Clinical trial results:
A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of Brivaracetam in subjects (16 to 80 years old) with partial onset seizures

Summary

EudraCT number	2010-019361-28
Trial protocol	BE DE CZ ES IT GB SE FR FI AT NL EE LT LV HU BG RO
Global end of trial date	22 May 2014

Results information

Result version number	v1 (current)
This version publication date	28 June 2016
First version publication date	30 July 2015

Trial information

Trial identification

Sponsor protocol code	N01358

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01261325
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB BIOSCIENCES Inc.
Sponsor organisation address	8010 Arco Corporate Drive, Raleigh, United States, 27617
Public contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, 0049 2173 48 15 15, clinicaltrials@ucb.com
Scientific contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, 0049 2173 48 15 15, clinicaltrials@ucb.com

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	30 June 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of brivaracetam (BRV) at doses of 100 and 200mg/day compared with placebo (PBO) as adjunctive treatment in adult focal epilepsy subjects with partial-onset seizures (POS) not fully controlled despite current treatment with 1 or 2 concomitant antiepileptic drugs (AEDs).

Protection of trial subjects:

Subject’s informed consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the subject in both oral and written form by the Investigator (or designee). Each subject will have the opportunity to discuss the study and its alternatives with the Investigator.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	10 December 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 22
Country: Number of subjects enrolled	United States: 165
Country: Number of subjects enrolled	Brazil: 20
Country: Number of subjects enrolled	Mexico: 66
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Finland: 7
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 26
Country: Number of subjects enrolled	Italy: 52
Country: Number of subjects enrolled	Netherlands: 4

Country: Number of subjects enrolled	Spain: 49
Country: Number of subjects enrolled	Sweden: 15
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	Bulgaria: 8
Country: Number of subjects enrolled	Czech Republic: 36
Country: Number of subjects enrolled	Estonia: 23
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	Latvia: 9
Country: Number of subjects enrolled	Lithuania: 11
Country: Number of subjects enrolled	Poland: 65
Country: Number of subjects enrolled	Russian Federation: 28
Country: Number of subjects enrolled	Hong Kong: 4
Country: Number of subjects enrolled	India: 36
Country: Number of subjects enrolled	Japan: 7
Country: Number of subjects enrolled	Korea, Republic of: 26
Country: Number of subjects enrolled	Taiwan: 18
Country: Number of subjects enrolled	Puerto Rico: 1
Worldwide total number of subjects	768
EEA total number of subjects	375

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)	20
Adults (18-64 years)	725
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment for the N01358 study began in December 2010. The study concluded in May 2014.

Pre-assignment

Screening details:

The Participant Flow and Baseline Demographics data is taken from the Randomized Set (RS). The RS consists of all subjects who were randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Matching placebo tablets administered twice daily

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

Dosage and administration details:

Oral film-coated tablets taken twice a day.

Arm title	Brivaracetam 100 mg/day

Arm description:

Brivaracetam 50 mg administered twice daily.

Arm type	Experimental
Investigational medicinal product name	Brivaracetam
Investigational medicinal product code	BRV
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Oral film-coated tablets of BRV 10mg, BRV 25mg, or BRV 50mg taken orally twice a day.

Arm title	Brivaracetam 200 mg/day

Arm description:

Brivaracetam 100 mg administered twice daily

Arm type	Experimental
Investigational medicinal product name	Brivaracetam
Investigational medicinal product code	BRV
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:
Oral film-coated tablets of BRV 10mg, BRV 25mg, or BRV 50mg taken orally twice a day.

