Clinical trial results:
An open-label, multinational, multicenter, follow-up study to evaluate the long-term safety and efficacy of brivaracetam used at a flexible dose up to a maximum of 200 mg/day in subjects aged 16 years or older suffering from epilepsy.

Summary

EudraCT number	2008-001433-98
Trial protocol	BE CZ SE ES FR HU FI IT DE
Global end of trial date	20 March 2017

Results information

Result version number	v1 (current)
This version publication date	05 April 2018
First version publication date	05 April 2018

Trial information

Trial identification

Sponsor protocol code	N01315

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00761774
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 March 2017
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 with a maximum of 200 mg/day in subjects suffering from epilepsy.

Protection of trial subjects:

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

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	19 November 2008
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	Australia: 7
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Czech Republic: 10
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Sweden: 10
Country: Number of subjects enrolled	United States: 43
Worldwide total number of subjects	108
EEA total number of subjects	52

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)	0
Adults (18-64 years)	103
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study started to enroll patients in November 2008 and concluded in March 2017.

Pre-assignment

Screening details:

Participant Flow refers to the Safety Set, which consisted of all subjects who took at least 1 dose of study drug.

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:

This arm consisted of subjects who received Brivaracetam (BRV) at flexible dosing up to 200 mg/day.

Arm type	Experimental
Investigational medicinal product name	Brivaracetam
Investigational medicinal product code	BRV
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Personalized daily doses of the investigational product (IP) Brivaracetam (BRV) were divided into 2 equal intakes (morning and evening). The suggested individual starting dose of each subject was 100 mg/day. Up- and down-titration could be made by increments of a maximum 50 mg/day on a weekly basis and up to a maximum dose of 200 mg/day.

Number of subjects in period 1	Brivaracetam
Started	108
Completed	29
Not completed	79
Subject IP non-compliance	1
End of study	2
Patient moved out of study area	1
Sponsor decision	1
Investigator clinical judgement	1
Consent withdrawn by subject	9
Adverse event, non-fatal	17
Reclassification of seizures	1
Non-compliance	4

Lost to follow-up	2
Coordinator leaving site	1
Medical decision to read SUSAR reports	1
IP stopped by hospital physician	1
Lack of efficacy	37

Baseline characteristics

Reporting groups	
Reporting group title	Brivaracetam
Reporting group description:	
This arm consisted of subjects who received Brivaracetam (BRV) at flexible dosing up to 200 mg/day.	

Reporting group values	Brivaracetam	Total	
Number of subjects	108	108	
Age categorical Units: Subjects			
<=18 years	0	0	
Between 18 and 65 years	103	103	
>=65 years	5	5	
Age continuous Units: years			
arithmetic mean	40.8		
standard deviation	± 13	-	
Gender categorical Units: Subjects			
Female	56	56	
Male	52	52	

End points

End points reporting groups

Reporting group title	Brivaracetam
Reporting group description:	
This arm consisted of subjects who received Brivaracetam (BRV) at flexible dosing up to 200 mg/day.	
Subject analysis set title	Brivaracetam (SS)
Subject analysis set type	Safety analysis
Subject analysis set description:	
This arm consisted of subjects who received Brivaracetam (BRV) at flexible dosing up to 200 mg/day.	
Subject analysis set title	Brivaracetam (ES)
Subject analysis set type	Full analysis
Subject analysis set description:	
This arm consisted of subjects who received Brivaracetam (BRV) at flexible dosing up to 200 mg/day.	

Primary: Percentage of subjects with at least one Treatment-emergent Adverse Event (TEAE) during the Evaluation Period from Entry Visit 1 through End of Treatment (up to 9 years)

End point title	Percentage of subjects with at least one Treatment-emergent Adverse Event (TEAE) during the Evaluation Period from Entry Visit 1 through End of Treatment (up to 9 years)[1]
End point description:	
Treatment-emergent Adverse events (TEAE) are any untoward medical occurrences in a subject during administered study treatment, whether or not these events are related to study treatment.	
End point type	Primary
End point timeframe:	
During the Evaluation Period (up to 9 years)	

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	108			
Units: percentage of participants				
number (not applicable)				
percentage of participants	90.7			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of subjects who withdrew due to Adverse Event (AE) during the Evaluation Period from Entry Visit 1 through End of Treatment (up to 9 years)

End point title	Percentage of subjects who withdrew due to Adverse Event (AE) during the Evaluation Period from Entry Visit 1 through End of Treatment (up to 9 years)[2]

End point description:

Adverse Events (AE) are any untoward medical occurrences in a subject during administered study treatment, whether or not these events are related to study treatment.

End point type	Primary

End point timeframe:

During the Evaluation Period (up to 9 years)

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	108			
Units: percentage of participants				
number (not applicable)				
percentage of participants	15.7			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of subjects with a Serious Adverse Event (SAE) during the Evaluation Period from Entry Visit 1 through End of Treatment (up to 9 years)

End point title	Percentage of subjects with a Serious Adverse Event (SAE) during the Evaluation Period from Entry Visit 1 through End of Treatment (up to 9 years)[3]

End point description:

An SAE was any untoward medical occurrence that, at any dose resulted in death, was life threatening, required in-subject hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or was a congenital anomaly/birth defect.

End point type	Primary

End point timeframe:

During the Evaluation Period (up to 9 years)

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	108			
Units: percentage of participants				
number (not applicable)				
percentage of participants	24.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects on continuous Brivaracetam monotherapy for at least 3 months of the Evaluation Period (up to 9 years)

End point title	Percentage of subjects on continuous Brivaracetam monotherapy for at least 3 months of the Evaluation Period (up to 9 years)

End point description:

BRV monotherapy is defined as continuous treatment with BRV only (ie, no treatment with another anti-epileptic drug (AED)). Use of rescue AED for a duration of no more than 2 consecutive days will not disqualify a subject from being defined as on continuous monotherapy provided the use of rescue AED does not exceed more than 1 time per week.

End point type	Secondary

End point timeframe:

During the Evaluation Period (up to 9 years)

End point values	Brivaracetam (ES)			
Subject group type	Subject analysis set			
Number of subjects analysed	108			
Units: percentage of participants				
number (not applicable)				
percentage of participants	38.89			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects on continuous Brivaracetam monotherapy for at least 6 months, of the Evaluation Period (up to 9 years)

End point title	Percentage of subjects on continuous Brivaracetam monotherapy for at least 6 months, of the Evaluation Period (up to 9 years)

End point description:

BRV monotherapy is defined as continuous treatment with BRV only (ie, no treatment with another anti-epileptic drug (AED)). Use of rescue AED for a duration of no more than 2 consecutive days will not disqualify a subject from being defined as on continuous monotherapy provided the use of rescue AED does not exceed more than 1 time per week.

End point type	Secondary

End point timeframe:

During the Evaluation Period (up to 9 years)

End point values	Brivaracetam (ES)			
Subject group type	Subject analysis set			
Number of subjects analysed	108			
Units: percentage of participants				
number (not applicable)				
percentage of participants	32.41			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects on continuous Brivaracetam monotherapy for at least 12 months of the Evaluation Period (up to 9 years)

End point title	Percentage of subjects on continuous Brivaracetam monotherapy for at least 12 months of the Evaluation Period (up to 9 years)

End point description:

BRV monotherapy is defined as continuous treatment with BRV only (ie, no treatment with another anti-epileptic drug (AED)). Use of rescue AED for a duration of no more than 2 consecutive days will not disqualify a subject from being defined as on continuous monotherapy provided the use of rescue AED does not exceed more than 1 time per week.

End point type	Secondary

End point timeframe:

During the Evaluation Period (up to 9 years)

End point values	Brivaracetam (ES)			
Subject group type	Subject analysis set			
Number of subjects analysed	108			
Units: percentage of participants				
number (not applicable)				
percentage of participants	25			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected throughout the study (up to 9 years).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Brivaracetam (SS)

Reporting group description:

This arm consisted of subjects who received Brivaracetam (BRV) at flexible dosing up to 200 mg/day.

Serious adverse events	Brivaracetam (SS)		
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 108 (24.07%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Sudden unexplained death in epilepsy			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Social circumstances			
Pregnancy of partner			

subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Factitious disorder			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychotic disorder			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Somnambulism			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 108 (1.85%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Craniocerebral injury			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Facial bones fracture			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intentional overdose			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Joint injury			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Laceration			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Snake bite			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	3 / 108 (2.78%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		

Atrial fibrillation				
subjects affected / exposed	2 / 108 (1.85%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Convulsion				
subjects affected / exposed	5 / 108 (4.63%)			
occurrences causally related to treatment / all	2 / 7			
deaths causally related to treatment / all	0 / 0			
Dysarthria				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Grand mal convulsion				
subjects affected / exposed	2 / 108 (1.85%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Hemiparesis				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Migraine				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Monoplegia				

subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Postictal state			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	2 / 108 (1.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Nephrolithiasis			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 108 (0.93%)		
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	81 / 108 (75.00%)		
Investigations			
Weight increased			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	6		
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	15 / 108 (13.89%)		
occurrences (all)	19		
Contusion			
subjects affected / exposed	9 / 108 (8.33%)		
occurrences (all)	11		
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	8		
Nervous system disorders			
Convulsion			
subjects affected / exposed	17 / 108 (15.74%)		
occurrences (all)	28		
Headache			
subjects affected / exposed	15 / 108 (13.89%)		
occurrences (all)	20		
Dizziness			
subjects affected / exposed	14 / 108 (12.96%)		
occurrences (all)	18		
Migraine			
subjects affected / exposed	7 / 108 (6.48%)		
occurrences (all)	11		
Paraesthesia			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	6		
Tremor			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	7		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	17 / 108 (15.74%)		
occurrences (all)	19		
Chest pain			
subjects affected / exposed	9 / 108 (8.33%)		
occurrences (all)	10		

Oedema peripheral subjects affected / exposed occurrences (all)	6 / 108 (5.56%) 7		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	12 / 108 (11.11%) 16		
Abdominal pain subjects affected / exposed occurrences (all)	9 / 108 (8.33%) 12		
Nausea subjects affected / exposed occurrences (all)	9 / 108 (8.33%) 11		
Toothache subjects affected / exposed occurrences (all)	7 / 108 (6.48%) 10		
Vomiting subjects affected / exposed occurrences (all)	6 / 108 (5.56%) 9		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	13 / 108 (12.04%) 16		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	18 / 108 (16.67%) 21		
Anxiety subjects affected / exposed occurrences (all)	15 / 108 (13.89%) 24		
Insomnia subjects affected / exposed occurrences (all)	15 / 108 (13.89%) 16		
Suicidal ideation subjects affected / exposed occurrences (all)	6 / 108 (5.56%) 7		
Musculoskeletal and connective tissue			

disorders Back pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all)	 12 / 108 (11.11%) 12 10 / 108 (9.26%) 16		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Viral infection subjects affected / exposed occurrences (all)	 19 / 108 (17.59%) 42 8 / 108 (7.41%) 13 8 / 108 (7.41%) 11 6 / 108 (5.56%) 8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 June 2010	Updated the protocol with regard to 5 areas: - Study personnel and contact details - Duration of the study and duration of participation were amended due to termination of the N01276 and N01306 studies - Typographical and spelling errors were corrected - Details concerning the Phase 3 partial onset seizures (POS) and Unverricht-Lundborg Disease (ULD) studies as those studies had completed since the start of this study - Further instruction was given with regard to visit windows
02 August 2011	- Increased maximum dose of BRV to 200 mg/day (instead of 150 mg/day) - Reduced the number of assessments for the subjects - Updated procedures for reporting serious adverse events (SAEs) to implement the Food and Drug Administration (FDA) Final Rule requirements - Added Columbia-Suicide Severity Rating Scale (C-SSRS) to address the requirement of the FDA that prospective assessments for suicidality should be included in clinical studies involving all drugs for neurological indications - Updated information on laboratory assessments, statistical analyses, and contact information - Further (minor) changes were made throughout the protocol for consistency between BRV studies
25 March 2015	- Study personnel and contact details were updated - The ability of the Sponsor to sign electronically was added - Outdated safety information was removed - Protocol language was updated to include the possibility of a named patient or compassionate use program (or similar) as a reason for ending the study duration - Language was revised regarding Investigator deviation from the protocol in the event of a medical emergency to align with the current UCB language

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported