Clinical trial results:
AN OPEN-LABEL, MULTICENTER, FOLLOW-UP STUDY TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF BRIVARACETAM USED AS ADJUNCTIVE TREATMENT IN SUBJECTS AGED 16 YEARS OR OLDER WITH EPILEPSY

Summary

EudraCT number	2010-020345-27
Trial protocol	BE DE CZ ES GB SE FR AT FI NL IT EE LT LV HU BG
Global end of trial date	18 April 2019

Results information

Result version number	v2 (current)
This version publication date	01 July 2020
First version publication date	01 November 2019
Version creation reason	• Correction of full data set Alignment with final posting on ClinicalTrials.gov after NIH review.

Trial information

Trial identification

Sponsor protocol code	N01379

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01339559
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB BIOSCIENCES Inc.
Sponsor organisation address	8010 Arco Corporate Drive, Raleigh, United States, NC 27617
Public contact	Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.com
Scientific contact	Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 April 2019
Global end of trial reached?	Yes
Global end of trial date	18 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety and tolerability of brivaracetam (BRV) at individualized doses up to a maximum of 200 mg/day in epilepsy subjects.

Protection of trial subjects:

During the conduct of the study all participants were closely monitored.

Background therapy:

Background therapy as permitted in the protocol.

Evidence for comparator:

Not Applicable

Actual start date of recruitment	10 May 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Brazil: 14
Country: Number of subjects enrolled	Bulgaria: 7
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Czech Republic: 42
Country: Number of subjects enrolled	Estonia: 22
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Hong Kong: 2
Country: Number of subjects enrolled	Hungary: 19
Country: Number of subjects enrolled	India: 33
Country: Number of subjects enrolled	Italy: 45
Country: Number of subjects enrolled	Japan: 7
Country: Number of subjects enrolled	Latvia: 8
Country: Number of subjects enrolled	Lithuania: 11
Country: Number of subjects enrolled	Mexico: 59
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Poland: 74

Country: Number of subjects enrolled	Russian Federation: 24
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 22
Country: Number of subjects enrolled	Spain: 44
Country: Number of subjects enrolled	Sweden: 15
Country: Number of subjects enrolled	Taiwan: 17
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	United States: 212
Worldwide total number of subjects	766
EEA total number of subjects	360

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)	13
Adults (18-64 years)	728
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study started to enroll patients in May 2011 and concluded in April 2019. 767 participants were included in the Enrolled Set but 1 participant from the United States of America was lost to follow-up and was excluded from the Safety Analysis Set.

Pre-assignment

Screening details:

Participants Flow refers to the Safety Set (SS).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Brivaracetam

Arm description:

Brivaracetam (BRV) was administered with a maximum of 200 mg/day, twice, daily, incremented by 50 mg/day on a weekly basis, during the Up-Titration. During the Down-Titration Period, the BRV dose was decreased in steps of a maximum of 50 mg/day on a weekly basis. A last down-titration step at 20 mg/day for 1 week was included prior to the Post-Treatment Period.

Arm type	Experimental
Investigational medicinal product name	BRIVARACETAM
Investigational medicinal product code	BRV
Other name	UCB34714
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Oral film-coated tablets of BRV 10mg, 25mg, and 50mg were used in this study. The BRV 10mg dose (20 mg/day) was used only for down-titration.

Number of subjects in period 1	Brivaracetam
Started	766
Completed	368
Not completed	398
Adverse event, serious fatal	5
Epilepsy surgery	1
Pregnancy planned	2
Left the country	1
PI decision	1
Adverse event, non-fatal	92
Patient didn't wish to continue	1
Investigator decision	2

Study closure at site	1
Incarcerated	2
Lost to follow-up	22
Subject choice	89
Lack of efficacy	164
Protocol deviation	15

Baseline characteristics

Reporting groups	
Reporting group title	Brivaracetam

Reporting group description:

Brivaracetam (BRV) was administered with a maximum of 200 mg/day, twice, daily, incremented by 50 mg/day on a weekly basis, during the Up-Titration. During the Down-Titration Period, the BRV dose was decreased in steps of a maximum of 50 mg/day on a weekly basis. A last down-titration step at 20 mg/day for 1 week was included prior to the Post-Treatment Period.

Reporting group values	Brivaracetam	Total	
Number of subjects	766	766	
Age categorical Units: Subjects			
<=18 years	19	19	
Between 18 and 65 years	722	722	
>=65 years	25	25	
Age continuous Units: years			
arithmetic mean	40.0		
standard deviation	± 12.9	-	
Gender categorical Units: Subjects			
Male	370	370	
Female	396	396	

End points

End points reporting groups

Reporting group title	Brivaracetam

Reporting group description:

Brivaracetam (BRV) was administered with a maximum of 200 mg/day, twice, daily, incremented by 50 mg/day on a weekly basis, during the Up-Titration. During the Down-Titration Period, the BRV dose was decreased in steps of a maximum of 50 mg/day on a weekly basis. A last down-titration step at 20 mg/day for 1 week was included prior to the Post-Treatment Period.

