pain			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Epiphyses premature fusion			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Joint swelling			

subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	0 / 114 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	0 / 48 (0.00%)	2 / 85 (2.35%)	2 / 114 (1.75%)
occurrences (all)	0	2	2
Myalgia			
subjects affected / exposed	1 / 48 (2.08%)	0 / 85 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0
Myositis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Muscle Spasms			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	2 / 114 (1.75%)
occurrences (all)	0	0	2
Pain In Extremity			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	2 / 114 (1.75%)
occurrences (all)	0	0	3
Tendonitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 85 (0.00%)	3 / 114 (2.63%)
occurrences (all)	1	0	3
Fungal skin infection			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Influenza			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	2 / 114 (1.75%)
occurrences (all)	0	1	3
Nasopharyngitis			
subjects affected / exposed	3 / 48 (6.25%)	3 / 85 (3.53%)	13 / 114 (11.40%)
occurrences (all)	4	4	16
Pharyngitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1

Respiratory tract infection			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Sinusitis			
subjects affected / exposed	1 / 48 (2.08%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	1	1	1
Skin infection			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Tonsillitis			
subjects affected / exposed	0 / 48 (0.00%)	2 / 85 (2.35%)	2 / 114 (1.75%)
occurrences (all)	0	2	2
Tracheitis			
subjects affected / exposed	1 / 48 (2.08%)	0 / 85 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	3 / 48 (6.25%)	4 / 85 (4.71%)	5 / 114 (4.39%)
occurrences (all)	3	5	6
Urinary tract infection			
subjects affected / exposed	1 / 48 (2.08%)	2 / 85 (2.35%)	3 / 114 (2.63%)
occurrences (all)	1	2	4
Vaginitis bacterial			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	0 / 114 (0.00%)
occurrences (all)	0	1	0
Varicella			
subjects affected / exposed	1 / 48 (2.08%)	0 / 85 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 48 (0.00%)	2 / 85 (2.35%)	3 / 114 (2.63%)
occurrences (all)	0	2	3
Acarodermatitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Cellulitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1

Cystitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Fungal infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	2 / 114 (1.75%)
occurrences (all)	0	0	2
Laryngitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Localised infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Oral Herpes			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Viral infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Bacterial vaginosis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 85 (0.00%)	1 / 114 (0.88%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Appetite disorder			
subjects affected / exposed	1 / 48 (2.08%)	0 / 85 (0.00%)	0 / 114 (0.00%)
occurrences (all)	1	0	0
Decreased appetite			

subjects affected / exposed	1 / 48 (2.08%)	3 / 85 (3.53%)	4 / 114 (3.51%)
occurrences (all)	1	3	5
Hypernatraemia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Hypertriglyceridaemia			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1
Increased appetite			
subjects affected / exposed	0 / 48 (0.00%)	4 / 85 (4.71%)	4 / 114 (3.51%)
occurrences (all)	0	4	4
Obesity			
subjects affected / exposed	0 / 48 (0.00%)	1 / 85 (1.18%)	1 / 114 (0.88%)
occurrences (all)	0	1	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Results were ready but could not be released before 21 July 2015 due to EudraCT System issues.

Notes: