Clinical trial results:
A Multi-center, Double-blind, Parallel-group, Placebo-Controlled, Randomized Study: Evaluation of the Efficacy and Safety of Brivaracetam in Subjects (>= 16 to 70 Years Old) With Partial Onset Seizures

Summary

EudraCT number	2006-006344-59
Trial protocol	BE NL FR GB HU FI IT DE ES
Global end of trial date	09 February 2009

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	N01252

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00490035
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB Pharma SA
Sponsor organisation address	Allée de la Recherche 60, Brussels, Belgium, B-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	16 April 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 February 2009
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 evaluate the efficacy of Brivaracetam (BRV) at doses of 20, 50, and 100 mg/day in reducing seizure frequency in subjects with partial onset seizures not fully controlled despite optimal treatment with 1 to 2 concomitant antiepileptic drug(s) (AED(s)), compared with Placebo (PBO).

Protection of trial subjects:

Standard measures to minimize pain and distress.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	10 September 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	Belgium: 6
Country: Number of subjects enrolled	Finland: 11
Country: Number of subjects enrolled	France: 60
Country: Number of subjects enrolled	Germany: 41
Country: Number of subjects enrolled	Hungary: 12
Country: Number of subjects enrolled	India: 91
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Poland: 108
Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	Switzerland: 15
Country: Number of subjects enrolled	United Kingdom: 6
Worldwide total number of subjects	399
EEA total number of subjects	293

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)	5
Adults (18-64 years)	383
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study started to enroll subjects in September 2007 and concluded in February 2009.

Pre-assignment

Screening details:

Participant Flow refers to the Randomized Set.

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 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 20 mg/day

Arm description:

Brivaracetam 20 mg/day, 10 mg administered twice a 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:

10 mg and 25 mg tablets. Two equal intakes, morning and evening, in a double-blinded way for the 12-week Treatment Period.

Arm title	Brivaracetam 50 mg/day

Arm description:

Brivaracetam 50 mg/day, 25 mg administered twice a 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:

10 mg and 25 mg tablets. Two equal intakes, morning and evening, in a double-blinded way for the 12-week Treatment Period.

Arm title	Brivaracetam 100 mg/day

Arm description:

Brivaracetam 100 mg/day, 50 mg administered twice a 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:

10 mg and 25 mg tablets. Two equal intakes, morning and evening, in a double-blinded way for the 12-week Treatment Period.

Number of subjects in period 1	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day
Started	100	99	100
Completed	92	93	88
Not completed	8	6	12
AE, serious fatal	1	-	-
Consent withdrawn by subject	2	1	1
AE, non-serious non-fatal	3	4	4
AE of unknown type	-	-	2
Other reason	-	1	3
Lost to follow-up	2	-	1
SAE, non-fatal	-	-	1

Number of subjects in period 1	Brivaracetam 100 mg/day
Started	100
Completed	94
Not completed	6
AE, serious fatal	-
Consent withdrawn by subject	-
AE, non-serious non-fatal	5
AE of unknown type	-
Other reason	1
Lost to follow-up	-
SAE, non-fatal	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: Matching Placebo tablets administered twice a day	
Reporting group title	Brivaracetam 20 mg/day
Reporting group description: Brivaracetam 20 mg/day, 10 mg administered twice a day	
Reporting group title	Brivaracetam 50 mg/day
Reporting group description: Brivaracetam 50 mg/day, 25 mg administered twice a day	
Reporting group title	Brivaracetam 100 mg/day
Reporting group description: Brivaracetam 100 mg/day, 50 mg administered twice a day	

Reporting group values	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day
Number of subjects	100	99	100
Age Categorical Units: Subjects			
<18 years	2	2	0
Between 18 and 65 years	96	94	97
>=65 years	2	3	3
Age Continuous Units: years			
arithmetic mean	36.4	35.7	39
standard deviation	± 13	± 12.5	± 13.5
Gender Categorical Units: Subjects			
Female	46	38	45
Male	54	61	55
Region of Enrollment Units: Subjects			
Hungary	4	2	3
Poland	26	28	27
India	23	22	23
Belgium	3	0	3
Finland	3	3	1
France	17	17	11
Germany	8	10	14
Italy	4	8	3
Netherlands	3	0	1
Spain	8	4	6
Switzerland	1	3	6
United Kingdom	0	2	2

Reporting group values	Brivaracetam 100 mg/day	Total	
Number of subjects	100	399	

Age Categorical Units: Subjects			
<18 years	1	5	
Between 18 and 65 years	96	383	
>=65 years	3	11	
Age Continuous Units: years			
arithmetic mean	38		
standard deviation	± 13.1	-	
Gender Categorical Units: Subjects			
Female	42	171	
Male	58	228	
Region of Enrollment Units: Subjects			
Hungary	3	12	
Poland	27	108	
India	23	91	
Belgium	0	6	
Finland	4	11	
France	15	60	
Germany	9	41	
Italy	5	20	
Netherlands	3	7	
Spain	4	22	
Switzerland	5	15	
United Kingdom	2	6	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Matching Placebo tablets administered twice a day	
Reporting group title	Brivaracetam 20 mg/day
Reporting group description:	
Brivaracetam 20 mg/day, 10 mg administered twice a day	
Reporting group title	Brivaracetam 50 mg/day
Reporting group description:	
Brivaracetam 50 mg/day, 25 mg administered twice a day	
Reporting group title	Brivaracetam 100 mg/day
Reporting group description:	
Brivaracetam 100 mg/day, 50 mg administered twice a day	

Primary: Partial Onset Seizure (Type I) frequency per week over the 12-week Treatment Period

End point title	Partial Onset Seizure (Type I) frequency per week over the 12-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 Secondarily Generalized Seizures.	
End point type	Primary
End point timeframe:	
From Baseline to 12-week Treatment Period	

End point values	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	100	99	99	100
Units: Seizure Frequency per Week				
median (inter-quartile range (Q1-Q3))				
Median (Q1-Q3)	1.75 (0.76 to 5.12)	1.34 (0.7 to 3.12)	1.49 (0.69 to 2.78)	1.26 (0.52 to 2.93)

Statistical analyses

Statistical analysis title	BRV 50 mg/day versus PBO
Statistical analysis description:	
In order to control the Type I error testing was performed in sequence starting with 50 mg, then 100 mg and finally 20 mg Brivaracetam per day versus Placebo, only moving to the next test if the previous one was significant at the 5 % level.	
Comparison groups	Placebo v Brivaracetam 50 mg/day

Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.261
Method	ANCOVA
Parameter estimate	Percentage Reduction over Placebo
Point estimate	6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	16.9

Secondary: Responder rate for partial onset seizures (Type I) frequency per week over the 12-week Treatment Period

End point title	Responder rate for partial onset seizures (Type I) frequency per week over the 12-week Treatment Period

End point description:

Responders are those subjects with at least 50 % reduction from Baseline to Treatment Period in Partial Onset Seizure frequency per week.
The Responder Rate for Partial Onset Seizures (Type I) is the proportion of subjects who have a >= 50 % reduction in seizure frequency per week from Baseline.

End point type	Secondary

End point timeframe:

From Baseline to 12-week Treatment Period

End point values	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	100	99	99	100
Units: Percentage of Participants				
number (not applicable)				
Non-responders	80	72.7	72.7	64
Responders	20	27.3	27.3	36

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

There are three types of Epilepsy: Partial Epilepsies (Type I), Generalized Epilepsies (Type II) and uncertain classification of Epilepsies (Type III).

End point type	Secondary

End point timeframe:

From Baseline to 12-week Treatment Period

End point values	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	100	99	99	100
Units: Times per week				
median (inter-quartile range (Q1-Q3))				
Median (Q1-Q3)	1.75 (0.76 to 5.61)	1.34 (0.7 to 3.12)	1.49 (0.69 to 2.78)	1.26 (0.52 to 2.93)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from Baseline to the 12-week Treatment Period in Partial Onset Seizure (Type I) Frequency per week

End point title	Percent change from Baseline to the 12-week Treatment Period in Partial Onset Seizure (Type I) Frequency per week

End point description:

The percent change from Baseline was computed as: Weekly Seizure Frequency (Treatment) - Weekly Seizure Frequency (Baseline) / Weekly Seizure Frequency (Baseline) * 100. Negative values indicate a reduction from Baseline with higher negative values showing higher reduction.

End point type	Secondary

End point timeframe:

From Baseline to 12-week Treatment Period

End point values	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	100	99	99	100
Units: Percent change in seizures per week				
median (inter-quartile range (Q1-Q3))				
Median (Q1-Q3)	-17.03 (-40.27 to 17.59)	-30.03 (-55.99 to -2.11)	-26.83 (-60.05 to 6.32)	-32.45 (-72.51 to 0.04)

Statistical analyses

No statistical analyses for this end point

Secondary: Categorized percentage change from Baseline in seizure frequency for

Partial Onset Seizure (Type I) over the 12-week Treatment Period

End point title	Categorized percentage change from Baseline in seizure frequency for Partial Onset Seizure (Type I) over the 12-week Treatment Period

End point description:

The categories are:
- <= 25 %
- - 25 % to < 25 %
- 25 % to < 50 %
- 50 % to < 75 %
- 75 % to < 100 %
- 100 %

End point type	Secondary

End point timeframe:

From Baseline to 12-week Treatment Period

End point values	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	100	99	99	100
Units: Percentage of Participants				
number (not applicable)				
<= 25 %	19	10.1	15.2	10
- 25 % to < 25 %	41	35.4	33.3	33
25 % to < 50 %	20	27.3	24.2	21
50 % to < 75 %	12	18.2	17.2	14
75 % to < 100 %	8	7.1	9.1	18
100 %	0	2	1	4

Statistical analyses

No statistical analyses for this end point

Secondary: Seizure Freedom Rate (all seizure types) over the 12-week Treatment Period

End point title	Seizure Freedom Rate (all seizure types) over the 12-week Treatment Period

End point description:

Subjects were considered seizure free if their seizure counts for every day over the entire Treatment Period was zero and if they completed the Treatment Period.

End point type	Secondary

End point timeframe:

From Baseline to 12-week Treatment Period

End point values	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	100	99	99	100
Units: Percentage of Participants				
number (not applicable)				
Seizure free	0	2	0	4
No Seizures but non-completer	0	0	1	0
Not Seizure-free	100	98	99	96

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first Type I Seizure during the 12-week Treatment Period

End point title	Time to first Type I Seizure during the 12-week Treatment Period

End point description:

The time to first Type I Seizure during the 12-week Treatment Period was measured in days.

End point type	Secondary

End point timeframe:

From Baseline to 12-week Treatment Period

End point values	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	100	99	99	100
Units: Days				
median (confidence interval 95%)				
Median (95 % CI)	4 (3 to 5)	6 (3 to 8)	6 (4 to 10)	4 (3 to 5)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Fifth Type I Seizure during the 12-week Treatment Period

End point title	Time to Fifth Type I Seizure during the 12-week Treatment Period

End point description:

The time to Fifth Type I Seizure during the 12-week Treatment Period was measured in days.

End point type	Secondary

End point timeframe:

From Baseline to 12-week Treatment Period

End point values	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	100	99	99	100
Units: Days				
median (confidence interval 95%)				
Median (95 % CI)	19 (14 to 25)	25 (20 to 34)	24 (20 to 32)	24 (18 to 34)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to tenth Type I seizure during the 12-week Treatment Period

End point title	Time to tenth Type I seizure during the 12-week Treatment Period

End point description:

The time to tenth Type I Seizure during the 12-week Treatment Period was measured in days.

End point type	Secondary

End point timeframe:

From Baseline to 12-week Treatment Period

End point values	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	100	99	99	100
Units: Days				
median (confidence interval 95%)				
Median (95 % CI)	39 (24 to 50)	49 (36 to 64)	40 (33 to 49)	46 (34 to 66)

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction of Type IC/Type I Seizure frequency ratio from Baseline to the 12- week Treatment Period.

End point title	Reduction of Type IC/Type I Seizure frequency ratio from Baseline to the 12- week Treatment Period.

End point description:

Reduction of Type IC/Type I Seizure frequency ratio from Baseline to the 12- week Treatment Period. This variable was not analyzed and no results are available.

End point type	Secondary

End point timeframe:

From Baseline to 12-week Treatment Period

End point values	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[1]	0[2]	0[3]	0[4]
Units: units on a scale				
arithmetic mean (standard deviation)				
Not applicable	()	()	()	()

Notes:

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

[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.

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

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 12-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 12-week Treatment Period in Total Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

End point description:

The QOLIE-31-P is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into seven 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. The subscale scores, the Total score and the Health Status item score are calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function. A positive value in Change from Baseline indicates an improvement from Baseline.

End point type	Secondary

End point timeframe:

From Baseline to 12-week Treatment Period

End point values	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	86	91	94	80
Units: units on a scale				
arithmetic mean (standard deviation)				
Arithmetic Mean (Standard Deviation)	2.29 (± 14.03)	4.5 (± 12.71)	3.09 (± 14.43)	1.78 (± 13.95)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 12-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 12-week Treatment Period in Seizure Worry Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

End point description:

The QOLIE-31-P is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into seven 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. The subscale scores, the Total score and the Health Status item score are calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function. A positive value in Change from Baseline indicates an improvement from Baseline.

End point type	Secondary

End point timeframe:

From Baseline to 12-week Treatment Period

End point values	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	88	93	96	86
Units: units on a scale				
arithmetic mean (standard deviation)				
Arithmetic Mean (Standard Deviation)	8.25 (± 22.01)	6.23 (± 17.97)	5.34 (± 23.81)	8.04 (± 26.26)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 12-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 12-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 QOLIE-31-P is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into seven 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. The subscale scores, the Total score and the Health Status item score are calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function. A positive value in Change from Baseline indicates an improvement from Baseline.

End point type	Secondary

End point timeframe:

From Baseline to 12-week Treatment Period

End point values	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	88	93	96	85
Units: units on a scale				
arithmetic mean (standard deviation)				
Arithmetic Mean (Standard Deviation)	-2.09 (± 20.26)	3.35 (± 19.72)	3.09 (± 20.79)	3.5 (± 22.52)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 12-week Treatment Period in Hospital Anxiety Score

End point title	Change from Baseline to the 12-week Treatment Period in Hospital Anxiety Score

End point description:

The Hospital Anxiety and Depression Scale (HADS) was used to evaluate anxiety and depression simultaneously. The HADS was developed as a self-administered scale that has been designed to assess the presence and severity of both 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 and higher scores indicating higher depression / anxiety. Negative values in Change from Baseline indicate a decrease of HADS from Baseline to Treatment Period.

End point type	Secondary

End point timeframe:

From Baseline to 12-week Treatment Period

End point values	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	86	91	95	83
Units: units on a scale				
arithmetic mean (standard deviation)				
Anxiety	-1.54 (± 3.89)	-0.59 (± 3.89)	-0.41 (± 3.82)	0.08 (± 3.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 12-week Treatment Period in Hospital Depression Score

End point title	Change from Baseline to the 12-week Treatment Period in

	Hospital Depression Score

End point description:

The Hospital Anxiety and Depression Scale (HADS) was used to evaluate anxiety and depression simultaneously. The HADS was developed as a self-administered scale that has been designed to assess the presence and severity of both 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 and higher scores indicating higher depression / anxiety. Negative values in Change from Baseline indicate a decrease of HADS from Baseline to Treatment Period.

End point type	Secondary

End point timeframe:

From Baseline to 12-week Treatment Period

End point values	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	86	91	95	83
Units: units on a scale				
arithmetic mean (standard deviation)				
Depression	-0.65 (± 3.58)	-0.1 (± 3.67)	0.26 (± 3.84)	-0.24 (± 3.69)

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 not mentally impaired had to complete it by answering the following question: "Overall, has there been a change in your seizures since the start of the study medication?"

End point type	Secondary

End point timeframe:

Last Visit or Early Discontinuation Visit in the 12-week Treatment Period

End point values	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	90	90	85
Units: units on a scale				
arithmetic mean (standard deviation)				
Arithmetic Mean (Standard Deviation)	4.93 (± 1.39)	5.17 (± 1.27)	5.04 (± 1.29)	5.47 (± 1.16)

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 reference time point. The Investigator was to complete it by answering the following question: "Assess the Overall change in the severity of patient's illness, compared to start of study medication."

End point type	Secondary

End point timeframe:

Last Visit or Early Discontinuation Visit in the 12-week Treatment Period

End point values	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	96	99	98	100
Units: units on a scale				
arithmetic mean (standard deviation)				
Arithmetic Mean (Standard Deviation)	4.78 (± 1.2)	4.99 (± 1.15)	4.99 (± 1.1)	5.34 (± 1.12)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 12-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 12-week Treatment Period in Energy/Fatigue Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

End point description:

The QOLIE-31-P is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into seven 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. The subscale scores, the Total score and the Health Status item score are calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function. A positive value in Change from Baseline indicates an improvement from Baseline.

End point type	Secondary

End point timeframe:

From Baseline to 12-week Treatment Period

End point values	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	86	92	95	83
Units: units on a scale				
arithmetic mean (standard deviation)				
Arithmetic Mean (Standard Deviation)	3.49 (± 19.22)	3.53 (± 17.04)	1.95 (± 20.74)	1.99 (± 20.42)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 12-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 12-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 QOLIE-31-P is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into seven 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. The subscale scores, the Total score and the Health Status item score are calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function. A positive value in Change from Baseline indicates an improvement from Baseline.

End point type	Secondary

End point timeframe:

From Baseline to 12-week Treatment Period

End point values	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	88	93	96	84
Units: units on a scale				
arithmetic mean (standard deviation)				
Arithmetic Mean (Standard Deviation)	3.8 (± 18.71)	3.75 (± 15.94)	3.13 (± 19.35)	-2.45 (± 18.55)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 12-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 12-week Treatment Period in Cognitive Functioning Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

End point description:

The QOLIE-31-P is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into seven 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. The subscale scores, the Total score and the Health Status item score are calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function. A positive value in Change from Baseline indicates an improvement from Baseline.

End point type	Secondary

End point timeframe:

From Baseline to 12-week Treatment Period

End point values	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	88	93	96	85
Units: units on a scale				
arithmetic mean (standard deviation)				
Arithmetic Mean (Standard Deviation)	1.8 (± 19.16)	5.36 (± 20.69)	1.02 (± 19.95)	0.69 (± 16.66)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 12-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 12-week Treatment Period in Medication Effects Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

End point description:

The QOLIE-31-P is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into seven 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. The subscale scores, the Total score and the Health Status item score are calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function. A positive value in Change from Baseline indicates an improvement from Baseline.

End point type	Secondary

End point timeframe:

From Baseline to 12-week Treatment Period

End point values	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	88	92	96	86
Units: units on a scale				
arithmetic mean (standard deviation)				
Arithmetic Mean (Standard Deviation)	0.92 (± 28.93)	3.64 (± 29.24)	-0.85 (± 24.36)	3 (± 28.22)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 12-week Treatment Period in Overall Quality of Life Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

End point title	Change from Baseline to the 12-week Treatment Period in Overall Quality of Life Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

End point description:

The QOLIE-31-P is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into seven 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. The subscale scores, the Total score and the Health Status item score are calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function. A positive value in Change from Baseline indicates an improvement from Baseline.

End point type	Secondary

End point timeframe:

From Baseline to 12-week Treatment Period

End point values	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	88	93	95	86
Units: units on a scale				
arithmetic mean (standard deviation)				
Arithmetic Mean (Standard Deviation)	5.11 (± 18.48)	4.52 (± 16.73)	4.55 (± 18.93)	2.24 (± 18.45)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to the 12-week Treatment Period in Health Status

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

End point title	Change from Baseline to the 12-week Treatment Period in Health Status of Life Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score

End point description:

The QOLIE-31-P is an adaptation of the original QOLIE-31 instrument that includes 30 items grouped into seven 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. The subscale scores, the Total score and the Health Status item score are calculated according to the scoring algorithm defined by the author with scores ranging from 0 to 100 and higher scores indicating better function. A positive value in Change from Baseline indicates an improvement from Baseline.

End point type	Secondary

End point timeframe:

From Baseline to 12-week Treatment Period

End point values	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day	Brivaracetam 100 mg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	88	93	95	84
Units: units on a scale				
arithmetic mean (standard deviation)				
Arithmetic Mean (Standard Deviation)	6.6 (± 16.3)	6.9 (± 20.1)	9.7 (± 19.8)	4.9 (± 18.1)

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 23 weeks from Visit 1 (Week -8) to the Safety Visit (Week 15).	
Adverse event reporting additional description:	
Adverse Events (AEs) refer to the Safety Set (SS) population wich contains the same set of subjects as the Itention-To-Treat (ITT) population.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Matching Placebo tablets administered twice a day	
Reporting group title	Brivaracetam 20 mg/day
Reporting group description:	
Brivaracetam 20 mg/day, 10 mg administered twice a day	
Reporting group title	Brivaracetam 50 mg/day
Reporting group description:	
Brivaracetam 50 mg/day, 25 mg administered twice a day	
Reporting group title	Brivaracetam 100 mg/day
Reporting group description:	
Brivaracetam 100 mg/day, 50 mg administered twice a day	

Serious adverse events	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 100 (6.00%)	2 / 99 (2.02%)	4 / 99 (4.04%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 100 (0.00%)	0 / 99 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw fracture			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	0 / 99 (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			
Angina pectoris			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	0 / 99 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	0 / 99 (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			
Convulsion			
subjects affected / exposed	3 / 100 (3.00%)	0 / 99 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Grand mal convulsion			
subjects affected / exposed	0 / 100 (0.00%)	0 / 99 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	0 / 100 (0.00%)	0 / 99 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastritis erosive			
subjects affected / exposed	0 / 100 (0.00%)	0 / 99 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Vaginal hemorrhage			

subjects affected / exposed	0 / 100 (0.00%)	1 / 99 (1.01%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Amnesia			
subjects affected / exposed	0 / 100 (0.00%)	0 / 99 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic Disorder			
subjects affected / exposed	0 / 100 (0.00%)	0 / 99 (0.00%)	1 / 99 (1.01%)
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			
Sepsis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 99 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Serious adverse events	Brivaracetam 100 mg/day		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 100 (2.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Jaw fracture			
subjects affected / exposed	0 / 100 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			

subjects affected / exposed	0 / 100 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 100 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy			
subjects affected / exposed	0 / 100 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 100 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Grand mal convulsion			
subjects affected / exposed	0 / 100 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Status epilepticus			
subjects affected / exposed	1 / 100 (1.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastritis erosive			
subjects affected / exposed	0 / 100 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Vaginal hemorrhage			

subjects affected / exposed	0 / 100 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Amnesia			
subjects affected / exposed	0 / 100 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychotic Disorder			
subjects affected / exposed	0 / 100 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 100 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	Brivaracetam 20 mg/day	Brivaracetam 50 mg/day
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 100 (22.00%)	31 / 99 (31.31%)	35 / 99 (35.35%)
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 100 (1.00%)	5 / 99 (5.05%)	1 / 99 (1.01%)
occurrences (all)	1	7	1
Dizziness			
subjects affected / exposed	5 / 100 (5.00%)	5 / 99 (5.05%)	7 / 99 (7.07%)
occurrences (all)	11	8	12
Headache			
subjects affected / exposed	10 / 100 (10.00%)	14 / 99 (14.14%)	18 / 99 (18.18%)
occurrences (all)	14	19	31
Somnolence			

subjects affected / exposed	6 / 100 (6.00%)	8 / 99 (8.08%)	6 / 99 (6.06%)
occurrences (all)	6	10	7
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 100 (2.00%)	3 / 99 (3.03%)	4 / 99 (4.04%)
occurrences (all)	2	4	5
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 100 (3.00%)	1 / 99 (1.01%)	2 / 99 (2.02%)
occurrences (all)	5	2	2
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 100 (4.00%)	0 / 99 (0.00%)	1 / 99 (1.01%)
occurrences (all)	4	0	1
Psychiatric disorders			
Irritability			
subjects affected / exposed	0 / 100 (0.00%)	0 / 99 (0.00%)	5 / 99 (5.05%)
occurrences (all)	0	0	5
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 100 (1.00%)	8 / 99 (8.08%)	1 / 99 (1.01%)
occurrences (all)	1	8	1

Non-serious adverse events	Brivaracetam 100 mg/day		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 100 (37.00%)		
Nervous system disorders			
Convulsion			
subjects affected / exposed	2 / 100 (2.00%)		
occurrences (all)	2		
Dizziness			
subjects affected / exposed	5 / 100 (5.00%)		
occurrences (all)	5		
Headache			
subjects affected / exposed	9 / 100 (9.00%)		
occurrences (all)	15		
Somnolence			

subjects affected / exposed occurrences (all)	8 / 100 (8.00%) 8		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	 8 / 100 (8.00%) 9		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	 8 / 100 (8.00%) 26		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	 6 / 100 (6.00%) 7		
Psychiatric disorders Irritability subjects affected / exposed occurrences (all)	 1 / 100 (1.00%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 2 / 100 (2.00%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2007	Protocol amendment 1 was issued on 02 Feb 2007. The following changes were implemented; no subjects were enrolled at the time: • A storage period of up to 20 years was proposed for the DNA samples in order to have the possibility to re-evaluate a possible correlation between SV2 (A, B, and C) gene variations and treatment response if, and when, new mutations are found to be relevant to SV2 pharmacogenomics. The initial genotyping will occur during the conduct of the study, but there is high likelihood that new mutations in SV2A, B or C will be found over the subsequent years as this is a rapidly evolving area. In addition, it will be of interest to examine the genetic variability in other disease-related genes of possible relevance for epileptic disorders and in genes related to SV2 biology. • The rationale for collecting the race has been added according to legal requirement in some countries. • Clarification of the electrocardiogram (ECG) tracings retrieval has been added to include the following text: Copies of all ECG tracings will be retrieved for all subjects presenting treatment-emergent, clinically significant abnormalities during the study.
08 May 2007	A protocol amendment was issued on 08 May 2007 in response to Food and Drug Administration (FDA) feedback on the N01253 final protocol, which was identical in design to N01252. The following changes were implemented; no subjects were enrolled at the time: • An additional 1 week step at 20 mg/day was added to the Down-Titration Period for subjects on 50 mg/day or on 100 mg/day. • A clinic visit was added 2 weeks after randomization which included a complete safety evaluation (including laboratory analysis and ECGs). • Microscopy evaluations for all urinalysis assessments were added at clinic visits when urinalysis samples were taken. Other changes implemented in this amendment included: • 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 (V) (V7), did not have any Early Discontinuation Visit (EDV), and entered the LTFU; or was randomized, underwent the Evaluation Visit (V7) and Safety Visit (SV), did not have any EDV, and did not enter the LTFU. Otherwise the subject was to be considered discontinued. • Specifications for the handling of missing data for primary efficacy analysis on the Intent-to- Treat (ITT) Population analyses 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/24256083