Clinical trial results:
An International, Randomized, Double-blind, Parallel-group, Placebo-controlled, Flexible Dose Study: Evaluation of the Safety and Efficacy of Brivaracetam in Subjects (16 to 70 Years Old) Suffering From Localization-related or Generalized Epilepsy

Summary

EudraCT number	2006-006346-34
Trial protocol	BE CZ SE DE AT IT
Global end of trial date	15 December 2008

Results information

Result version number	v1 (current)
This version publication date	22 October 2016
First version publication date	22 October 2016

Trial information

Trial identification

Sponsor protocol code	N01254

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00504881
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB Pharma S.A.
Sponsor organisation address	Allée de la Recherche 70, Brussels, Belgium, 1070
Public contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 2173 4815 15, clinicaltrials@ucb.com
Scientific contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 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	31 March 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 December 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the safety and tolerability of brivaracetam (BRV) at the dose range from 20 to 150 mg/day in twice daily administration in subjects suffering from localization-related or generalized epilepsy not fully controlled despite optimal treatment with 1 to 3 concomitant antiepileptic drug(s) (AED[s]), compared to placebo (PBO).

Protection of trial subjects:

Standard measure to minimize pain and distress.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	15 October 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	8 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 29
Country: Number of subjects enrolled	Belgium: 21
Country: Number of subjects enrolled	Czech Republic: 35
Country: Number of subjects enrolled	Germany: 33
Country: Number of subjects enrolled	Hong Kong: 11
Country: Number of subjects enrolled	India: 65
Country: Number of subjects enrolled	Italy: 23
Country: Number of subjects enrolled	Korea, Republic of: 88
Country: Number of subjects enrolled	Norway: 15
Country: Number of subjects enrolled	Russian Federation: 51
Country: Number of subjects enrolled	Singapore: 9
Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	Sweden: 19
Country: Number of subjects enrolled	Taiwan: 27
Country: Number of subjects enrolled	Ukraine: 52

Worldwide total number of subjects	480
EEA total number of subjects	175

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)	8
Adults (18-64 years)	468
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This multicenter study was conducted in 15 countries. It started in October 2007 and concluded in December 2008.

Pre-assignment

Screening details:

The Participant Flow refers to the Randomized Set (RS).

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	Investigator, Carer, Subject, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Matching Placebo tablets administered twice a day

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	PBO
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Matching Placebo to Brivaracetam tablets.

Arm title	Brivaracetam

Arm description:

A flexible dose of Brivaracetam tablets, administered twice a day, starting with a dose of 20 mg/day and could increase to 50 mg/day, 100 mg/day or 150 mg/day

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:

Brivaracetam
- Pharmaceutical form: Film-coated tablet
- Route of Administration: Oral use
- Concentration: 10 mg and 25 mg tablets

Number of subjects in period 1	Placebo	Brivaracetam
Started	121	359
Completed	111	323
Not completed	10	36
AE, serious fatal	-	1
Consent withdrawn by subject	1	4
Non-Compliance	1	-
No Birth Control	-	1
AE, non-serious non-fatal	4	14
AE of unknown type	1	-
Safety Visit not performed	-	1
Lost to follow-up	-	2
SAE, non-fatal	2	6
Lack of efficacy	1	5
SAE, non-fatal + AE, non-serious non-fatal	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Matching Placebo tablets administered twice a day	
Reporting group title	Brivaracetam
Reporting group description:	
A flexible dose of Brivaracetam tablets, administered twice a day, starting with a dose of 20 mg/day and could increase to 50 mg/day, 100 mg/day or 150 mg/day	

Reporting group values	Placebo	Brivaracetam	Total
Number of subjects	121	359	480
Age categorical			
Units: Subjects			
< 18 years	3	5	8
18 - < 65 years	116	352	468
65 - < 85 years	2	2	4
Age Continuous			
Units: years			
arithmetic mean	36.5	35.6	
standard deviation	± 11.5	± 11.5	-
Gender Categorical			
Units: Subjects			
Female	52	178	230
Male	69	181	250

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Matching Placebo tablets administered twice a day	
Reporting group title	Brivaracetam
Reporting group description:	
A flexible dose of Brivaracetam tablets, administered twice a day, starting with a dose of 20 mg/day and could increase to 50 mg/day, 100 mg/day or 150 mg/day	

Primary: Percentage of subjects with at least one Adverse Event during the 16-week Treatment Period

End point title	Percentage of subjects with at least one Adverse Event during the 16-week Treatment Period[1]
End point description:	
An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.	
End point type	Primary
End point timeframe:	
Week 2 to the end of the Treatment Period (Week 16)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical hypothesis testing was planned for this study. Results were summarized in tables as descriptive statistics only.

End point values	Placebo	Brivaracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	359		
Units: percentage of participants				
number (not applicable)				
Percentage of participants	66.1	66.6		

Statistical analyses

No statistical analyses for this end point

Primary: Partial Onset Seizure (Type I) frequency per week over the 16-week Treatment Period

End point title	Partial Onset Seizure (Type I) frequency per week over the 16-week Treatment Period
End point description:	

Partial (Type I) seizures can be classified into one of the following three groups:
- Simple partial seizures
- Complex partial seizures
- Partial seizures evolving to generalized tonic-clonic convulsions.

Partial Onset Seizure (POS) frequency per week over the Treatment Period (TP) was calculated as: (Total Type I seizures over the TP)*7/(Total number of days with no missing seizure count in the TP)

End point type	Primary

End point timeframe:

Baseline (Week 0) to the end of the Treatment Period (Week 16)

End point values	Placebo	Brivaracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	323		
Units: seizures per week				
median (inter-quartile range (Q1-Q3))				
Median (Q1 - Q3)	1.86 (1 to 3.98)	1.74 (0.86 to 4.04)		

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

ANCOVA on log-transformed partial seizure frequency per week over the treatment period, with log-transformed baseline seizure frequency per week as covariate, and including terms for treatment and stratification factors.

Comparison groups	Placebo v Brivaracetam
Number of subjects included in analysis	431
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.125
Method	ANCOVA
Parameter estimate	Percent Reduction over Placebo
Point estimate	7.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	15.9

Secondary: Responder rate for partial onset seizures (Type I) frequency per week over the 16-week Treatment Period

End point title	Responder rate for partial onset seizures (Type I) frequency per week over the 16-week Treatment Period

End point description:

The responder rate was presented as the percentage of responders and non-responders. A subject is a responder, if the subject has at least 50 % reduction in Partial Onset Seizure frequency per week from Baseline to Treatment Period. Subjects with zero seizure frequency per week at Baseline were considered as non-responders.

End point type	Secondary

End point timeframe:

Baseline (Week 0) to the end of Treatment Period (Week 16)

End point values	Placebo	Brivaracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	323		
Units: percentage of participants				
number (not applicable)				
Responders	16.7	30.3		
Non-Responders	83.3	69.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Seizure frequency (all seizure types) per week over the 16-week Treatment Period

End point title	Seizure frequency (all seizure types) per week over the 16-week Treatment Period

End point description:

There are three different types of seizures:
- Type I: Partial seizures
- Type II: Generalized seizures
- Type III: Unclassified epileptic seizures.

All seizure frequency per week over Treatment Period (TP) was calculated as: (Total number of seizures over the TP)*7/(Total number of days with no missing seizure count in the TP)

End point type	Secondary

End point timeframe:

Baseline (Week 0) to the end of Treatment Period (Week 16)

End point values	Placebo	Brivaracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	323		
Units: seizure frequency per week				
median (inter-quartile range (Q1-Q3))				
Median (Q1 - Q3)	1.87 (1 to 4.59)	1.74 (0.86 to 4.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from Baseline to the 16-week Treatment Period in Partial Onset Seizure (Type I) frequency per week

End point title	Percent change from Baseline to the 16-week Treatment Period in Partial Onset Seizure (Type I) frequency per week

End point description:

Percent change from Baseline was calculated as percent reduction by:
(weekly seizure frequency Baseline - weekly seizure frequency Treatment)*100/(weekly seizure frequency Baseline).
A negative value in percent Change from Baseline indicates an improvement from Baseline.
The higher the negative values for percent change in Partial Onset Seizure (POS) frequency, the higher the improvement from Baseline.

End point type	Secondary

End point timeframe:

Baseline (Week 0) to end of Treatment Period (Week 16)

End point values	Placebo	Brivaracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	323		
Units: seizure frequency per week				
median (inter-quartile range (Q1-Q3))				
Median (Q1 - Q3)	-18.93 (-39.05 to -7.83)	-26.92 (-55.98 to 11.44)		

Statistical analyses

No statistical analyses for this end point

Secondary: Categorized response from Baseline in seizure frequency for Partial Onset Seizure (Type I) over the 16-week Treatment Period

End point title	Categorized response from Baseline in seizure frequency for Partial Onset Seizure (Type I) over the 16-week Treatment Period

End point description:

Subjects were classified in 1 of the following categories based on their percent reduction from Baseline to Treatment Period in Partial Onset Seizure (POS) frequency per week: <-25 %, -25 % to <25 %, 25 % to <50 %, 50 % to <75 %, 75 % to <100 %, and 100 %.
Subjects having zero for Baseline seizure frequency per week were classified in the <-25 % category.

End point type	Secondary

End point timeframe:

Baseline to 16-week Treatment Period

End point values	Placebo	Brivaracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	323		
Units: percentage of participants				
number (not applicable)				
<- 25 %	14.8	18.3		
-25 % to < 25 %	44.4	29.1		
25 % to < 50 %	24.1	22.3		
50 % to < 75 %	13.9	17		
75 % to < 100 %	2.8	11.8		
100 %	0	1.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Seizure freedom rate (all seizure types) over the 16-week Treatment Period

End point title	Seizure freedom rate (all seizure types) over the 16-week Treatment Period

End point description:

Subjects were considered seizure free if their seizure counts for every day over the Treatment Period (TP) was zero and if they did not discontinue before the end of the TP. Seizure freedom rate was calculated as:
(total number of seizure - free subjects in treatment group during TP)/(total number of evaluable Intent-To-Treat (ITT) subjects in treatment group)

End point type	Secondary

End point timeframe:

Baseline (Week 0) to the end of Treatment Period (Week 16)

End point values	Placebo	Brivaracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	323		
Units: percentage of participants				
number (not applicable)				
Seizure-free	0	1.5		
No Seizure but non-completer	0	0		
Not Seizure free	100	98.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction of Type IC/Type I seizure frequency ratio from Baseline to the 16-week Treatment Period

End point title	Reduction of Type IC/Type I seizure frequency ratio from Baseline to the 16-week Treatment Period

End point description:

This variable was not analyzed and no results are available.

End point type	Secondary

End point timeframe:

Baseline to 16-week Treatment Period

End point values	Placebo	Brivaracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Not applicable	()	()		

Notes:

[2] - This analysis was not performed as it was not needed for labeling purposes.

[3] - This analysis was not performed as it was not needed for labeling purposes.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first Type I seizure during the 16-week Treatment Period

End point title	Time to first Type I seizure during the 16-week Treatment Period

End point description:

Time to first Type I seizure during the 16-week Treatment Period was measured in days.

End point type	Secondary

End point timeframe:

Baseline to 16-week Treatment Period

End point values	Placebo	Brivaracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	323		
Units: days				
median (confidence interval 95%)				
Median (95 % CI)	3 (2 to 4)	4 (4 to 5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to fifth Type I seizure during the 16-week Treatment Period

End point title	Time to fifth Type I seizure during the 16-week Treatment Period

End point description:

Time to fifth Type I seizure during the 16-week Treatment Period was measured in days.

End point type	Secondary

End point timeframe:

Baseline to 16-week Treatment Period

End point values	Placebo	Brivaracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	323		
Units: days				
median (confidence interval 95%)				
Median (95 % CI)	14 (11 to 19)	18 (16 to 21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to tenth Type I seizure during Treatment Period

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

End point description:

Time to tenth Type I seizure during the 16-week Treatment Period was measured in days.

End point type	Secondary

End point timeframe:

Baseline to 16-week Treatment Period

End point values	Placebo	Brivaracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	323		
Units: days				
median (confidence interval 95%)				
Median (95 % CI)	36 (23 to 44)	38 (31 to 43)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 16-week Treatment Period in Total Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

End point title	Change from Baseline to the 16-week Treatment Period in Total

	Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

End point description:

The Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into 7 multi-item subscales: Seizure Worry (5 items), Overall Quality of Life (2 items), Emotional Well-being (5 items), Energy/Fatigue (4 items), Cognitive Functioning (6 items), Medication Effects (3 items) and Daily Activities/Social Functioning (5 items), and a Health Status item. In addition to the 31 items of the QOLIE-31, the QOLIE-31-P contains 7 items asking the subjects to rate the degree of 'distress' related to the topic of each subscale (ie, distress items). The QOLIE-31-P also contains an item asking about the relative importance of each subscale topic (ie, prioritization item). The subscale scores, the total score and the Health Status item score were calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function.

End point type	Secondary

End point timeframe:

Baseline to 16-week Treatment Period

End point values	Placebo	Brivaracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	284		
Units: units on a scale				
arithmetic mean (standard deviation)				
Arithmetic Mean (Standard Deviation)	3.04 (± 12.58)	4.22 (± 13.73)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 16-week Treatment Period in Seizure Worry Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

End point title	Change from Baseline to the 16-week Treatment Period in Seizure Worry Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

End point description:

The Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into 7 multi-item subscales: Seizure Worry (5 items), Overall Quality of Life (2 items), Emotional Well-being (5 items), Energy/Fatigue (4 items), Cognitive Functioning (6 items), Medication Effects (3 items) and Daily Activities/Social Functioning (5 items), and a Health Status item. In addition to the 31 items of the QOLIE-31, the QOLIE-31-P contains 7 items asking the subjects to rate the degree of 'distress' related to the topic of each subscale (ie, distress items). The QOLIE-31-P also contains an item asking about the relative importance of each subscale topic (ie, prioritization item). The subscale scores, the total score
and the Health Status item score were calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function.

End point type	Secondary

End point timeframe:

Baseline to 16-week Treatment Period

End point values	Placebo	Brivaracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	291		
Units: units on a scale				
arithmetic mean (standard deviation)				
Arithmetic Mean (Standard Deviation)	4.66 (± 23.23)	10.29 (± 21.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 16-week Treatment Period in Daily Activities / Social Functioning Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

End point title	Change from Baseline to the 16-week Treatment Period in Daily Activities / Social Functioning Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

End point description:

The Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into 7 multi-item subscales: Seizure Worry (5 items), Overall Quality of Life (2 items), Emotional Well-being (5 items), Energy/Fatigue (4 items), Cognitive Functioning (6 items), Medication Effects (3 items) and Daily Activities/Social Functioning (5 items), and a Health Status item. In addition to the 31 items of the QOLIE-31, the QOLIE-31-P contains 7 items asking the subjects to rate the degree of 'distress' related to the topic of each subscale (ie, distress items). The QOLIE-31-P also contains an item asking about the relative importance of each subscale topic (ie, prioritization item). The subscale scores, the total score
and the Health Status item score were calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function.

End point type	Secondary

End point timeframe:

Baseline to 16-week Treatment Period

End point values	Placebo	Brivaracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	290		
Units: units on a scale				
arithmetic mean (standard deviation)				
Arithmetic Mean (Standard Deviation)	5.61 (± 21.87)	2.66 (± 23.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 16-week Treatment Period in Hospital Anxiety score

End point title	Change from Baseline to the 16-week Treatment Period in

	Hospital Anxiety score

End point description:

The Hospital Anxiety and Depression Scale (HADS) was used to evaluate Anxiety and Depression. The HADS was developed as a self-administered scale to assess the presence and severity of Anxiety and Depression. It consists of 14 items that are scored on a 4-point severity scale ranging from 0 to 3. A score per dimension was calculated with each score ranging from 0 to 21 (higher scores indicating greater problems). A negative value in change from Baseline indicates an improvement from Baseline.

End point type	Secondary

End point timeframe:

Baseline to 16-week Treatment Period

End point values	Placebo	Brivaracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	286		
Units: units on a scale				
arithmetic mean (standard deviation)				
Arithmetic Mean (Standard Deviation)	-0.57 (± 3.35)	-0.85 (± 3.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 16-week Treatment Period in Hospital Depression score

End point title	Change from Baseline to the 16-week Treatment Period in Hospital Depression score

End point description:

The Hospital Anxiety and Depression Scale (HADS) was used to eveluate Anxiety and Depression.The HADS was developed as a self-administered scale to assess the presence and severity of Anxiety and Depression. It consists of 14 items that are scored on a 4-point severity scale ranging from 0 to 3. A score per dimension was calculated with each score ranging from 0 to 21 (higher scores indicating greater problems). A negative value in change from Baseline indicates an improvement from Baseline.

End point type	Secondary

End point timeframe:

Baseline to 16-week Treatment Period

End point values	Placebo	Brivaracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	285		
Units: units on a scale				
arithmetic mean (standard deviation)				
Arithmetic Mean (Standard Deviation)	0.3 (± 3.08)	-0.41 (± 3.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patient's Global Evaluation Scale (P-GES) evaluated at last visit or early discontinuation visit

End point title	Patient's Global Evaluation Scale (P-GES) evaluated at last visit or early discontinuation visit

End point description:

The Patient's Global Evaluation Scale (P-GES) is a global assessment of the disease evolution which was performed using a seven-point scale (1= Marked worsening to 7= Marked improvement) with the start of the study medication as the reference time point. The subject completed it by answering to the following: 'Overall, has there been a change in your seizures since the start of the study medication?'

End point type	Secondary

End point timeframe:

Baseline to last visit or early discontinuation visit in the 16-week Treatment Period

End point values	Placebo	Brivaracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	282		
Units: units on a scale				
arithmetic mean (standard deviation)				
Arithmetic Mean (Standard Deviation)	4.73 (± 1.37)	5.07 (± 1.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator's Global Evaluation Scale (I-GES) evaluated at Last Visit or Early Discontinuation Visit

End point title	Investigator's Global Evaluation Scale (I-GES) evaluated at Last Visit or Early Discontinuation Visit

End point description:

The Investigator's Global Evaluation Scale (I-GES) is a global assessment of the disease evolution which was performed using a seven-point scale (1= Marked worsening to 7= Marked improvement) with the start of the study medication as the reference time point. The Investigator completed it by answering to the following: 'Assess the overall change in the severity of patient's illness, compared to start of study medication.'

End point type	Secondary

End point timeframe:

Baseline to Last Visit or Early Discontinuation Visit in the 16-week Treatment Period

End point values	Placebo	Brivaracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	319		
Units: units on a scale				
arithmetic mean (standard deviation)				
Arithmetic Mean (Standard Deviation)	4.79 (± 1.14)	5 (± 1.22)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 16-week Treatment Period in Energy/Fatigue Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

End point title	Change from Baseline to the 16-week Treatment Period in Energy/Fatigue Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

End point description:

The Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into 7 multi-item subscales: Seizure Worry (5 items), Overall Quality of Life (2 items), Emotional Well-being (5 items), Energy/Fatigue (4 items), Cognitive Functioning (6 items), Medication Effects (3 items) and Daily Activities/Social Functioning (5 items), and a Health Status item. In addition to the 31 items of the QOLIE-31, the QOLIE-31-P contains 7 items asking the subjects to rate the degree of 'distress' related to the topic of each subscale (ie, distress items). The QOLIE-31-P also contains an item asking about the relative importance of each subscale topic (ie, prioritization item). The subscale scores, the total score
and the Health Status item score were calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function.

End point type	Secondary

End point timeframe:

Baseline to 16-week Treatment Period

End point values	Placebo	Brivaracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	286		
Units: units on a scale				
arithmetic mean (standard deviation)				
Arithmetic Mean (Standard Deviation)	2.98 (± 18)	3.34 (± 19.06)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 16-week Treatment Period in Emotional Well-being Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

End point title	Change from Baseline to the 16-week Treatment Period in

	Emotional Well-being Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

End point description:

The Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into 7 multi-item subscales: Seizure Worry (5 items), Overall Quality of Life (2 items), Emotional Well-being (5 items), Energy/Fatigue (4 items), Cognitive Functioning (6 items), Medication Effects (3 items) and Daily Activities/Social Functioning (5 items), and a Health Status item. In addition to the 31 items of the QOLIE-31, the QOLIE-31-P contains 7 items asking the subjects to rate the degree of 'distress' related to the topic of each subscale (ie, distress items). The QOLIE-31-P also contains an item asking about the relative importance of each subscale topic (ie, prioritization item). The subscale scores, the total score
and the Health Status item score were calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function.

End point type	Secondary

End point timeframe:

Baseline to 16-week Treatment Period

End point values	Placebo	Brivaracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	287		
Units: units on a scale				
arithmetic mean (standard deviation)				
Arithmetic Mean (Standard Deviation)	1.97 (± 19.29)	2.84 (± 18.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 16-week Treatment Period in Cognitive Functioning Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

End point title	Change from Baseline to the 16-week Treatment Period in Cognitive Functioning Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

End point description:

The Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into 7 multi-item subscales: Seizure Worry (5 items), Overall Quality of Life (2 items), Emotional Well-being (5 items), Energy/Fatigue (4 items), Cognitive Functioning (6 items), Medication Effects (3 items) and Daily Activities/Social Functioning (5 items), and a Health Status item. In addition to the 31 items of the QOLIE-31, the QOLIE-31-P contains 7 items asking the subjects to rate the degree of 'distress' related to the topic of each subscale (ie, distress items). The QOLIE-31-P also contains an item asking about the relative importance of each subscale topic (ie, prioritization item). The subscale scores, the total score
and the Health Status item score were calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function.

End point type	Secondary

End point timeframe:

Baseline to 16-week Treatment Period

End point values	Placebo	Brivaracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	290		
Units: units on a scale				
arithmetic mean (standard deviation)				
Arithmetic Mean (Standard Deviation)	2.28 (± 19.88)	5.51 (± 18.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 16-week Treatment Period in overall Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

End point title	Change from Baseline to the 16-week Treatment Period in overall Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

End point description:

The Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into 7 multi-item subscales: Seizure Worry (5 items), Overall Quality of Life (2 items), Emotional Well-being (5 items), Energy/Fatigue (4 items), Cognitive Functioning (6 items), Medication Effects (3 items) and Daily Activities/Social Functioning (5 items), and a Health Status item. In addition to the 31 items of the QOLIE-31, the QOLIE-31-P contains 7 items asking the subjects to rate the degree of 'distress' related to the topic of each subscale (ie, distress items). The QOLIE-31-P also contains an item asking about the relative importance of each subscale topic (ie, prioritization item). The subscale scores, the total score
and the Health Status item score were calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function.

End point type	Secondary

End point timeframe:

Baseline to 16-week Treatment Period

End point values	Placebo	Brivaracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	291		
Units: units on a scale				
arithmetic mean (standard deviation)				
Arithmetic Mean (Standard Deviation)	-0.48 (± 17.4)	4.08 (± 19.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 16-week Treatment Period in Medication effects Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

End point title	Change from Baseline to the 16-week Treatment Period in Medication effects Patient Weighted Quality of Life in Epilepsy

	Inventory-Form 31 (QOLIE-31-P) score

End point description:

The Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into 7 multi-item subscales: Seizure Worry (5 items), Overall Quality of Life (2 items), Emotional Well-being (5 items), Energy/Fatigue (4 items), Cognitive Functioning (6 items), Medication Effects (3 items) and Daily Activities/Social Functioning (5 items), and a Health Status item. In addition to the 31 items of the QOLIE-31, the QOLIE-31-P contains 7 items asking the subjects to rate the degree of 'distress' related to the topic of each subscale (ie, distress items). The QOLIE-31-P also contains an item asking about the relative importance of each subscale topic (ie, prioritization item). The subscale scores, the total score
and the Health Status item score were calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function.

End point type	Secondary

End point timeframe:

Baseline to 16-week Treatment Period

End point values	Placebo	Brivaracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	290		
Units: units on a scale				
arithmetic mean (standard deviation)				
Arithmetic Mean (Standard Deviation)	2.83 (± 27.21)	-0.24 (± 25.84)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected up to 24 weeks from Visit 1 (Week -4) to the Safety Visit (Week 20).

Adverse event reporting additional description:

Adverse Events (AEs) refer to the Safety Population, including all randomized subjects who received at least 1 dose of study medication.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups

Reporting group title	Brivaracetam

Reporting group description:

A flexible dose of Brivaracetam tablets, administered twice a day, starting with a dose of 20 mg/day and could increase to 50 mg/day, 100 mg/day or 150 mg/day

Reporting group title	Placebo

Reporting group description:

Matching Placebo tablets administered twice a day

Serious adverse events	Brivaracetam	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 359 (5.57%)	9 / 121 (7.44%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Drug toxity			
subjects affected / exposed	1 / 359 (0.28%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 359 (0.28%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 359 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Burns second degree			
subjects affected / exposed	1 / 359 (0.28%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face injury			
subjects affected / exposed	0 / 359 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 359 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 359 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	1 / 359 (0.28%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 359 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial ischaemia			
subjects affected / exposed	1 / 359 (0.28%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 359 (0.28%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Tremor			
subjects affected / exposed	0 / 359 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 359 (0.28%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postictal state			
subjects affected / exposed	1 / 359 (0.28%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	7 / 359 (1.95%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	5 / 9	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 359 (0.28%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	2 / 359 (0.56%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 359 (0.28%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			

subjects affected / exposed	1 / 359 (0.28%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drowning			
subjects affected / exposed	1 / 359 (0.28%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
subjects affected / exposed	1 / 359 (0.28%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 359 (0.28%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 359 (0.28%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 359 (0.28%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 359 (0.28%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Hepatitis B			

subjects affected / exposed	0 / 359 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 359 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetis mellitus inadequate control			
subjects affected / exposed	1 / 359 (0.28%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Brivaracetam	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	139 / 359 (38.72%)	40 / 121 (33.06%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	31 / 359 (8.64%)	7 / 121 (5.79%)	
occurrences (all)	36	9	
Headache			
subjects affected / exposed	52 / 359 (14.48%)	24 / 121 (19.83%)	
occurrences (all)	79	45	
Somnolence			
subjects affected / exposed	40 / 359 (11.14%)	5 / 121 (4.13%)	
occurrences (all)	47	7	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	27 / 359 (7.52%)	5 / 121 (4.13%)	
occurrences (all)	31	5	
Gastrointestinal disorders			
Nausea			

subjects affected / exposed	20 / 359 (5.57%)	11 / 121 (9.09%)	
occurrences (all)	26	14	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	11 / 359 (3.06%)	8 / 121 (6.61%)	
occurrences (all)	11	9	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	14 / 359 (3.90%)	8 / 121 (6.61%)	
occurrences (all)	16	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 May 2007	A global protocol amendment was issued on 08 May 2007 in response to Food and Drug Administration (FDA) feedback on the N01253 final protocol. The following changes were implemented; no subjects were enrolled at the time: • One step was added in the Down-Titration Scheme to reduce subjects from BRV 50 mg/day to BRV 20 mg/day before entering the Study Drug-Free Period. For subjects not entering the LTFU study and taking doses of BRV 50 mg/day, 100 mg/day, or 150 mg/day (or corresponding matching PBO) a down-titration of 1, 2, or 3 weeks, respectively, was required prior to entering the Study Drug-Free Period. • Addition of a clinic visit requiring a complete safety evaluation, including laboratory safety assessments and electrocardiogram (ECG), at 2-weeks after randomization. • Addition of microscopy evaluations for all urinalysis assessments.
08 May 2007	In order to harmonize the 3 studies for the BRV POS Phase 3 program, the following changes were applied for N01254: • One step was added in the Down-Titration Scheme to reduce subjects from BRV 50 mg/day to BRV 20 mg/day before entering the Study Drug-Free Period. • An ECG was added at Visit (V) 3 (2 weeks after randomization). • Laboratory safety assessments, pregnancy test (if applicable), AED plasma level, and BRV plasma level were added at V3 (2 weeks after randomization). • Weight was also measured at V3. Other changes implemented in this amendment include: • Details of the statistical methods used to analyze the Type IC/Type I seizure frequency ratio were removed from the protocol. A reference to the statistical analysis plan (SAP) was added. • The definition of a completed subject was clarified. A subject completed the study if either he/she was randomized, underwent the Evaluation Visit (V8), did not have any Early Discontinuation Visit (EDV), and entered the LTFU study; or was randomized, underwent the V8 and Safety Visit (SV), did not have any EDV, and did not enter the LTFU study. Otherwise, the subject was considered discontinued. • Specifications for the handling of missing data for primary efficacy analysis on the Intent-to-Treat (ITT) Population were added. The primary efficacy analysis assumes that subjects who prematurely withdrew from the Treatment Period had the same seizure frequency for the remaining unobserved period. In addition, a sensitivity analysis was further described in the SAP. • Additional instructions for blood sampling volumes for laboratory assessments and genotyping were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24116853