Number of subjects in period 1	Placebo	Brivaracetam 100 mg/day	Brivaracetam 200 mg/day
Started	263	254	251
Completed	246	225	225
Not completed	17	29	26
Randomized in error	-	-	1
AE, serious fatal	-	-	2
Non Compliance	2	-	-
Screen Failure	1	-	-
AE, non-serious non-fatal	9	15	13
Randomized by mistake	-	1	-
SAE, non-fatal + AE, non-serious non-fatal	-	1	1
Consent withdrawn by subject	2	2	4
Erroneously Randomized	1	-	-
Lost to follow-up	-	1	3
SAE, non-fatal	1	5	1
Lack of efficacy	1	1	-
Protocol deviation	-	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Matching placebo tablets administered twice daily	
Reporting group title	Brivaracetam 100 mg/day
Reporting group description:	
Brivaracetam 50 mg administered twice daily.	
Reporting group title	Brivaracetam 200 mg/day
Reporting group description:	
Brivaracetam 100 mg administered twice daily	

Reporting group values	Placebo	Brivaracetam 100 mg/day	Brivaracetam 200 mg/day
Number of subjects	263	254	251
Age Categorical			
This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study.			
Units: Subjects			
12-<18	7	6	7
18-<65	250	237	238
65-<85	6	11	6
Age Continuous			
This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study.			
Units: years			
arithmetic mean	39.8	39	39.7
standard deviation	± 12.8	± 13.4	± 12.8
Gender Categorical			
This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study.			
Units: Subjects			
Male	135	102	134
Female	128	152	117
Racial Group			
This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study.			
Units: Subjects			
American Indian or Alaska Native	10	8	11
Asian	32	32	29
Black or African American	11	8	7
White	190	183	183
Other	17	21	18
Missing	3	2	3
Weight			
This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study.			
Units: kilograms			
median	76.1	74.1	75.5
standard deviation	± 19.9	± 16.8	± 19

Height			
This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study.			
Units: centimeters			
arithmetic mean	168.4	166.6	168.7
standard deviation	± 10	± 9.8	± 9.9
BMI			
This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study.			
Units: kg/m^2			
arithmetic mean	26.6	26.7	26.4
standard deviation	± 5.7	± 5.6	± 6

Reporting group values	Total		
Number of subjects	768		
Age Categorical			
This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study.			
Units: Subjects			
12-<18	20		
18-<65	725		
65-<85	23		
Age Continuous			
This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical			
This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study.			
Units: Subjects			
Male	371		
Female	397		
Racial Group			
This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study.			
Units: Subjects			
American Indian or Alaska Native	29		
Asian	93		
Black or African American	26		
White	556		
Other	56		
Missing	8		
Weight			
This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study.			
Units: kilograms			
median			
standard deviation	-		
Height			
This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study.			
Units: centimeters			

arithmetic mean standard deviation	- 		
BMI			
This analysis set consists of the Randomized Subjects (RS), which is all subjects randomized into the study.			
Units: kg/m^2 arithmetic mean standard deviation	- 		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Matching placebo tablets administered twice daily	
Reporting group title	Brivaracetam 100 mg/day
Reporting group description: Brivaracetam 50 mg administered twice daily.	
Reporting group title	Brivaracetam 200 mg/day
Reporting group description: Brivaracetam 100 mg administered twice daily	

Primary: Percent reduction over placebo for partial onset seizure (Type I) frequency over the Treatment Period standardized to a 28-day duration

End point title	Percent reduction over placebo for partial onset seizure (Type I) frequency over the Treatment Period standardized to a 28-day duration
End point description: Primary endpoint: United States of America (FDA)	
End point type	Primary
End point timeframe: 12 week Treatment Period	

End point values	Placebo	Brivaracetam 100 mg/day	Brivaracetam 200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259[1]	252[2]	249[3]	
Units: Percentage of reduction				
number (not applicable)				
percentage	0	22.8	23.2	

Notes:

[1] - Intent-to-Treat (ITT) Population

[2] - Intent-to-Treat (ITT) Population

[3] - Intent-to-Treat (ITT) Population

Statistical analyses

Statistical analysis title	Statistical Analysis - BRV 100 mg/ day v Placebo
Statistical analysis description: Statistically significant with control of Type I error rate based on a Hochberg multiple comparison procedure.	
Comparison groups	Brivaracetam 100 mg/day v Placebo

Number of subjects included in analysis	511
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	< 0.001 [5]
Method	ANCOVA
Parameter estimate	Percent reduction over PBO
Point estimate	22.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.3
upper limit	31.2

Notes:

[4] - ANCOVA (analysis of covariance), with Log-transformed Treatment Period 28-day adjusted POS frequency as the outcome, and effects of treatment, country, and the four possible combinations of LEV status (never used or prior use) with number of previous AEDs (≤2 or >2), and log-transformed baseline seizure frequency as a continuous covariate.

[5] - Multiplicity-adjusted p-values based on a Hochberg multiple comparison procedure.

Statistical analysis title	Statistical Analysis - BRV 200 mg/ day v Placebo

Statistical analysis description:

Statistically significant with control of Type I error rate based on a Hochberg multiple comparison procedure.

Comparison groups	Placebo v Brivaracetam 200 mg/day
Number of subjects included in analysis	508
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	< 0.001 [7]
Method	ANCOVA
Parameter estimate	Percent reduction over PBO
Point estimate	23.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.8
upper limit	31.6

Notes:

[6] - ANCOVA (analysis of covariance), with Log-transformed Treatment Period 28-day adjusted POS frequency as the outcome, and effects of treatment, country, and the four possible combinations of LEV status (never used or prior use) with number of previous AEDs (≤2 or >2), and log-transformed baseline seizure frequency as a continuous covariate.

[7] - Multiplicity-adjusted p-values based on a Hochberg multiple comparison procedure.

Primary: 50% responder rate for partial onset seizure (Type I) frequency over the Treatment Period standardized to a 28-day duration

End point title	50% responder rate for partial onset seizure (Type I) frequency over the Treatment Period standardized to a 28-day duration

End point description:

Primary Endpoint: European Regulatory Authorities

End point type	Primary

End point timeframe:

Baseline to 12 week Treatment Period

End point values	Placebo	Brivaracetam 100 mg/day	Brivaracetam 200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259[8]	252[9]	249[10]	
Units: Percentage of responders				
number (not applicable)				
Responders	21.6	38.9	37.8	
Non-Responders	78.4	61.1	62.2	

Notes:

[8] - Intent-to-Treat (ITT) Population

[9] - Intent-to-Treat (ITT) Population

[10] - Intent-to-Treat (ITT) Population

Statistical analyses

Statistical analysis title	Statistical Analysis - BRV 100 mg/ day v Placebo

Statistical analysis description:

Statistically significant with control of Type I error rate based on a Hochberg multiple comparison procedure.

Comparison groups	Brivaracetam 100 mg/day v Placebo
Number of subjects included in analysis	511
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	< 0.001 [12]
Method	Regression, Logistic
Parameter estimate	Odds ratio (BRV versus PBO)
Point estimate	2.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.6
upper limit	3.6

Notes:

[11] - Logistic regression model, with effects of treatment, country, and the four possible combinations of LEV status (never used or prior use) with number of previous AEDs (≤2 or >2), and log-transformed baseline seizure frequency as a continuous covariate.

[12] - Multiplicity-adjusted p-values based on a Hochberg multiple comparison procedure.

Statistical analysis title	Statistical Analysis - BRV 200 mg/ day v Placebo

Statistical analysis description:

Statistically significant with control of Type I error rate based on a Hochberg multiple comparison procedure.

Comparison groups	Brivaracetam 200 mg/day v Placebo
Number of subjects included in analysis	508
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	< 0.001 [14]
Method	Regression, Logistic
Parameter estimate	Odds ratio (BRV versus PBO)
Point estimate	2.19

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.5
upper limit	3.3

Notes:

[13] - Logistic regression model, with effects of treatment, country, and the four possible combinations of LEV status (never used or prior use) with number of previous AEDs (≤2 or >2), and log-transformed baseline seizure frequency as a continuous covariate.

[14] - Multiplicity-adjusted p-values based on a Hochberg multiple comparison procedure.

Secondary: Percent reduction in partial onset seizure (Type I) frequency from the Baseline to the Treatment Period

End point title	Percent reduction in partial onset seizure (Type I) frequency from the Baseline to the Treatment Period

End point description:

End point type	Secondary

End point timeframe:

Baseline to 12 week Treatment Period

End point values	Placebo	Brivaracetam 100 mg/day	Brivaracetam 200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259[15]	252[16]	249[17]	
Units: percentage of reduction				
median (inter-quartile range (Q1-Q3))				
median (Q1 - Q3)	17.6 (-8.3 to 46)	37.2 (0.1 to 69.4)	35.6 (4.8 to 66.2)	

Notes:

[15] - Intent-to-Treat (ITT) Population

[16] - Intent-to-Treat (ITT) Population

[17] - Intent-to-Treat (ITT) Population

Statistical analyses

Statistical analysis title	Statistical Analysis - BRV 100 mg/ day v Placebo

Statistical analysis description:

Treatment group comparisons are based on the Wilcoxon-Mann-Whitney test. Hodges-Lehmann non-parametric effect estimates and corresponding two-sided 95% confidence intervals are provided for the effect difference between each BRV treatment group and placebo.

Comparison groups	Brivaracetam 100 mg/day v Placebo
Number of subjects included in analysis	511
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	< 0.001 [19]
Method	Hodges-Lehmann non-parametric analysis
Parameter estimate	Median difference vs placebo
Point estimate	15.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	7.6
upper limit	24.2

Notes:

[18] - Treatment group comparisons are based on the Wilcoxon-Mann-Whitney test.

[19] - p-values not adjusted for multiplicity.

Statistical analysis title	Statistical Analysis - BRV 200 mg/ day v Placebo

Statistical analysis description:

Treatment group comparisons are based on the Wilcoxon-Mann-Whitney test. Hodges-Lehmann non-parametric effect estimates and corresponding two-sided 95% confidence intervals are provided for the effect difference between each BRV treatment group and placebo.

Comparison groups	Placebo v Brivaracetam 200 mg/day
Number of subjects included in analysis	508
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	< 0.001 [21]
Method	Hodges-Lehmann non-parametric analysis
Parameter estimate	Median difference vs placebo
Point estimate	18.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.4
upper limit	26.4

Notes:

[20] - Treatment group comparisons are based on the Wilcoxon-Mann-Whitney test.

[21] - p-values not adjusted for multiplicity.

Secondary: Categorized percent reduction form Baseline in seizure frequency for partial onset seizure (Type I) over the Treatment Period

End point title	Categorized percent reduction form Baseline in seizure frequency for partial onset seizure (Type I) over the Treatment Period

End point description:

End point type	Secondary

End point timeframe:

Baseline to 12 week Treatment Period

End point values	Placebo	Brivaracetam 100 mg/day	Brivaracetam 200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259[22]	252[23]	249[24]	
Units: percentage of subjects				
number (not applicable)				
<-25 %	16.6	14.3	10.8	
-25 % to <25 %	40.5	28.6	29.3	
25 % to <50 %	21.2	18.3	22.1	

50 % to <75 %	13.9	19	18.1	
75 % to <100 %	6.9	13.9	13.7	
100 %	0.8	6	6	

Notes:

[22] - Intent-to-Treat (ITT) Population

[23] - Intent-to-Treat (ITT) Population

[24] - Intent-to-Treat (ITT) Population

Statistical analyses

No statistical analyses for this end point

Secondary: Seizure freedom rate (all seizure types) during the 12-week Treatment Period

End point title	Seizure freedom rate (all seizure types) during the 12-week Treatment Period

End point description:

End point type	Secondary

End point timeframe:

12 week Treatment Period

End point values	Placebo	Brivaracetam 100 mg/day	Brivaracetam 200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259[25]	252[26]	249[27]	
Units: percentage of subjects				
number (not applicable)				
Seizure free	0.8	5.2	4	
No seizures but discontinued	0.4	1.2	1.2	
Not seizure free	98.8	93.7	94.8	

Notes:

[25] - Intent-to-Treat (ITT) Population

[26] - Intent-to-Treat (ITT) Population

[27] - Intent-to-Treat (ITT) Population

Statistical analyses

No statistical analyses for this end point

Secondary: All seizure frequency (Type I + II + III) during the 12-week Treatment Period

End point title	All seizure frequency (Type I + II + III) during the 12-week Treatment Period

End point description:

End point type	Secondary

End point timeframe:

12 week Treatment Period

End point values	Placebo	Brivaracetam 100 mg/day	Brivaracetam 200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259[28]	252[29]	249[30]	
Units: seizure frequency				
median (inter-quartile range (Q1-Q3))				
median (Q1 - Q3)	8.7 (4.3 to 23.6)	6.3 (2.7 to 17.8)	5.8 (2.3 to 14.2)	

Notes:

[28] - Intent-to-Treat Population

[29] - Intent-to-Treat Population

[30] - Intent-to-Treat Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to the first Type I seizure during the Treatment Period

End point title	Time to the first Type I seizure during the Treatment Period

End point description:

End point type	Secondary

End point timeframe:

12 week Treatment Period

End point values	Placebo	Brivaracetam 100 mg/day	Brivaracetam 200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259[31]	252[32]	249[33]	
Units: days				
median (confidence interval 95%)				
median days (CI)	3 (2 to 3)	5 (3 to 7)	6 (4 to 7)	

Notes:

[31] - Intent-to-Treat (ITT) Population

[32] - Intent-to-Treat (ITT) Population

[33] - Intent-to-Treat (ITT) Population

Statistical analyses

Statistical analysis title	Statistical Analysis - Brivaracetam 100 mg/ day

Statistical analysis description:

Hazard ratios and treatment group comparisons are based on a semi-parametric hazards regression model with number of days to nth seizure as the outcome and an effect for treatment, an effect for pooled country, and an effect for the four combinations of stratification levels for number of previous AEDs and LEV Status, and log-transformed Baseline POS frequency as a continuous covariate.

Comparison groups	Brivaracetam 100 mg/day v Placebo

Number of subjects included in analysis	511
Analysis specification	Pre-specified
Analysis type	other[34]
P-value	< 0.001
Method	Semi-parametric hazards regression model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	0.82

Notes:

[34] - N/A

Statistical analysis title	Statistical Analysis - Brivaracetam 200 mg/ day

Statistical analysis description:

Hazard ratios and treatment group comparisons are based on a semi-parametric hazards regression model with number of days to nth seizure as the outcome and an effect for treatment, an effect for pooled country, and an effect for the four combinations of stratification levels for number of previous AEDs and LEV Status, and log-transformed Baseline POS frequency as a continuous covariate.

Comparison groups	Brivaracetam 200 mg/day v Placebo
Number of subjects included in analysis	508
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	< 0.001
Method	Semi-parametric hazards regression model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.79

Notes:

[35] - N/A

Secondary: Time to the fifth Type I seizure during the Treatment Period

End point title	Time to the fifth Type I seizure during the Treatment Period

End point description:

End point type	Secondary

End point timeframe:

12 week Treatment Period

End point values	Placebo	Brivaracetam 100 mg/day	Brivaracetam 200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259[36]	252[37]	249[38]	
Units: days				
median (confidence interval 95%)				
median days (CI)	16 (12 to 19)	21 (17 to 25)	23 (20 to 26)	

Notes:

[36] - Intent-to-Treat (ITT) Population

[37] - Intent-to-Treat (ITT) Population

[38] - Intent-to-Treat (ITT) Population

Statistical analyses

Statistical analysis title	Statistical Analysis - Brivaracetam 200 mg/ day

Statistical analysis description:

Hazard ratios and treatment group comparisons are based on a semi-parametric hazards regression model with number of days to nth seizure as the outcome and an effect for treatment, an effect for pooled country, and an effect for the four combinations of stratification levels for number of previous AEDs and LEV Status, and log-transformed Baseline POS frequency as a continuous covariate.

Comparison groups	Brivaracetam 200 mg/day v Placebo
Number of subjects included in analysis	508
Analysis specification	Pre-specified
Analysis type	other[39]
P-value	< 0.001
Method	Semi-parametric hazards regression model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.71

Notes:

[39] - N/A

Statistical analysis title	Statistical Analysis - Brivaracetam 100 mg/ day

Statistical analysis description:

Hazard ratios and treatment group comparisons are based on a semi-parametric hazards regression model with number of days to nth seizure as the outcome and an effect for treatment, an effect for pooled country, and an effect for the four combinations of stratification levels for number of previous AEDs and LEV Status, and log-transformed Baseline POS frequency as a continuous covariate.

Comparison groups	Brivaracetam 100 mg/day v Placebo
Number of subjects included in analysis	511
Analysis specification	Pre-specified
Analysis type	other[40]
P-value	< 0.001
Method	Semi-parametric hazards regression model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	0.8

Notes:

[40] - N/A

Secondary: Time to the tenth Type I seizure during the Treatment Period

End point title	Time to the tenth Type I seizure during the Treatment Period

End point description:

End point type	Secondary

End point timeframe:

12 week Treatment Period

End point values	Placebo	Brivaracetam 100 mg/day	Brivaracetam 200 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259[41]	252[42]	249[43]	
Units: days				
median (confidence interval 95%)				
median days (CI)	32 (24 to 36)	37 (29 to 46)	43 (36 to 49)	

Notes:

[41] - Intent-to-Treat (ITT) Population

[42] - Intent-to-Treat (ITT) Population

[43] - Intent-to-Treat (ITT) Population

Statistical analyses

Statistical analysis title	Statistical Analysis - Brivaracetam 100 mg/ day
Comparison groups	Placebo v Brivaracetam 100 mg/day
Number of subjects included in analysis	511
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.009
Method	Semi-parametric hazards regression model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	0.93

Statistical analysis title	Statistical Analysis - Brivaracetam 200 mg/ day

Comparison groups	Placebo v Brivaracetam 200 mg/day
Number of subjects included in analysis	508
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Semi-parametric hazards regression model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	0.85

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent Adverse Events (TEAE) were collected during the study, which began in Dec 2010 and concluded in May 2014.

Adverse event reporting additional description:

TEAEs are comprised of the Safety Population, which consists of all randomized subjects who receive at least 1 dose of study medication.

The Non-serious Adverse Events section represents a >= 5% threshold of subjects experiencing Non-serious TEAEs in any treatment group and not the total population.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Matching placebo tablets administered twice daily

Reporting group title	Brivaracetam 100 mg/day

Reporting group description:

Brivaracetam 50 mg administered twice daily.

Reporting group title	Brivaracetam 200 mg/day

Reporting group description:

Brivaracetam 100 mg administered twice daily

Serious adverse events	Placebo	Brivaracetam 100 mg/day	Brivaracetam 200 mg/day
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 261 (3.45%)	8 / 253 (3.16%)	8 / 250 (3.20%)
number of deaths (all causes)	0	0	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Thymoma			
subjects affected / exposed	1 / 261 (0.38%)	0 / 253 (0.00%)	0 / 250 (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
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 261 (0.00%)	1 / 253 (0.40%)	2 / 250 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Craniocerebral injury			
subjects affected / exposed	0 / 261 (0.00%)	0 / 253 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 261 (0.00%)	0 / 253 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 261 (0.00%)	1 / 253 (0.40%)	0 / 250 (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
Traumatic renal injury			
subjects affected / exposed	0 / 261 (0.00%)	1 / 253 (0.40%)	0 / 250 (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
Clavicle fracture			
subjects affected / exposed	1 / 261 (0.38%)	0 / 253 (0.00%)	0 / 250 (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
Joint dislocation			
subjects affected / exposed	1 / 261 (0.38%)	0 / 253 (0.00%)	0 / 250 (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
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 261 (0.00%)	1 / 253 (0.40%)	0 / 250 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 261 (0.00%)	1 / 253 (0.40%)	0 / 250 (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

Coronary artery stenosis			
subjects affected / exposed	1 / 261 (0.38%)	0 / 253 (0.00%)	0 / 250 (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
Nervous system disorders			
Grand mal convulsion			
subjects affected / exposed	1 / 261 (0.38%)	0 / 253 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure cluster			
subjects affected / exposed	0 / 261 (0.00%)	0 / 253 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	0 / 261 (0.00%)	1 / 253 (0.40%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 261 (0.38%)	0 / 253 (0.00%)	0 / 250 (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
Postictal state			
subjects affected / exposed	1 / 261 (0.38%)	0 / 253 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 261 (0.00%)	0 / 253 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sudden unexplained death in epilepsy			

subjects affected / exposed	0 / 261 (0.00%)	0 / 253 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			
Adjustment disorder			
subjects affected / exposed	0 / 261 (0.00%)	1 / 253 (0.40%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			
subjects affected / exposed	0 / 261 (0.00%)	1 / 253 (0.40%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Conversion disorder			
subjects affected / exposed	0 / 261 (0.00%)	1 / 253 (0.40%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epileptic psychosis			
subjects affected / exposed	0 / 261 (0.00%)	1 / 253 (0.40%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	0 / 261 (0.00%)	1 / 253 (0.40%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Localised infection			
subjects affected / exposed	0 / 261 (0.00%)	0 / 253 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis viral			
subjects affected / exposed	1 / 261 (0.38%)	0 / 253 (0.00%)	0 / 250 (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
Pneumonia			

subjects affected / exposed	1 / 261 (0.38%)	0 / 253 (0.00%)	0 / 250 (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

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

Non-serious adverse events	Placebo	Brivaracetam 100 mg/day	Brivaracetam 200 mg/day
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 261 (23.37%)	96 / 253 (37.94%)	97 / 250 (38.80%)
Nervous system disorders			
Somnolence			
subjects affected / exposed	20 / 261 (7.66%)	49 / 253 (19.37%)	42 / 250 (16.80%)
occurrences (all)	20	53	43
Dizziness			
subjects affected / exposed	13 / 261 (4.98%)	26 / 253 (10.28%)	36 / 250 (14.40%)
occurrences (all)	14	27	38
Headache			
subjects affected / exposed	22 / 261 (8.43%)	17 / 253 (6.72%)	20 / 250 (8.00%)
occurrences (all)	30	18	21
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	10 / 261 (3.83%)	19 / 253 (7.51%)	29 / 250 (11.60%)
occurrences (all)	10	19	32
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	8 / 261 (3.07%)	13 / 253 (5.14%)	2 / 250 (0.80%)
occurrences (all)	8	13	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 September 2011	The protocol was amended for the following reasons: •Procedures for reporting SAEs were updated to implement the Food and Drug Administration (FDA) Final Rule requirements (Investigational new drug safety reporting requirements for human drug and biological products and safety reporting requirements for bioavailability and bioequivalence studies in humans, 21 Code of Federal Regulations Parts 312 and 320, 2010). •The Columbia-Suicide Severity Rating Scale (C-SSRS) was added to address the requirement of the FDA that prospective assessments for suicidality be included in clinical studies involving all drugs for neurological indications. There were also a few minor changes made to the protocol to update the name of the company, name and address of Study Physician, and SAE reporting contact numbers, and to clarify some study conduct details.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported