Clinical trial results:
An international, double-blind, randomized, multi-center, parallel group, historical-control conversion to monotherapy study to evaluate the efficacy and safety of brivaracetam in subjects (16 to 75 years old) with partial onset seizures with or without secondary generalization

Summary

EudraCT number	2008-000145-58
Trial protocol	DE ES HU FI FR IT
Global end of trial date	09 March 2010

Results information

Result version number	v1 (current)
This version publication date	07 December 2016
First version publication date	07 December 2016

Trial information

Trial identification

Sponsor protocol code	N01306

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00699283
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB Pharma S.A.
Sponsor organisation address	Chemin du Foriest, Braine-l'Alleud, Belgium, B-1420
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	15 October 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 March 2010
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the efficacy of Brivaracetam (BRV) in the conversion to monotherapy at the doses of 50 and 100 mg/day (administered in two equal doses per day) in subjects with partial onset seizures when compared to a historical pseudo-placebo control group.

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	06 August 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	8 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United States: 25
Worldwide total number of subjects	62
EEA total number of subjects	37

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)	59
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This multi-Center study started to enroll subjects in August 2008 and concluded in March 2010.

Pre-assignment

Screening details:

The Participant Flow refers to the Randomized Set (RS).
Subjects withdrawn due to meeting an exit criterion are included in the count of early discontinuations with a reason of "Adverse Event" or "Lack of efficacy" as reported by the Investigator.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Carer, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Brivaracetam (BRV) 50 mg

Arm description:

50 mg daily for 17 weeks (or 21 weeks if down-titrated (50 mg > 20 mg) for subjects not participating in the follow-up study).

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:

25 mg tablet - 50 mg or 100 mg daily for 17 weeks (or 21 weeks if down-titrated for subjects not participating in the follow-up study).

Arm title	Brivaracetam (BRV) 100 mg

Arm description:

100 mg daily for 17 weeks (or 21 weeks if down-titrated (100 mg > 50 mg > 20 mg) for subjects not participating in the follow-up study).

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:

25 mg tablet - 50 mg or 100 mg daily for 17 weeks (or 21 weeks if down-titrated for subjects not participating in the follow-up study).

Number of subjects in period 1	Brivaracetam (BRV) 50 mg	Brivaracetam (BRV) 100 mg
Started	47	15
Completed	14	7
Not completed	33	8
Consent withdrawn by subject	1	-
Other Reason	5	1
AE, non-serious non-fatal	8	1
AE of unknown type	1	-
Lost to follow-up	2	-
SAE, non-fatal	1	1
Lack of efficacy	15	5

Baseline characteristics

Reporting groups	
Reporting group title	Brivaracetam (BRV) 50 mg
Reporting group description:	
50 mg daily for 17 weeks (or 21 weeks if down-titrated (50 mg > 20 mg) for subjects not participating in the follow-up study).	
Reporting group title	Brivaracetam (BRV) 100 mg
Reporting group description:	
100 mg daily for 17 weeks (or 21 weeks if down-titrated (100 mg > 50 mg > 20 mg) for subjects not participating in the follow-up study).	

Reporting group values	Brivaracetam (BRV) 50 mg	Brivaracetam (BRV) 100 mg	Total
Number of subjects	47	15	62
Age Categorical Units: Subjects			
<18 Years	0	0	0
Between 18 and 65 Years	45	14	59
>= 65 Years	2	1	3
Age Continuous Units: years			
arithmetic mean	39	44.3	
standard deviation	± 13.8	± 15.9	-
Gender Categorical Units: Subjects			
Male	20	4	24
Female	27	11	38

End points

End points reporting groups

Reporting group title	Brivaracetam (BRV) 50 mg

Reporting group description:

50 mg daily for 17 weeks (or 21 weeks if down-titrated (50 mg > 20 mg) for subjects not participating in the follow-up study).

Reporting group title	Brivaracetam (BRV) 100 mg

Reporting group description:

100 mg daily for 17 weeks (or 21 weeks if down-titrated (100 mg > 50 mg > 20 mg) for subjects not participating in the follow-up study).

Subject analysis set title	Efficacy Set (Brivaracetam 50 mg treated subjects)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

50 mg daily for 17 weeks (or 21 weeks if down-titrated (50 mg > 20 mg) for subjects not participating in the follow-up study).

The Efficacy Analysis Set (EFF) consisted of all randomized subjects with at least 1 intake of study medication who also entered into the Baseline antiepileptic drug (AED) Tapering Phase (during the Evaluation Period) and started with the withdrawal of Baseline AEDs.

Primary: The Cumulative Exit Rate at 112 days after the beginning of the Baseline Antiepileptic Drug (AED) tapering phase

End point title	The Cumulative Exit Rate at 112 days after the beginning of the Baseline Antiepileptic Drug (AED) tapering phase[1]

End point description:

The cumulative exit rate was estimated using Kaplan-Meier methods and was based on the duration between start of the Evaluation Period (EP) and the earliest date the first exit criterion was met for each subject. Subjects completing the EP without meeting an exit criterion were censored on Day 112. The primary comparison was BRV 50 mg/day vs a historical control. The upper limit of the 2-sided 95 % Confidence Interval for the estimate was compared to the historical lower bound estimate of 0.722.

End point type	Primary

End point timeframe:

From Visit 4 (week 1) to the end of the Evaluation Period (week 17) (approximately 16 weeks)

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: Values presented below are from the statistical analysis of this Primary Endpoint. The upper limit of the two-sided 95% CI for the estimate of the exit rate at Day 112 for the BRV 50 mg/day arm, 0.638, was lower than the historical control exit rate of 0.722. Therefore the BRV 50 mg/day arm was considered statistically superior to historical control.

End point values	Efficacy Set (Brivaracetam 50 mg treated subjects)			
Subject group type	Subject analysis set			
Number of subjects analysed	45			
Units: percentage of subjects				
number (confidence interval 95%)	0.474 (0.31 to 0.638)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected from Week 0 over the 1-week BRV Add-On Period and the 15-week Evaluation Period until the end fo Follow-Up Period (Week 23) or Early Discontinuation Visit.

Adverse event reporting additional description:

Adverse Events refer to the Intent-to-Treat (ITT) Set, consisting of all randomized subjects with at least 1 intake of study medication.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Brivaracetam (BRV) 50 mg

Reporting group description:

50 mg daily for 17 weeks (or 21 weeks if down-titrated (50 mg > 20 mg) for subjects not participating in the follow-up study).

Reporting group title	Brivaracetam (BRV) 100 mg

Reporting group description:

100 mg daily for 17 weeks (or 21 weeks if down-titrated (100 mg > 50 mg > 20 mg) for subjects not participating in the follow-up study).

Serious adverse events	Brivaracetam (BRV) 50 mg	Brivaracetam (BRV) 100 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 47 (6.38%)	1 / 15 (6.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Intentional overdose			
subjects affected / exposed	1 / 47 (2.13%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 47 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			

subjects affected / exposed	1 / 47 (2.13%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 47 (2.13%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 47 (2.13%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 47 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Brivaracetam (BRV) 50 mg	Brivaracetam (BRV) 100 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 47 (65.96%)	10 / 15 (66.67%)	
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 47 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 47 (8.51%)	2 / 15 (13.33%)	
occurrences (all)	4	2	
Irritability			
subjects affected / exposed	5 / 47 (10.64%)	0 / 15 (0.00%)	
occurrences (all)	6	0	
Asthenia			

subjects affected / exposed	4 / 47 (8.51%)	0 / 15 (0.00%)	
occurrences (all)	4	0	
Chest pain			
subjects affected / exposed	0 / 47 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Psychiatric disorders			
Depression			
subjects affected / exposed	3 / 47 (6.38%)	2 / 15 (13.33%)	
occurrences (all)	3	2	
Anxiety			
subjects affected / exposed	4 / 47 (8.51%)	0 / 15 (0.00%)	
occurrences (all)	5	0	
Insomnia			
subjects affected / exposed	4 / 47 (8.51%)	0 / 15 (0.00%)	
occurrences (all)	4	0	
Suicidal ideation			
subjects affected / exposed	0 / 47 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Investigations			
White blood cells urine positive			
subjects affected / exposed	1 / 47 (2.13%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Electrocardiogram ST segment depression			
subjects affected / exposed	0 / 47 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Skin laceration			
subjects affected / exposed	1 / 47 (2.13%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Muscle strain			
subjects affected / exposed	0 / 47 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 47 (14.89%)	2 / 15 (13.33%)	
occurrences (all)	8	2	

Convulsion subjects affected / exposed occurrences (all)	5 / 47 (10.64%) 11	2 / 15 (13.33%) 2	
Headache subjects affected / exposed occurrences (all)	4 / 47 (8.51%) 5	1 / 15 (6.67%) 1	
Grand mal convulsion subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 4	0 / 15 (0.00%) 0	
Lethargy subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	1 / 15 (6.67%) 1	
Memory impairment subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	1 / 15 (6.67%) 1	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	1 / 15 (6.67%) 1	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	2 / 47 (4.26%) 2	1 / 15 (6.67%) 1	
Vomiting subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 3	0 / 15 (0.00%) 0	
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	3 / 47 (6.38%) 3	0 / 15 (0.00%) 0	
Renal and urinary disorders Renal failure acute subjects affected / exposed occurrences (all)	0 / 47 (0.00%) 0	1 / 15 (6.67%) 1	
Musculoskeletal and connective tissue disorders			

Musculoskeletal chest pain			
subjects affected / exposed	0 / 47 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Infections and infestations			
Asymptomatic bacteriuria			
subjects affected / exposed	0 / 47 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 47 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 47 (2.13%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Hypophosphataemia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 April 2008	Protocol Amendment 1 was finalized on 04 Apr 2008, before any subjects were enrolled, and resulted in the following: • Replacement of the option for enrollment in N01199 and N01125 with the option of enrollment in N01315. This change was based on feedback received from ethics committees and regulatory authorities in some European countries. Addition of text describing randomization stratification by region to provide clarity with regard to the percentage of the subjects anticipated for enrollment in the US • Clarification that the total duration of the Baseline Period was 8 weeks ±1 week • Replacement of exclusion criteria referring to "clusters" of seizures with "seizure patterns being too frequent or indistinctively separated to reliably be counted." in order to more clearly define the term "clusters" • Addition of a recommendation for the sites to call subjects weekly to promote good completion of the subject diary. Text referring to this recommendation was added to the Informed Consent
04 April 2008	Protocol Amendment 1 was finalized on 04 Apr 2008, before any subjects were enrolled, and resulted in the following: • Replacement of the interactive voice response system (IVRS) with EDC for screening subjects. This change was made in accordance with recommendations of the IVRS and Seizure Frequency EDC system provider • Replacement of the subject's daily record card (DRC) with the CRF as the location for recording the "Investigator Seizure Assessment" • Addition of requirement that Investigator confirm AEs next to subject's entry of seizure data on DRC itself • Correction of typographical errors • Revision of the methods for handling missing data in acknowledgement of the fact that no details were known regarding the way missing data were handled, if at all, in the historical-control studies. Thus the application of any imputation rule for the assessment of Exit Criterion 2 during the study (and implemented in the study EDC system) leading to subjects being prematurely or incorrectly exited from the study was avoided. Final sensitivity analyses were to include these revised methods. The possibility for the Investigator exiting subjects on the basis of Exit Criterion 4 was considered an adequate safeguard against subjects remaining too long in the study if missing data interfered with the assessment of Exit Criteria 1 or 2.
02 November 2009	Protocol Amendment 2 was finalized on 02 Nov 2009 and resulted in the following: • Addition of a recruitment hold and interim analysis. This change was motivated by ongoing monitoring that suggested a higher than expected number of subjects discontinuing either for predefined exit criteria or other reasons. The interim analysis was to include efficacy information for all subjects who had an opportunity to complete 112 days of treatment after initiation of concomitant AED tapering by the time of the defined clinical cut-off date • Establishment of an IDMC to review primary efficacy, sensitivity, and safety data for the purpose of making a recommendation to the Sponsor regarding study continuation • Elimination of the requirement for restricted database access of the study team before approval of the final Statistical Analysis Plan (SAP) in accordance UCB Standard Operating Procedures (SOPs) revised subsequent to study initiation. Due to this change and because the primary efficacy analysis was fully specified in the original and amended protocols, this requirement was eliminated from this protocol • Updates of UCB study personnel and the List of Abbreviations Following the recruitment hold a decision was made to require subjects who were in the Baseline Period, the BRV Add-On Period, and the AED Tapering Phase to terminate the study. Subjects who had already progressed to the Monotherapy Phase were permitted to remain in the study.

16 November 2009	Protocol Amendment 3 was finalized on 16 Nov 2009 (after the recruitment hold) and resulted in the following: • Provision for enrollment in N01315 for subjects discontinued from the BRV Add-On Period or the Baseline AED Tapering Phase due to recruitment hold and interim analysis. This enrollment option was made available to provide continued treatment with BRV to these subjects as deemed beneficial by both subjects and Investigators • Correction of an error in Amendment 2 that placed information pertaining to database access and SAP finalization in an incorrect section of the protocol

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
02 November 2009	Concerning high discontinuation rate and subsequent determination of low probabilty of success (eg, criteria for futility were met).	-

Notes:

Limitations and caveats

None reported