Subject analysis set title	Brivaracetam (SS)
Subject analysis set type	Safety analysis

Subject analysis set description:

Brivaracetam (BRV) was administered with a maximum of 200 mg/day, twice, daily, incremented by 50 mg/day on a weekly basis, during the Up-Titration. During the Down-Titration Period, the BRV dose was decreased in steps of a maximum of 50 mg/day on a weekly basis. A last down-titration step at 20 mg/day for 1 week was included prior to the Post-Treatment Period. Participants formed the Safety Set (SS).

Subject analysis set title	Brivaracetam (POS Efficacy)
Subject analysis set type	Per protocol

Subject analysis set description:

Brivaracetam (BRV) was administered with a maximum of 200 mg/day, twice, daily, incremented by 50 mg/day on a weekly basis, during the Up-Titration. During the Down-Titration Period, the BRV dose was decreased in steps of a maximum of 50 mg/day on a weekly basis. A last down-titration step at 20 mg/day for 1 week was included prior to the Post-Treatment Period. Participants formed the Partial Onset Seizure Efficacy Set (POS Efficacy).

Primary: Percentage of participants with at least one Treatment-Emergent Adverse Event (TEAE)

End point title	Percentage of participants with at least one Treatment-Emergent Adverse Event (TEAE)[1]

End point description:

Treatment-emergent Adverse Events (TEAEs) were defined as those events which started on or after the date of first dose of investigational medicinal product (IMP), or events in which severity worsened on or after the date of first dose of study medication. The event does not necessarily have a causal relationship with that treatment or usage.

End point type	Primary

End point timeframe:

From Entry Visit (Month 0) until the Last Visit (up to 84 months)

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 as descriptive statistics only.

End point values	Brivaracetam (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	766			
Units: Percentage of participants				
number (not applicable)	83.9			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants who withdrew due to Adverse Events (AEs)

End point title	Percentage of participants who withdrew due to Adverse Events (AEs)[2]

End point description:

An AE is any untoward medical occurrence in a participant or trial subject that is administered a drug or biologic (medicinal product) or that is using a medical device. The event does not necessarily have a causal relationship with that treatment or usage.

End point type	Primary

End point timeframe:

From Entry Visit (Month 0) until the Last Visit (up to 84 months)

Notes:

[2] - 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 as descriptive statistics only.

End point values	Brivaracetam (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	766			
Units: Percentage of participants				
number (not applicable)	11.9			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of participants with at least one Serious Adverse Event (SAE)

End point title	Percentage of participants with at least one Serious Adverse Event (SAE)[3]

End point description:

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:
- Results in death
- Is life-threatening
- Requires in patient hospitalization or prolongation of existing hospitalization
- Is a congenital anomaly or birth defect
- Is as infection that requires treatment parenteral antibiotics
- Other important medical events which based on medical or scientific judgement may jeopardize the patients or may require medical or surgical intervention to prevent any of the above.

End point type	Primary

End point timeframe:

From Entry Visit (Month 0) until the Last Visit (up to 84 months)

Notes:

[3] - 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 as descriptive statistics only.

End point values	Brivaracetam (SS)			
Subject group type	Subject analysis set			
Number of subjects analysed	766			
Units: Percentage of participants				
number (not applicable)	18.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Partial onset seizure (POS) (type I) frequency per 28 days during the Evaluation Period

End point title	Partial onset seizure (POS) (type I) frequency per 28 days during the Evaluation Period

End point description:

The 28 day adjusted seizure frequency was calculated by dividing the number of partial seizures by the number of days for which the diary was completed, and multiplying the resulting value by 28.

End point type	Secondary

End point timeframe:

From Baseline of the previous study until the Last Visit (up to 84 months)

End point values	Brivaracetam (POS Efficacy)			
Subject group type	Subject analysis set			
Number of subjects analysed	749			
Units: Seizures per 28 days				
median (inter-quartile range (Q1-Q3))				
Baseline	9.7 (5.5 to 23.7)			
On Treatment	4.2 (1.4 to 12.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in Partial Onset Seizure (POS) (Type I) frequency per 28 days from Baseline of the previous study to the Evaluation Period

End point title	Percent change in Partial Onset Seizure (POS) (Type I) frequency per 28 days from Baseline of the previous study to the Evaluation Period

End point description:

The percent change from the previous study baselines, in Partial Onset Seizure (POS) (Type I) frequency per 28 days is defined as:
(the value at the previous study baselines) minus (the value at each time-points during the evaluation period) divided by the value at the previous study baselines.

Note: Since N01258 was a safety study, participants were not required to meet seizure frequency requirements during the Baseline Period, and the Baseline Period was short (ie, 7 days). Therefore, participants from N01258 were excluded from efficacy summaries in the variable of percent change in POS frequency.

End point type	Secondary

End point timeframe:

From Baseline of the previous study until the Last Visit (up to 84 months)

End point values	Brivaracetam (POS Efficacy)			
Subject group type	Subject analysis set			
Number of subjects analysed	675			
Units: Percent change				
median (inter-quartile range (Q1-Q3))	52.0 (16.8 to 81.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Responder rate in POS (type I) frequency over the Evaluation Period

End point title	Responder rate in POS (type I) frequency over the Evaluation Period

End point description:

A responder is defined as a subject with a ≥ 50% reduction in seizure frequency from the Baseline Period of the previous study.

Note: Since N01258 was a safety study, participants were not required to meet seizure frequency requirements during the Baseline Period, and the Baseline Period was short (ie, 7 days). Therefore, participants from N01258 were excluded from efficacy summaries in the variable of responder rates in POS frequency.

End point type	Secondary

End point timeframe:

From Baseline of the previous study until the Last Visit (up to 84 months)

End point values	Brivaracetam (POS Efficacy)			
Subject group type	Subject analysis set			
Number of subjects analysed	675			
Units: Percentage of participants				
number (not applicable)	51.7			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Entry Visit (Month 0) until the Last Visit (up to 84 months)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups	
Reporting group title	Brivaracetam (SS)

Reporting group description:

Brivaracetam (BRV) was administered with a maximum of 200 mg/day, twice, daily, incremented by 50 mg/day on a weekly basis, during the Up-Titration. During the Down-Titration Period, the BRV dose was decreased in steps of a maximum of 50 mg/day on a weekly basis. A last down-titration step at 20 mg/day for 1 week was included prior to the Post-Treatment Period. Participants formed the Safety Set (SS).

Serious adverse events	Brivaracetam (SS)		
Total subjects affected by serious adverse events			
subjects affected / exposed	140 / 766 (18.28%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gliomatosis cerebri			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thymoma			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Intervertebral disc operation			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tenodesis			

subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Imminent abortion			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 766 (0.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Asthenia			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device malfunction			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	2 / 766 (0.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Menometrorrhagia			

subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spermatic cord haemorrhage				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Uterine polyp				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea exertional				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hiccups				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				

subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Suicide attempt				
subjects affected / exposed	7 / 766 (0.91%)			
occurrences causally related to treatment / all	2 / 7			
deaths causally related to treatment / all	0 / 0			
Suicidal ideation				
subjects affected / exposed	5 / 766 (0.65%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
Acute psychosis				
subjects affected / exposed	2 / 766 (0.26%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Depression				
subjects affected / exposed	2 / 766 (0.26%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Aggression				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Anxiety				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anxiety disorder				

subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Delirium			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Delirium febrile			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Emotional disorder			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Diagnostic procedure			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Troponin increased			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Weight decreased			

subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	3 / 766 (0.39%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Accidental overdose			
subjects affected / exposed	2 / 766 (0.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Brain contusion			
subjects affected / exposed	2 / 766 (0.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Contusion			
subjects affected / exposed	2 / 766 (0.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	2 / 766 (0.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Head injury			
subjects affected / exposed	2 / 766 (0.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Joint dislocation			
subjects affected / exposed	2 / 766 (0.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			

subjects affected / exposed	2 / 766 (0.26%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cervical vertebral fracture				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Concussion				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Craniocerebral injury				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Eye injury				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Foot fracture				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intentional overdose				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Jaw fracture				

subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Laceration				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Limb injury				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nail injury				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post procedural complication				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Procedural pain				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pubis fracture				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Radius fracture				

subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skeletal injury				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skull fracture				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal compression fracture				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal cord injury cervical				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tendon rupture				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thermal burn				

subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tibia fracture			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Sickle cell anaemia			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	2 / 766 (0.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	2 / 766 (0.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	2 / 766 (0.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Angina pectoris			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Coronary artery stenosis				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Convulsion				
subjects affected / exposed	15 / 766 (1.96%)			
occurrences causally related to treatment / all	3 / 16			
deaths causally related to treatment / all	0 / 0			
Status epilepticus				
subjects affected / exposed	11 / 766 (1.44%)			
occurrences causally related to treatment / all	1 / 11			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	7 / 766 (0.91%)			
occurrences causally related to treatment / all	1 / 7			
deaths causally related to treatment / all	0 / 0			
Seizure cluster				
subjects affected / exposed	4 / 766 (0.52%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	2 / 766 (0.26%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	2 / 766 (0.26%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Partial seizures with secondary generalisation				
subjects affected / exposed	2 / 766 (0.26%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Transient ischaemic attack			
subjects affected / exposed	2 / 766 (0.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ataxia			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Balance disorder			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Carpal tunnel syndrome			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebellar syndrome			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cervical cord compression			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Complex partial seizures			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dementia Alzheimer's type			

subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Encephalitis				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Grand mal convulsion				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hemiparesis				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hydrocephalus				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Loss of consciousness				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolic encephalopathy				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myelopathy				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neuropathy peripheral				

subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Polyneuropathy				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Radiculopathy				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Simple partial seizures				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	1 / 1			
Somnolence				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	1 / 1			
Blood and lymphatic system disorders				
Haemorrhagic anaemia				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoplastic anaemia				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Iron deficiency anaemia				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Microcytic anaemia				

subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 766 (0.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	2 / 766 (0.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 766 (0.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal perforation			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			

subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	3 / 766 (0.39%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cholecystitis chronic			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal colic			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Cervical spinal stenosis			
subjects affected / exposed	2 / 766 (0.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteonecrosis			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rhabdomyolysis			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	5 / 766 (0.65%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 1		
Sepsis			

subjects affected / exposed	2 / 766 (0.26%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Appendicitis perforated				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis escherichia coli				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infected cyst				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis				
subjects affected / exposed	1 / 766 (0.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Otitis media chronic				

subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Perineal abscess			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pharyngitis bacterial			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Typhoid fever			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	3 / 766 (0.39%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Metabolic acidosis			
subjects affected / exposed	1 / 766 (0.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Brivaracetam (SS)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	421 / 766 (54.96%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	44 / 766 (5.74%)		
occurrences (all)	71		
Fall			
subjects affected / exposed	43 / 766 (5.61%)		
occurrences (all)	60		
Nervous system disorders			
Headache			
subjects affected / exposed	102 / 766 (13.32%)		
occurrences (all)	187		
Dizziness			
subjects affected / exposed	100 / 766 (13.05%)		
occurrences (all)	123		
Somnolence			
subjects affected / exposed	73 / 766 (9.53%)		
occurrences (all)	88		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	59 / 766 (7.70%)		
occurrences (all)	67		
Psychiatric disorders			
Depression			
subjects affected / exposed	45 / 766 (5.87%)		
occurrences (all)	53		
Anxiety			
subjects affected / exposed	42 / 766 (5.48%)		
occurrences (all)	48		
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	46 / 766 (6.01%)		
occurrences (all)	59		
Arthralgia			
subjects affected / exposed	41 / 766 (5.35%)		
occurrences (all)	56		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	65 / 766 (8.49%)		
occurrences (all)	102		
Upper respiratory tract infection			
subjects affected / exposed	59 / 766 (7.70%)		
occurrences (all)	101		
Urinary tract infection			
subjects affected / exposed	57 / 766 (7.44%)		
occurrences (all)	86		
Influenza			
subjects affected / exposed	40 / 766 (5.22%)		
occurrences (all)	47		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2011	Addition of deoxyribonucleic acid (DNA) analysis to assess the role of gene variants of synaptic vesicle protein 2A (SV2) in affecting response to BRV. Allowed study participants coming from N01258. Addition of laboratory assessments of liver function at 3-month intervals during the first year and a yearly thyroid-stimulating hormone (TSH) measurement in response to a regulatory agency request.
14 September 2011	Procedures for reporting serious adverse events (SAEs) were updated to implement the Food and Drug Administration (FDA) Final Rule requirements. The Columbia-Suicide Severity Rating Scale (C-SSRS) was added to address the requirement of the FDA that prospective assessments for suicidality should be included in clinical studies involving all drugs for neurological indications. The study variables were rearranged to more appropriately show that the main purpose of N01379 was to evaluate long-term safety of BRV in this patient population.
15 May 2015	Aligned existing language with updated UCB Standard Operating Procedures (SOPs) and/or best practices as well as to allow for a named patient or compassionate use program (or similar) or for participants to switch to another BRV study or to commercial BRV, if, when, and where available. The following changes were made where applicable in these protocols: • In accordance with a new UCB SOP, the sponsor signature block was removed and replaced with a Sponsor Declaration and electronic signature. • Outdated safety information was deleted from Section 2.4 of the protocol. • The protocol contact information was updated. • The study duration language was revised to include the possibility of a named patient or compassionate use program (or similar) as a reason for ending the study. • Language regarding Investigator deviation from the protocol in the event of a medical emergency was revised to align with current UCB standard language.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported