Clinical trial results:
A multi-center, open-label, four-arm, randomized trial evaluating the safety and tolerability of Brivaracetam intravenous infusion and bolus, administered in BID regimen as an adjunctive antiepileptic treatment in subjects from 16 to 70 years suffering from epilepsy

Summary

EudraCT number	2008-004714-27
Trial protocol	CZ DE
Global end of trial date	20 July 2012

Results information

Result version number	v1 (current)
This version publication date	02 April 2016
First version publication date	02 April 2016

Trial information

Trial identification

Sponsor protocol code	N01258

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01405508
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	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 2173 4815 15, clinicaltrials@ucb.com
Scientific contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 2173 48 15 15, clinicaltrials@ucb.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 September 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 July 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the safety and tolerability of Brivaracetam (BRV) 200 mg/day administered intravenous (iv) as an infusion or a bolus, according to an initiation or a conversion scheme, during repeated dosing (100 mg/Administration twice a day (bid) for 4.5 days) as an adjunctive treatment in adult subjects suffering from localization-related or generalized epilepsy.

Protection of trial subjects:

Standard measures to minimize pain and distress.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	09 August 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 74
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Czech Republic: 8
Worldwide total number of subjects	105
EEA total number of subjects	31

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)	0
Adults (18-64 years)	103
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study started to recruit patients in August 2011 and concluded in July 2012.
105 subjects were randomized to 4 different treatment groups.

Pre-assignment

Screening details:

Participant Flow refers to the Randomized Set (RS).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo tablets / Brivaracetam bolus

Arm description:

Subjects will receive Placebo (PBO) tablets for one week followed by Brivaracetam (BRV) bolus for 4.5 days.
Down-Titration:
- If subject discontinues the study during the Run-In Period, then the subject will receive the treatment that he/she was assigned during Run-In
- If subject discontinues during the Evaluation Period or after Day 12, the subject will receive Placebo tablets during Down-Titration: Tablets will be provided for 4 weeks; 75 mg / intake BID for the first week, 50 mg / intake BID for the second week, 25 mg / intake BID for the third week, 10 mg / intake BID for the fourth week

Arm type	Experimental
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:

100 mg twice daily (BID) for 7 days during Run-In Period.

Investigational medicinal product name	Brivaracetam bolus
Investigational medicinal product code	BRV bolus
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

10 mL (= 100 mg) of Brivaracetam administered intravenously over 2 minutes twice daily (BID) during Evaluation Period.

Arm title	Placebo tablets / Brivaracetam infusion

Arm description:

Subjects will receive Placebo (PBO) tablets for one week followed by Brivaracetam (BRV) intravenous infusion for 4.5 days.
Down-Titration:
- If subject discontinues the study during the Run-In Period, then the subject will receive the treatment that he/she was assigned during Run-In
- If subject discontinues during the Evaluation Period or after Day 12, the subject will receive BRV tablets during Down-Titration: Tablets will be provided for 4 weeks; 75 mg / intake BID for the first week, 50 mg / intake BID for the second week, 25 mg / intake BID for the third week, 10 mg / intake

BID for the fourth week

Arm type	Experimental
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:

100 mg twice daily (BID) for 7 days during Run-In Period.

Investigational medicinal product name	Brivaracetam infusion
Investigational medicinal product code	BRV infusion
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

10 mL (= 100 mg) of Brivaracetam diluted in 90 mL 0.9 % isotonic saline sterile solution for intravenous administration infused over 15 minutes twice daily (BID) during Evaluation Period.

Arm title	Brivaracetam (BRV) tablets / BRV bolus

Arm description:

Subjects will receive Brivaracetam (BRV) tablets for one week followed by BRV bolus for 4.5 days.
Down-Titration:
- If subject discontinues the study during the Run-In Period, then the subject will receive the treatment that he/she was assigned during Run-In
- If subject discontinues during the Evaluation Period or after Day 12, the subject will receive BRV tablets during Down-Titration: Tablets will be provided for 4 weeks; 75 mg / intake BID for the first week, 50 mg / intake BID for the second week, 25 mg / intake BID for the third week, 10 mg / intake bid for the fourth week

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

Dosage and administration details:

100 mg, intake twice daily (BID) for 7 days during Run-In Period.

Investigational medicinal product name	Brivaracetam bolus
Investigational medicinal product code	BRV bolus
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

10 mL (= 100 mg) of Brivaracetam administered intravenously over 2 minutes twice daily (BID) during Evaluation Period.

Arm title	Brivaracetam (BRV) tablets / BRV infusion

Arm description:

Subjects will receive Brivaracetam (BRV) tablets for one week followed by Brivaracetam intravenous infusion for 4.5 days.
Down-Titration:
- If subject discontinues the study during the Run-In Period, then the subject will receive the treatment that he/she was assigned during Run-In
- If subject discontinues during the Evaluation Period or after Day 12, the subject will receive BRV tablets during Down-Titration: Tablets will be provided for 4 weeks; 75 mg / intake BID for the first week, 50 mg / intake BID for the second week, 25 mg / intake BID for the third week, 10 mg / intake BID for the fourth week

Arm type	Experimental

Investigational medicinal product name	Brivaracetam tablets
Investigational medicinal product code	BRV tablets
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg, intake twice daily (BID) for 7 days during Run-In Period.

Investigational medicinal product name	Brivaracetam infusion
Investigational medicinal product code	BRV infusion
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

10 mL (= 100 mg) of Brivaracetam diluted in 90 mL 0.9 % isotonic saline sterile solution for intravenous administration infused over 15 minutes twice daily (BID) during Evaluation Period.

Number of subjects in period 1	Placebo tablets / Brivaracetam bolus	Placebo tablets / Brivaracetam infusion	Brivaracetam (BRV) tablets / BRV bolus
Started	26	26	27
Completed	25	25	27
Not completed	1	1	0
AE, non-serious non-fatal	1	1	-

Number of subjects in period 1	Brivaracetam (BRV) tablets / BRV infusion
Started	26
Completed	26
Not completed	0
AE, non-serious non-fatal	-

Baseline characteristics

Reporting groups

Reporting group title	Placebo tablets / Brivaracetam bolus

Reporting group description:

Subjects will receive Placebo (PBO) tablets for one week followed by Brivaracetam (BRV) bolus for 4.5 days.
Down-Titration:
- If subject discontinues the study during the Run-In Period, then the subject will receive the treatment that he/she was assigned during Run-In
- If subject discontinues during the Evaluation Period or after Day 12, the subject will receive Placebo tablets during Down-Titration: Tablets will be provided for 4 weeks; 75 mg / intake BID for the first week, 50 mg / intake BID for the second week, 25 mg / intake BID for the third week, 10 mg / intake BID for the fourth week

Reporting group title	Placebo tablets / Brivaracetam infusion

Reporting group description:

Subjects will receive Placebo (PBO) tablets for one week followed by Brivaracetam (BRV) intravenous infusion for 4.5 days.
Down-Titration:
- If subject discontinues the study during the Run-In Period, then the subject will receive the treatment that he/she was assigned during Run-In
- If subject discontinues during the Evaluation Period or after Day 12, the subject will receive BRV tablets during Down-Titration: Tablets will be provided for 4 weeks; 75 mg / intake BID for the first week, 50 mg / intake BID for the second week, 25 mg / intake BID for the third week, 10 mg / intake BID for the fourth week

Reporting group title	Brivaracetam (BRV) tablets / BRV bolus

Reporting group description:

Subjects will receive Brivaracetam (BRV) tablets for one week followed by BRV bolus for 4.5 days.
Down-Titration:
- If subject discontinues the study during the Run-In Period, then the subject will receive the treatment that he/she was assigned during Run-In
- If subject discontinues during the Evaluation Period or after Day 12, the subject will receive BRV tablets during Down-Titration: Tablets will be provided for 4 weeks; 75 mg / intake BID for the first week, 50 mg / intake BID for the second week, 25 mg / intake BID for the third week, 10 mg / intake bid for the fourth week

Reporting group title	Brivaracetam (BRV) tablets / BRV infusion

Reporting group description:

Subjects will receive Brivaracetam (BRV) tablets for one week followed by Brivaracetam intravenous infusion for 4.5 days.
Down-Titration:
- If subject discontinues the study during the Run-In Period, then the subject will receive the treatment that he/she was assigned during Run-In
- If subject discontinues during the Evaluation Period or after Day 12, the subject will receive BRV tablets during Down-Titration: Tablets will be provided for 4 weeks; 75 mg / intake BID for the first week, 50 mg / intake BID for the second week, 25 mg / intake BID for the third week, 10 mg / intake BID for the fourth week

Reporting group values	Placebo tablets / Brivaracetam bolus	Placebo tablets / Brivaracetam infusion	Brivaracetam (BRV) tablets / BRV bolus
Number of subjects	26	26	27
Age Categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	26	25	27
>=65 years	0	1	0

Age Continuous Units: years			
arithmetic mean	40.6	39.5	42
standard deviation	± 12.2	± 14.4	± 9.2
Gender Categorical Units: Subjects			
Male	14	16	10
Female	12	10	17

Reporting group values	Brivaracetam (BRV) tablets / BRV infusion	Total	
Number of subjects	26	105	
Age Categorical Units: Subjects			
<=18 years	0	0	
Between 18 and 65 years	25	103	
>=65 years	1	2	
Age Continuous Units: years			
arithmetic mean	44.4		
standard deviation	± 12.6	-	
Gender Categorical Units: Subjects			
Male	9	49	
Female	17	56	

End points

End points reporting groups

Reporting group title	Placebo tablets / Brivaracetam bolus

Reporting group description:

Subjects will receive Placebo (PBO) tablets for one week followed by Brivaracetam (BRV) bolus for 4.5 days.
Down-Titration:
- If subject discontinues the study during the Run-In Period, then the subject will receive the treatment that he/she was assigned during Run-In
- If subject discontinues during the Evaluation Period or after Day 12, the subject will receive Placebo tablets during Down-Titration: Tablets will be provided for 4 weeks; 75 mg / intake BID for the first week, 50 mg / intake BID for the second week, 25 mg / intake BID for the third week, 10 mg / intake BID for the fourth week

Reporting group title	Placebo tablets / Brivaracetam infusion

Reporting group description:

Subjects will receive Placebo (PBO) tablets for one week followed by Brivaracetam (BRV) intravenous infusion for 4.5 days.
Down-Titration:
- If subject discontinues the study during the Run-In Period, then the subject will receive the treatment that he/she was assigned during Run-In
- If subject discontinues during the Evaluation Period or after Day 12, the subject will receive BRV tablets during Down-Titration: Tablets will be provided for 4 weeks; 75 mg / intake BID for the first week, 50 mg / intake BID for the second week, 25 mg / intake BID for the third week, 10 mg / intake BID for the fourth week

Reporting group title	Brivaracetam (BRV) tablets / BRV bolus

Reporting group description:

Subjects will receive Brivaracetam (BRV) tablets for one week followed by BRV bolus for 4.5 days.
Down-Titration:
- If subject discontinues the study during the Run-In Period, then the subject will receive the treatment that he/she was assigned during Run-In
- If subject discontinues during the Evaluation Period or after Day 12, the subject will receive BRV tablets during Down-Titration: Tablets will be provided for 4 weeks; 75 mg / intake BID for the first week, 50 mg / intake BID for the second week, 25 mg / intake BID for the third week, 10 mg / intake bid for the fourth week

Reporting group title	Brivaracetam (BRV) tablets / BRV infusion

Reporting group description:

Subjects will receive Brivaracetam (BRV) tablets for one week followed by Brivaracetam intravenous infusion for 4.5 days.
Down-Titration:
- If subject discontinues the study during the Run-In Period, then the subject will receive the treatment that he/she was assigned during Run-In
- If subject discontinues during the Evaluation Period or after Day 12, the subject will receive BRV tablets during Down-Titration: Tablets will be provided for 4 weeks; 75 mg / intake BID for the first week, 50 mg / intake BID for the second week, 25 mg / intake BID for the third week, 10 mg / intake BID for the fourth week

Primary: Number of subjects with at least one treatment-emergent adverse event during the study (maximum 40 days)

End point title	Number of subjects with at least one treatment-emergent adverse event during the study (maximum 40 days)[1]

End point description:

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

End point type	Primary

End point timeframe:

40 days

Notes:

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

End point values	Placebo tablets / Brivaracetam bolus	Placebo tablets / Brivaracetam infusion	Brivaracetam (BRV) tablets / BRV bolus	Brivaracetam (BRV) tablets / BRV infusion
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	26	27	26
Units: Participants				
Number of subjects	20	19	21	20

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects who withdrew due to a treatment-emergent adverse event during the study (maximum 40 days)

End point title	Number of subjects who withdrew due to a treatment-emergent adverse event during the study (maximum 40 days)

End point description:

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

End point type	Secondary

End point timeframe:

40 days

End point values	Placebo tablets / Brivaracetam bolus	Placebo tablets / Brivaracetam infusion	Brivaracetam (BRV) tablets / BRV bolus	Brivaracetam (BRV) tablets / BRV infusion
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	26	27	26
Units: Participants				
Number of subjects	1	1	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with at least one injection-related treatment-emergent adverse event (TEAE) during the Evaluation Period.

End point title	Number of subjects with at least one injection-related treatment-emergent adverse event (TEAE) during the Evaluation Period.

End point description:

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

End point type	Secondary

End point timeframe:

4.5-day Evaluation Period

End point values	Placebo tablets / Brivaracetam bolus	Placebo tablets / Brivaracetam infusion	Brivaracetam (BRV) tablets / BRV bolus	Brivaracetam (BRV) tablets / BRV infusion
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	26	27	26
Units: Participants				
Number of subjects	1	3	4	3

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected from Baseline over Run-In (Day 1) and Evaluation Period (Day 8 to Day 12) to the Safety Visit or Early Discontinuation Visit (up to 54 days).

Adverse event reporting additional description:

Adverse Events refer to the Safety Population consisting of all subjects who took at least 1 dose of study drug.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Placebo tablets / Brivaracetam bolus

Reporting group description:

Subjects will receive Placebo (PBO) tablets for one week followed by Brivaracetam (BRV) bolus for 4.5 days.
Down-Titration:
o If subject discontinues the study during the Run-In Period, then the subject will receive the treatment that he/she was assigned during Run-In
o If subject discontinues during the Evaluation Period or after Day 12, the subject will receive Placebo tablets during Down-Titration:
Tablets will be provided for 4 weeks; 75 mg / intake BID for the first week, 50 mg / intake BID for the second week, 25 mg / intake BID for the third week, 10 mg / intake BID for the fourth week

Reporting group title	Brivaracetam (BRV) tablets / BRV bolus

Reporting group description:

Subjects will receive Brivaracetam (BRV) tablets for one week followed by BRV bolus for 4.5 days.
Down-Titration:
o If subject discontinues the study during the Run-In Period, then the subject will receive the treatment that he/she was assigned during Run-In
o If subject discontinues during the Evaluation Period or after Day 12, the subject will receive BRV tablets during Down-Titration:
Tablets will be provided for 4 weeks; 75 mg / intake BID for the first week, 50 mg / intake BID for the second week, 25 mg / intake BID for the third week, 10 mg / intake bid for the fourth week

Reporting group title	Brivaracetam (BRV) tablets / BRV infusion

Reporting group description:

Subjects will receive Brivaracetam (BRV) tablets for one week followed by Brivaracetam intravenous infusion for 4.5 days.
Down-Titration:
o If subject discontinues the study during the Run-In Period, then the subject will receive the treatment that he/she was assigned during Run-In
o If subject discontinues during the Evaluation Period or after Day 12, the subject will receive BRV tablets during Down-Titration:
Tablets will be provided for 4 weeks; 75 mg / intake BID for the first week, 50 mg / intake BID for the second week, 25 mg / intake BID for the third week, 10 mg / intake BID for the fourth week

Reporting group title	Placebo tablets / Brivaracetam infusion

Reporting group description:

Subjects will receive Placebo (PBO) tablets for one week followed by Brivaracetam (BRV) intravenous infusion for 4.5 days.
Down-Titration:
o If subject discontinues the study during the Run-In Period, then the subject will receive the treatment that he/she was assigned during Run-In
o If subject discontinues during the Evaluation Period or after Day 12, the subject will receive BRV tablets during Down-Titration:
Tablets will be provided for 4 weeks; 75 mg / intake BID for the first week, 50 mg / intake BID for the second week, 25 mg / intake BID for the third week, 10 mg / intake BID for the fourth week

Serious adverse events	Placebo tablets / Brivaracetam bolus	Brivaracetam (BRV) tablets / BRV bolus	Brivaracetam (BRV) tablets / BRV infusion
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)	0 / 27 (0.00%)	0 / 26 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Placebo tablets / Brivaracetam infusion		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Placebo tablets / Brivaracetam bolus	Brivaracetam (BRV) tablets / BRV bolus	Brivaracetam (BRV) tablets / BRV infusion
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 26 (65.38%)	15 / 27 (55.56%)	14 / 26 (53.85%)
Cardiac disorders			
Postural orthostatic tachycardia syndrome			
subjects affected / exposed	2 / 26 (7.69%)	1 / 27 (3.70%)	0 / 26 (0.00%)
occurrences (all)	2	1	0
Nervous system disorders			
Somnolence			
subjects affected / exposed	8 / 26 (30.77%)	7 / 27 (25.93%)	9 / 26 (34.62%)
occurrences (all)	8	9	10
Dizziness			
subjects affected / exposed	4 / 26 (15.38%)	3 / 27 (11.11%)	4 / 26 (15.38%)
occurrences (all)	4	3	4
Headache			
subjects affected / exposed	2 / 26 (7.69%)	2 / 27 (7.41%)	2 / 26 (7.69%)
occurrences (all)	2	3	2

Dysgeusia			
subjects affected / exposed	2 / 26 (7.69%)	2 / 27 (7.41%)	0 / 26 (0.00%)
occurrences (all)	2	2	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 26 (3.85%)	3 / 27 (11.11%)	0 / 26 (0.00%)
occurrences (all)	1	4	0
Infusion site pain			
subjects affected / exposed	0 / 26 (0.00%)	2 / 27 (7.41%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Injection site erythema			
subjects affected / exposed	0 / 26 (0.00%)	2 / 27 (7.41%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Injection site pain			
subjects affected / exposed	0 / 26 (0.00%)	2 / 27 (7.41%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 26 (3.85%)	2 / 27 (7.41%)	1 / 26 (3.85%)
occurrences (all)	1	2	1
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	1 / 26 (3.85%)	2 / 27 (7.41%)	0 / 26 (0.00%)
occurrences (all)	1	2	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 26 (0.00%)	0 / 27 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 26 (11.54%)	0 / 27 (0.00%)	0 / 26 (0.00%)
occurrences (all)	3	0	0

Non-serious adverse events	Placebo tablets / Brivaracetam infusion		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 26 (57.69%)		

Cardiac disorders			
Postural orthostatic tachycardia syndrome			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Somnolence			
subjects affected / exposed	7 / 26 (26.92%)		
occurrences (all)	7		
Dizziness			
subjects affected / exposed	4 / 26 (15.38%)		
occurrences (all)	4		
Headache			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	4		
Infusion site pain			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	3		
Injection site erythema			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Injection site pain			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Gastrointestinal disorders			

Dyspepsia subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 December 2008	Protocol Amendment 1 was approved and effective prior to the date of first patient first visit (FPFV). The rationale for this amendment was to integrate the USA Food and Drug Administration (FDA) recommendations regarding cardiac monitoring, received on 20 Nov 2008: - At V2, an ECG was added - Immediately after each BRV iv administration, ECGs were added - A central reader was organized for the ECG tracings - The section describing the adverse events (AEs) was updated to be consistent with the new CRF AE module - The recently defined IND number for BRV iv development was implemented
05 March 2009	Protocol Amendment 2 was approved and effective prior to the date of FPFV. The rationale for this amendment was to integrate the USA FDA recommendations regarding cardiac monitoring, as expressed in their letter received on 19 Feb 2009, in response to the Investigational New Drug (IND) submission for BRV iv solution: - 12-lead ECGs were to be recorded; predose and at 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, and 12 hours immediately after the initiation of BRV iv administration - During the BRV iv administration, continuous live monitoring of ECG was included - There was a change in the statistical analysis of the ECG data, with only the central readings of the ECG data to be used in the descriptive and shift tables
01 April 2011	Protocol Amendment 3 was approved and effective prior to the date of FPFV. The rationale for this amendment was to increase the total daily dose of BRV to 200 mg/day (100 mg/intake bid) from the original dose of 100 mg/day (50 mg/intake bid) in line with the recommendation of the regulatory authorities and in accordance with the oral dose that UCB had selected for Evaluation in the new Phase 3 study (N01358). The following changes were made throughout the protocol: - The dose in the LTFU study (N01379) was increased from 100 mg/day to 200 mg/day - The Down-Titration Period was increased from 2 weeks to 4 weeks with a 4-step down-titration instead of the previous 2-step down-titration - The dosing schedule for the Down-Titration Period was clarified - The duration of the iv bolus was increased from 60 seconds to 2 minutes - The maximum study and treatment durations for each subject were increased - The number of sites expected to participate in the study was increased to approximately 35 - Information on blinding during the Run-In Period and the Down-Titration Period was added - Information on the description of the study drug, packaging, and supply was updated - The timing of serum and urine pregnancy tests was revised - The randomization and IVRS processes was updated

01 April 2011	The following changes were made throughout the protocol: - The patient-reported outcomes (PRO) questionnaires (Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 [QOLIE-31-P] and Hospital Anxiety and Depression Scale [HADS]) were removed from the exploratory objectives and variables. Only baseline data were collected at V2 to allow for evaluation later in the LTFU study, N01379 - The EuroQoL-5 Dimensions questionnaire was removed - Socio-professional data were added at V2 to provide baseline data to allow for eEvaluation later in the LTFU study, N01379 - The collection and analysis of deoxyribonucleic acid (DNA) samples were removed, as this analysis will be conducted in another study - The exploratory objective for healthcare resource utilization was corrected to include this assessment at other visits as well as baseline data - The number of the LTFU study was added - The timing of the BRV and AED sampling during the iv administration was revised, and the sampling of concomitant AED levels at the SV (V8) was removed - Healthcare provider consultations not foreseen by the protocol was added as a component of the healthcare resource utilization variable - The Sponsor contact information was updated - The contract research organization (CRO) information was added - The protocol summary and introduction sections were updated - Other minor editorial changes were made to ensure consistency within the protocol and across the BRV program
12 September 2011	Protocol Amendment 4 was approved and effective after subjects had been enrolled in the study. The rationale for this amendment was to implement the USA FDA Final Rule requirements with regard to procedures for reporting serious adverse events (SAEs) and 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 following changes were made throughout the protocol: - A suicidality assessment using the Columbia-Suicide Severity Rating Scale (C-SSRS) in response to the USA FDA requirement was included - The prospective assessment for suicidality using the C-SSRS was added to the exclusion criteria, withdrawal criteria, and safety assessments - The list of Anticipated SAEs in response to the USA FDA Final Rule was added - A few minor changes were made to the protocol to update the name of the Clinical Project Manager (CPM), to clarify some study conduct details, and to correct grammatical errors

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported