Clinical trial results:
A multicenter, randomized, double-blind, placebo-controlled, parallel study to evaluate the efficacy and safety of brivaracetam used as adjunctive treatment for 12 weeks in adolescent and adult patients (>=16 years) with genetically ascertained Unverricht-Lundborg disease

Summary

EudraCT number	2006-001536-46
Trial protocol	FR FI
Global end of trial date	08 January 2008

Results information

Result version number	v1 (current)
This version publication date	31 March 2016
First version publication date	31 March 2016

Trial information

Trial identification

Sponsor protocol code	N01236

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00368251
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB Pharma SA
Sponsor organisation address	Chemin du Foriest, Braine-l'Alleud, Belgium, 1420
Public contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 2173 48 15 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	12 March 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 January 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 compare the efficacy of Brivaracetam 5 and 150 mg/day in bid administration with Placebo, on the symptom relief of Action Myoclonus in patients with Unverricht-Lundborg disease (ULD).

Protection of trial subjects:

Standard safety measures to minimize pain and distress

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	07 November 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Finland: 9
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Russian Federation: 8
Country: Number of subjects enrolled	Serbia: 6
Country: Number of subjects enrolled	Tunisia: 5
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	56
EEA total number of subjects	17

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	2
Adults (18-64 years)	54
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

72 subjects were screened, 56 subjects were randomized.

Pre-assignment

Screening details:

Participant Flow refers to all subjects randomized who are identical with the Intent-To-Treat (ITT) Population, which consists of all randomized subjects who took at least one dose of study medication.

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:

Placebo twice a day (bid), 14 weeks (2 week Up-Titration Period + 12 week Maintenance Period)

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 Tablets

Arm title	Brivaracetam 5 mg/day

Arm description:

Brivaracetam (BRV) 5 mg/day 2.5 mg twice a day (bid) using 2.5 mg tablets for 12 weeks (after 2 week Up- Titration Period)

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:

BRV 5 mg: oral tablet of 2.5 mg
BRV 150 mg: oral tablet of 25 mg and 50 mg

Arm title	Brivaracetam 150 mg/day

Arm description:

Brivaracetam (BRV) 150 mg/day 75 mg twice a day (bid) using 25 mg and 50 mg tablets for 12 weeks (after 2 week Up-Titration Period)

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:

BRV 5 mg: oral tablet of 2.5 mg
BRV 150 mg: oral tablet of 25 mg and 50 mg

Number of subjects in period 1	Placebo	Brivaracetam 5 mg/day	Brivaracetam 150 mg/day
Started	18	20	18
Completed	17	20	17
Not completed	1	0	1
AE, non-serious non-fatal	-	-	1
SAE, non-fatal	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo twice a day (bid), 14 weeks (2 week Up-Titration Period + 12 week Maintenance Period)	
Reporting group title	Brivaracetam 5 mg/day
Reporting group description:	
Brivaracetam (BRV) 5 mg/day 2.5 mg twice a day (bid) using 2.5 mg tablets for 12 weeks (after 2 week Up- Titration Period)	
Reporting group title	Brivaracetam 150 mg/day
Reporting group description:	
Brivaracetam (BRV) 150 mg/day 75 mg twice a day (bid) using 25 mg and 50 mg tablets for 12 weeks (after 2 week Up-Titration Period)	

Reporting group values	Placebo	Brivaracetam 5 mg/day	Brivaracetam 150 mg/day
Number of subjects	18	20	18
Age Categorical Units: Subjects			
<=18 years	0	1	1
Between 18 and 65 years	18	19	17
>=65 years	0	0	0
Age Continuous Units: years			
arithmetic mean	34.3	35.8	33.7
standard deviation	± 9.2	± 10.9	± 11.4
Gender Categorical Units: Subjects			
Female	12	11	9
Male	6	9	9
Region of Enrollment Units: Subjects			
Serbia	2	2	2
France	3	2	3
United States	2	3	4
Canada	4	3	2
Finland	3	4	2
Russian Federation	2	3	3
Israel	0	0	2
Tunisia	2	3	0

Reporting group values	Total		
Number of subjects	56		
Age Categorical Units: Subjects			
<=18 years	2		
Between 18 and 65 years	54		
>=65 years	0		

Age Continuous Units: years arithmetic mean standard deviation	- 		
Gender Categorical Units: Subjects			
Female	32		
Male	24		
Region of Enrollment Units: Subjects			
Serbia	6		
France	8		
United States	9		
Canada	9		
Finland	9		
Russian Federation	8		
Israel	2		
Tunisia	5		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo twice a day (bid), 14 weeks (2 week Up-Titration Period + 12 week Maintenance Period)	
Reporting group title	Brivaracetam 5 mg/day
Reporting group description:	
Brivaracetam (BRV) 5 mg/day 2.5 mg twice a day (bid) using 2.5 mg tablets for 12 weeks (after 2 week Up- Titration Period)	
Reporting group title	Brivaracetam 150 mg/day
Reporting group description:	
Brivaracetam (BRV) 150 mg/day 75 mg twice a day (bid) using 25 mg and 50 mg tablets for 12 weeks (after 2 week Up-Titration Period)	

Primary: Percent change from Baseline to the End of Treatment Period on the Action Myoclonus Score (Unified Myoclonus Rating Scale (UMRS) Section 4)

End point title	Percent change from Baseline to the End of Treatment Period on the Action Myoclonus Score (Unified Myoclonus Rating Scale (UMRS) Section 4)
End point description:	
The range for Action Myoclonus Score (centrally read) is 0 (best) - 160 (worst). Percent change from Baseline = 100 X ((Baseline UMRS4 - Treatment UMRS4) / Baseline UMRS4). Baseline is defined as the last non-missing value prior to or on Randomization Visit.	
End point type	Primary
End point timeframe:	
From Baseline to End of Treatment Period (Week 14 or Early Discontinuation Visit)	

End point values	Placebo	Brivaracetam 5 mg/day	Brivaracetam 150 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	20	18	
Units: Percent Reduction				
median (full range (min-max))				
median (full range)	17.45 (-170 to 61.5)	-4.6 (-430 to 81.8)	12.34 (-58.3 to 96.9)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
The first hypothesis for the primary efficacy variable compares placebo versus Brivaracetam (BRV) 150 mg/day. The second hypothesis for the primary efficacy variable compares placebo versus BRV 5 mg/day. However, this second hypothesis will only be tested when all the hypotheses for placebo versus BRV 150 mg/day are significant for the primary three UMRS related secondary endpoints.	

The hypotheses will be tested using nonparametric analysis. The study was designed to have 80 % power.

Comparison groups	Placebo v Brivaracetam 150 mg/day
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.942
Method	stratified Wilcoxon Test
Parameter estimate	Hodges-Lehmann-estimator of difference
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.12
upper limit	24.96

Notes:

[1] - All hypotheses are tested at the 5 % level. The multiplicity scheme (hierarchical testing procedure) assures strong control of the type I error at the 5 % level.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Brivaracetam 5 mg/day
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.105
Method	stratified Wilcoxon Test
Parameter estimate	Hodges-Lehmann-estimator of difference
Point estimate	-18.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.31
upper limit	4.86

Notes:

[2] - Tested at the 5 % level - given the primary endpoint and the three UMRS related secondary endpoints comparing placebo versus Brivaracetam (BRV) 150 mg/day are significant at the 5 % level (hierarchical testing procedure).

Secondary: Percent change from Baseline to the end of Treatment Period on the Functional Disability Score (Unified Myoclonus Rating Scale (UMRS) Section 5)

End point title	Percent change from Baseline to the end of Treatment Period on the Functional Disability Score (Unified Myoclonus Rating Scale (UMRS) Section 5)

End point description:

The range for Functional Disability Score is 0 (best) to 28 (worst). Percent change from Baseline = 100 X ((Baseline UMRS5 - Treatment UMRS5) / Baseline UMRS5). Baseline is defined as the last non-missing value prior to or on Randomization Visit.

End point type	Secondary

End point timeframe:

Baseline to End of Treatment Period (Week 14 or Early Discontinuation Visit)

End point values	Placebo	Brivaracetam 5 mg/day	Brivaracetam 150 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	20	18	
Units: Percent Reduction				
median (full range (min-max))				
median (full range)	0 (-380 to 53.8)	0 (-380 to 60)	0 (-85.7 to 75)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

If primary efficacy is proven for Brivaracetam (BRV) 150 mg/day, the following secondary endpoints will be tested for Placebo versus BRV 150 mg/day. The testing scheme will be hierarchical, thus statistical significance at 5 % on BRV 150 mg/day on a secondary endpoint is needed to continue testing BRV 150 mg/day at 5 % significance level for the next secondary endpoint.

Comparison groups	Placebo v Brivaracetam 150 mg/day
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.672
Method	stratified Wilcoxon Test
Parameter estimate	Hodges-Lehmann-estimator of difference
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.9
upper limit	31.06

Notes:

[3] - Tested at the 5 % level - given the Primary Outcome testing Placebo versus BRV 150 mg/day is significant at the 5 % level (hierarchical testing procedure).

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

In case the three endpoints are significant for placebo versus Brivaracetam (BRV) 150 mg/day, the primary endpoint will be tested for Placebo versus BRV 5 mg/day. In case of significance, the three UMRS related secondary endpoints will be tested for Placebo versus BRV 5 mg/day, provided the previous is significant at 5 %. Secondary endpoints are tested in the following order:
- Functional Disability
- Stimulus Sensitivity
- Myoclonus Patient Questionnaire

Comparison groups	Placebo v Brivaracetam 5 mg/day
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.806
Method	stratified Wilcoxon Test
Parameter estimate	Hodges-Lehmann-estimator of difference
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.33
upper limit	18.75

Notes:

[4] - Tested at the 5 % level - given the primary endpoint testing Placebo versus Brivaracetam (BRV) 5 mg/day is significant at the 5 % level (hierarchical testing procedure).

Secondary: Percent change from Baseline to the end of Treatment Period on the Stimulus Sensitivity Score (Unified Myoclonus Rating Scale (UMRS) Section 3)

End point title	Percent change from Baseline to the end of Treatment Period on the Stimulus Sensitivity Score (Unified Myoclonus Rating Scale (UMRS) Section 3)

End point description:

The range for Stimulus Sensitivity Score is 0 (best) to 17 (worst). Percent change from Baseline = 100 X ((Baseline UMRS3 - Treatment UMRS3) / Baseline UMRS3). Baseline is defined as the last non-missing value prior to or on Randomization Visit.

End point type	Secondary

End point timeframe:

Baseline to End of Treatment Period (Week 14 or Early Discontinuation Visit)

End point values	Placebo	Brivaracetam 5 mg/day	Brivaracetam 150 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	20	18	
Units: Percent Reduction				
median (full range (min-max))				
median (full range)	0 (-300 to 100)	43.44 (-300 to 100)	0 (-300 to 100)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Brivaracetam 150 mg/day
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.549
Method	stratified Willcoxon Test
Parameter estimate	Hodges-Lehmann-estimator of difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25
upper limit	100

Notes:

[5] - Tested at the 5 % level - given the Functional Disability Score comparing Placebo versus Brivaracetam (BRV) 5 mg/day is significant at the 5 % level (hierarchical testing procedure).

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Brivaracetam 5 mg/day
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.654
Method	stratified Wilcoxon Test
Parameter estimate	Hodges-Lehmann-estimator of difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-50
upper limit	66.67

Notes:

[6] - Tested at the 5 % level - given the Functional Disability Score comparing Placebo versus Brivaracetam (BRV) 5 mg/day is significant at the 5 % level (hierarchical testing procedure).

Secondary: Percent change from Baseline to the end of Treatment Period on the Myoclonus Patient Questionnaire (Unified Myoclonus Rating Scale (UMRS) Section 1)

End point title	Percent change from Baseline to the end of Treatment Period on the Myoclonus Patient Questionnaire (Unified Myoclonus Rating Scale (UMRS) Section 1)

End point description:

The range for Myoclonus Patient Questionnaire is 0 (best) to 44 (worst). Percent change from Baseline = 100 X ((Baseline UMRS1 - Treatment UMRS1) / Baseline UMRS1). Baseline is defined as the last non-missing value prior to or on Randomization Visit.

End point type	Secondary

End point timeframe:

Baseline to End of Treatment Period (Week 14 or Early Discontinuation Visit)

End point values	Placebo	Brivaracetam 5 mg/day	Brivaracetam 150 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	20	18	
Units: Percent Reduction				
median (full range (min-max))				
median (full range)	-9.68 (-125 to 63)	0 (-95 to 55.6)	5.41 (-24 to 100)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Brivaracetam 150 mg/day

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.037
Method	stratified Wilcoxon Test
Parameter estimate	Hodges-Lehmann-estimator of difference
Point estimate	14.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.76
upper limit	39.39

Notes:

[7] - Tested at the 5 % level - given the Functional Disability Score comparing Placebo versus Brivaracetam (BRV) 150 mg/day is significant at the 5 % level (hierarchical testing procedure).

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Brivaracetam 5 mg/day
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.111
Method	stratified Wilcoxon Test
Parameter estimate	Hodges-Lehmann-estimator of difference
Point estimate	10
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.56
upper limit	30

Notes:

[8] - Tested at the 5 % level - given the Functional Disability Score comparing Placebo versus Brivaracetam (BRV) 5 mg/day is significant at the 5 % level (hierarchical testing procedure).

Secondary: Global Evaluation Score (Investigator) at the end of Treatment Period

End point title	Global Evaluation Score (Investigator) at the end of Treatment Period

End point description:

The Global Evaluation Scale Score (Investigator) ranges from 1 (Marked worsening) to 7 (Marked improvement).

End point type	Secondary

End point timeframe:

End of Treatment Period (Week 14 or Early Discontinuation Visit)

End point values	Placebo	Brivaracetam 5 mg/day	Brivaracetam 150 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	20	18	
Units: percentage of participants				
number (not applicable)				
Marked improvement	0	10	11.1	
Moderate improvement	11.1	0	11.1	
Slight improvement	33.3	30	33.3	
No change	50	50	33.3	
Slight worsening	0	10	5.6	
Moderate worsening	0	0	5.6	
Marked worsening	5.6	0	0	

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v Brivaracetam 150 mg/day
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.253 [10]
Method	Stratified Wilcoxon test

Notes:

[9] - P-value for pairwise comparison of each Brivaracetam dose versus Placebo.

[10] - The Global Evaluation Scale by Investigator (I-GES) was compared between placebo and each dose at 5 % significance level independently from the previous secondary endpoints.

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Brivaracetam 5 mg/day
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.931
Method	Stratified Wilcoxon test

Notes:

[11] - The Global Evaluation Scale by Investigator (I-GES) was compared between placebo and each dose at 5 % significance level independently from the previous secondary endpoints

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse Events (AEs) were collected from Visit 1 (Week -2) until final Visit 10 (Week 18).	
Adverse event reporting additional description:	
The Intent-To-Treat (ITT) population consists of all randomized subjects who took at least one dose of study medication.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo twice a day (bid), 14 weeks (2 week Up-Titration Period + 12 week Maintenance Period)	
Reporting group title	Brivaracetam 150 mg/day
Reporting group description:	
Brivaracetam (BRV) 150 mg/day 75 mg twice a day (bid) using 25 mg and 50 mg tablets for 12 weeks (after 2 week Up-Titration Period)	
Reporting group title	Brivaracetam 5 mg/day
Reporting group description:	
Brivaracetam (BRV) 5 mg/day 2.5 mg twice a day (bid) using 2.5 mg tablets for 12 weeks (after 2 week Up- Titration Period)	

Serious adverse events	Placebo	Brivaracetam 150 mg/day	Brivaracetam 5 mg/day
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 18 (11.11%)	2 / 18 (11.11%)	3 / 20 (15.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Grand mal convulsion			

subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (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
Status epilepticus			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myoclonic epilepsy			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (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
Psychiatric disorders			
Attention-seeking behavior			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 18 (0.00%)	2 / 20 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Brivaracetam 150 mg/day	Brivaracetam 5 mg/day
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 18 (72.22%)	15 / 18 (83.33%)	13 / 20 (65.00%)
Vascular disorders			

Haematoma			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 18 (11.11%)	3 / 18 (16.67%)	1 / 20 (5.00%)
occurrences (all)	2	6	1
Oedema peripheral			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Pyrexia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Genital pruritus female			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Sinus congestion			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract congestion			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	2 / 20 (10.00%)
occurrences (all)	1	0	2
Insomnia			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	2 / 20 (10.00%)
occurrences (all)	2	0	2
Anxiety			

subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	1	1	0
Depression			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Bradyphrenia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Depressed mood			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Disorientation			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Memory impairment			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Excoriation			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Joint injury			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Limb injury			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Joint sprain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram QT corrected interval prolonged			

subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Myoclonus			
subjects affected / exposed	1 / 18 (5.56%)	3 / 18 (16.67%)	4 / 20 (20.00%)
occurrences (all)	2	4	4
Somnolence			
subjects affected / exposed	2 / 18 (11.11%)	4 / 18 (22.22%)	3 / 20 (15.00%)
occurrences (all)	2	7	3
Headache			
subjects affected / exposed	7 / 18 (38.89%)	2 / 18 (11.11%)	3 / 20 (15.00%)
occurrences (all)	8	2	4
Balance disorder			
subjects affected / exposed	0 / 18 (0.00%)	2 / 18 (11.11%)	1 / 20 (5.00%)
occurrences (all)	0	4	1
Dizziness			
subjects affected / exposed	2 / 18 (11.11%)	1 / 18 (5.56%)	1 / 20 (5.00%)
occurrences (all)	2	1	1
Grand mal convulsion			
subjects affected / exposed	0 / 18 (0.00%)	0 / 18 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Hyporeflexia			
subjects affected / exposed	0 / 18 (0.00%)	2 / 18 (11.11%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Complex partial seizures			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Coordination abnormal			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Dysarthria			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	1	2	0
Migraine			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	3	0

Nystagmus			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	3 / 18 (16.67%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	4	1	0
Convulsion			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Myoclonic epilepsy			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Sciatica			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Granulocytopenia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Lymphadenopathy			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Thrombocytopenia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Middle ear inflammation			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	2 / 20 (10.00%)
occurrences (all)	1	1	2
Abdominal pain upper			

subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	2 / 20 (10.00%)
occurrences (all)	2	0	2
Diarrhoea			
subjects affected / exposed	2 / 18 (11.11%)	1 / 18 (5.56%)	1 / 20 (5.00%)
occurrences (all)	3	1	1
Abdominal pain			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	3	1	0
Constipation			
subjects affected / exposed	2 / 18 (11.11%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	2	1	0
Gingival bleeding			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Ingrowing nail			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Night sweats			

subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Skin ulcer			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Enuresis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Pollakiuria			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	1 / 20 (5.00%)
occurrences (all)	1	1	1
Arthralgia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	1	2	0
Arthritis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Back pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Pain in extremity			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Shoulder pain			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 18 (16.67%)	1 / 18 (5.56%)	1 / 20 (5.00%)
occurrences (all)	4	1	1
Respiratory tract infection viral			

subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	1 / 20 (5.00%)
occurrences (all)	0	3	1
Gastrointestinal infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Gastroenteritis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Otitis externa			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	3	0	0
Pharyngitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Metabolism and nutrition disorders			
Weight decreased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Anorexia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Increased appetite			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Weight increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2007	Allowed two study visits (Visit 3 and Visit 8) to be performed by telephone, where appropriate.
20 March 2007	Adaptation of the hypothesis testing strategy for dealing with multiple endpoints and multiple doses. The sample size calculations assumptions were corrected. It was specified that the primary efficacy analysis will be performed adding in a covariate for the stratification factor used in the randomization process, and some adjustments and additions to the sensitivity analyses for the primary efficacy analysis were provided. Stimulus sensitivity was added to the secondary objectives. Inconsistency between secondary objectives and secondary endpoints was corrected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported